Universidade do Algarve

Structural Effects for the Improvement of Synthetic Methods

Nelson Cabrita Martins

Doutoramento em Química

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co-orientada por Professor Doutor Jianliang Xiao

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A investigação envolvida na realização da presente tese foi financiada pela **Fundação pela Ciência e a Tecnologia**, **MCTES** - bolsa de Investigação com a referência:

SFRH / BD / 17262 / 2004 - e co-financiada pelo **POCI 2010** e pelo **FSE**.

FCT Fundação para a Ciência e a Tecnologia
MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR

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Aos meus pais, irmã e sobrinho

(To my parents, sister and nephew)

“Na verdade, nenhuma correcção parece no momento ser motivo de gozo, porém de tristeza; mas depois produz um fruto pacífico de justiça nos que por ela têm sido exercitados. Pois eu sei que o meu Redentor vive, e que por fim se levantará sobre a terra. E depois de consumida esta minha pele, ainda na minha carne verei a Deus.”

Hebreus 12:11, Job 19:25-26

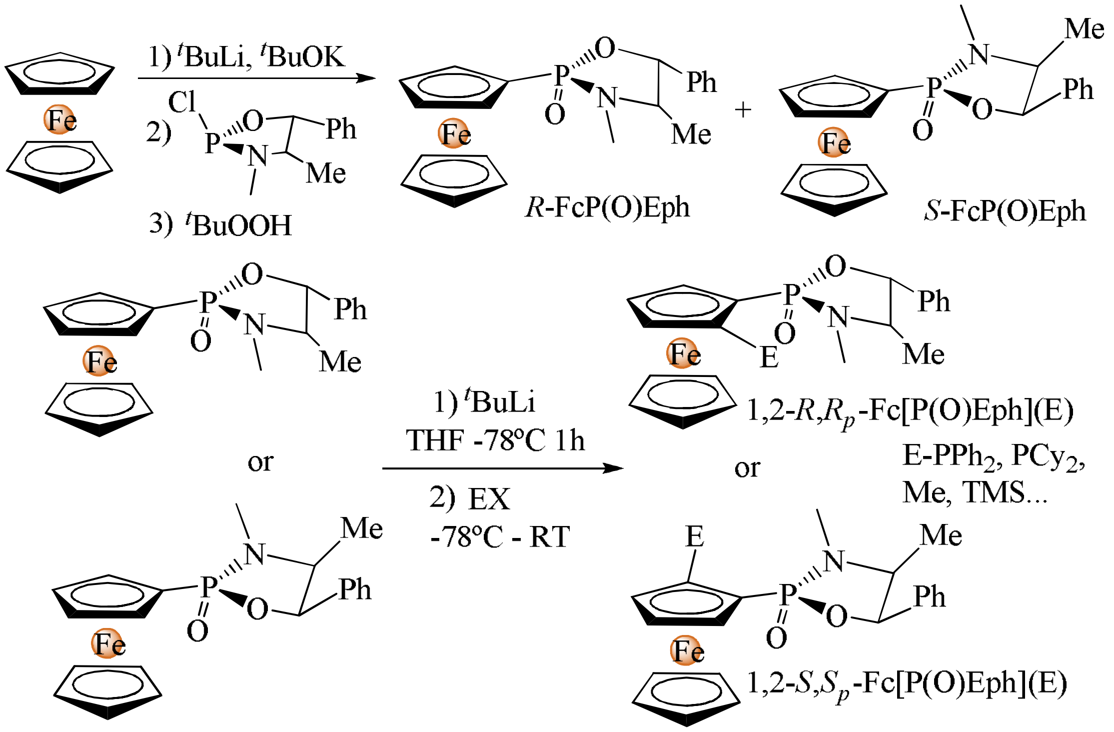
“Now no chastening for the present seemeth to be joyous, but grievous: nevertheless afterward it yieldeth the peaceable fruit of righteousness unto them which are exercised thereby. For I know that my redeemer liveth, and that he shall stand at the latter day upon the earth. And though after my skin worms destroy this body, yet in my flesh shall I see God.”

Hebrews 12:11, Job 19:25-26

Abstract

The demand for enantiopure compounds in society motivates chemists to develop methods for asymmetric synthesis. Asymmetric catalysis is central in this context, its development significantly depending on the discovery of new successful chiral ligands. Ferrocenes represent powerful and unique chiral ligands which may contain a chiral plane. Such chirality is often built in the ferrocene backbone via diastereoselective *ortho*-lithiation and functionalization of monosubstituted ferrocenes containing a chiral *ortho*-directing group (CDG). Accordingly the oxazaphospholidine oxide group has been studied allowing highly stereoselective synthesis of planar chiral 1,2-disubstituted ferrocenes. Herein we expand on the exploration of this interesting group aiming to further access on its potential for the synthesis of useful chiral ferrocenyl phosphines to be applied in catalysis.

Thus observation of two P-epimers during the formation of the starting ferrocenyl oxazaphospholidine oxide led to the synthesis of novel ligands, including diastereopure 1,2-disubstituted ferrocenes with opposite planar chirality, as shown below.



Additional investigation included a second lithiation step at the 1,2-disubstituted ferrocenes, preparation of P-chiral ligands based on stereoselective induction by the oxazaphospholidine oxide, and its reduction, all together leading to new structures.

Coordination chemistry and catalysis involving our ligands were approached revealing oxazaphospholidine oxide group ability to act as a hemilabile ligand coordinating to palladium at the phosphoryl oxygen. The ligands displayed potential activity, both on the Suzuki-Miyaura cross-coupling and Asymmetric Allylic Alkylation, this last case involving moderate enantioselectivities, up to 70 % ee.

Finally the possibility to use phenolic benzisothiazolyl and tetrazolyl ethers in Suzuki-Miyaura reaction was evaluated revealing positive results, with the tetrazolyl ones.

Keywords: Ferrocenyl oxazaphospholidine oxide; chiral *ortho*-directing group; planar chirality; reduction; asymmetric catalysis; phenolic benzisothiazolyl and tetrazolyl ethers.

RESUMO

Os compostos enantiomericamente puros fazem parte da nossa vida quotidiana, seja na forma de fármacos, aromas alimentares e fragrâncias, seja na forma de pesticidas ou polímeros. Efectivamente os sistemas biológicos existentes na natureza, inclusive o ser humano, caracterizam-se por um reconhecimento quiral das substâncias. Frequentemente apenas um enantiómero de um dado composto é benéfico, sendo o outro ineficaz se não letal.

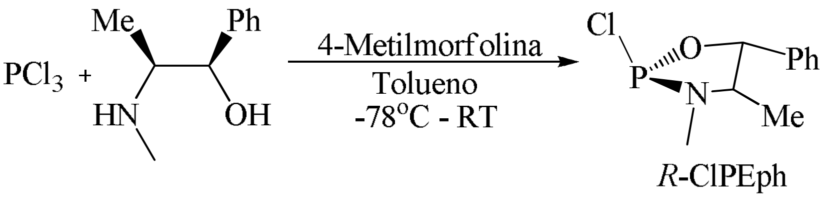
Várias circunstâncias levaram a que sobretudo desde a década de 1990 se verificasse um crescimento na procura de substâncias com elevado grau de pureza óptica. Neste contexto a catálise assimétrica tem vindo a tomar um papel preponderante no desenvolvimento de processos para a produção de compostos enantiomericamente puros. De importância central neste objectivo está a descoberta de novos ligandos quirais eficazes, passíveis de serem aplicados nos mais variados processos químicos e aos incontáveis substratos da catálise assimétrica. Na realidade constata-se a inexistência de ligandos que sejam, por assim dizer, "universais". Consequentemente tem sido suscitado interesse na síntese de famílias de ligandos cuja estrutura seja facilmente modificada e cujas propriedades sejam moduladas, de acordo com a reacção e o substrato em causa.

Os derivados de ferroceno apresentam inúmeras características que os tornam atractivos na síntese de ligandos quirais. Nomeadamente a sua rigidez e dimensão, reactividade e flexibilidade na sua derivatização, estabilidade mesmo na presença de ar e água, e o seu preço e disponibilidade. Inclusivamente os compostos derivados de ferroceno podem conter um plano quiral resultante da presença de dois grupos substituintes distintos no mesmo anel ciclopentadienil. A incorporação estéreo-selectiva destes dois substituintes tem sido preferencialmente efectuada via litiação e derivatização diastéreo-selectiva de ferrocenos mono-substituídos, possuidores de um grupo *orto*-director quiral (GDQ).

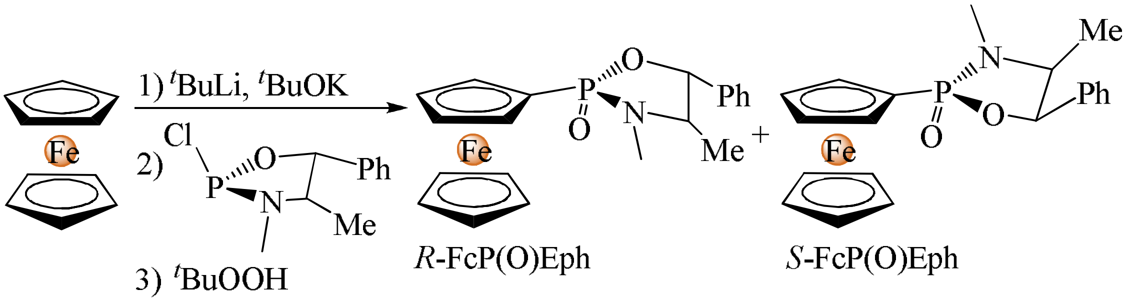
Em investigações realizadas anteriormente no nosso grupo, o óxido de oxazafosfolidina demonstrou ser um GDQ eficaz na síntese de ferrocenos planares 1,2-di-substituídos. Para além de envolver elevado grau de estéreo-selectividade a estratégia utilizada demonstrou tolerância a uma gama de substituintes. Nestes ferrocenos di-substituídos, a derivatização do óxido de oxazafosfolidina noutros grupos, especialmente fosfinas estereogénicas, possibilitaria a formação de uma nova família de ligandos, com quiralidade planar e central. Idealmente, a combinação de ambos os tipos de quiralidade, caso durante a catálise assimétrica induzissem estéreo-selectividade sinergeticamente, resultaria na eficaz transferência de quiralidade e na obtenção de produtos com maior grau de pureza óptica.

De facto para além de outras vantagens, a escolha de oxazafosfolidina, derivada de (1*R*,2*S*)-(-)-efedrina, baseou-se na prévia aplicabilidade da técnica de deslocamento de Jugé a oxazafosfolidinas. Nesta técnica o anel de oxazafosfolidina é aberto, via ataque nucleofílico sobre o fósforo, levando à formação de uma nova ligação fósforo-carbono (P-C) de forma estéreo-selectiva. Na sequência de um novo ataque nucleofílico o fragmento de efedrina é removido, uma nova ligação P-C é formada, obtendo-se uma nova fosfina estereogénica. Embora em trabalho anterior esta técnica tivesse falhado quando aplicada aos nossos ferrocenos 1,2-di-substituídos contendo o óxido de oxazafosfolidina, ficou em aberto a redução total do mesmo grupo levando à formação de fosfinas primárias. Assim neste trabalho propusemo-nos a dar curso à investigação da redução mencionada, bem como a explorar o potencial do óxido de oxazafosfolidina ferroceno quando aplicado à síntese de 1,2-ferrocenos com um plano quiral.

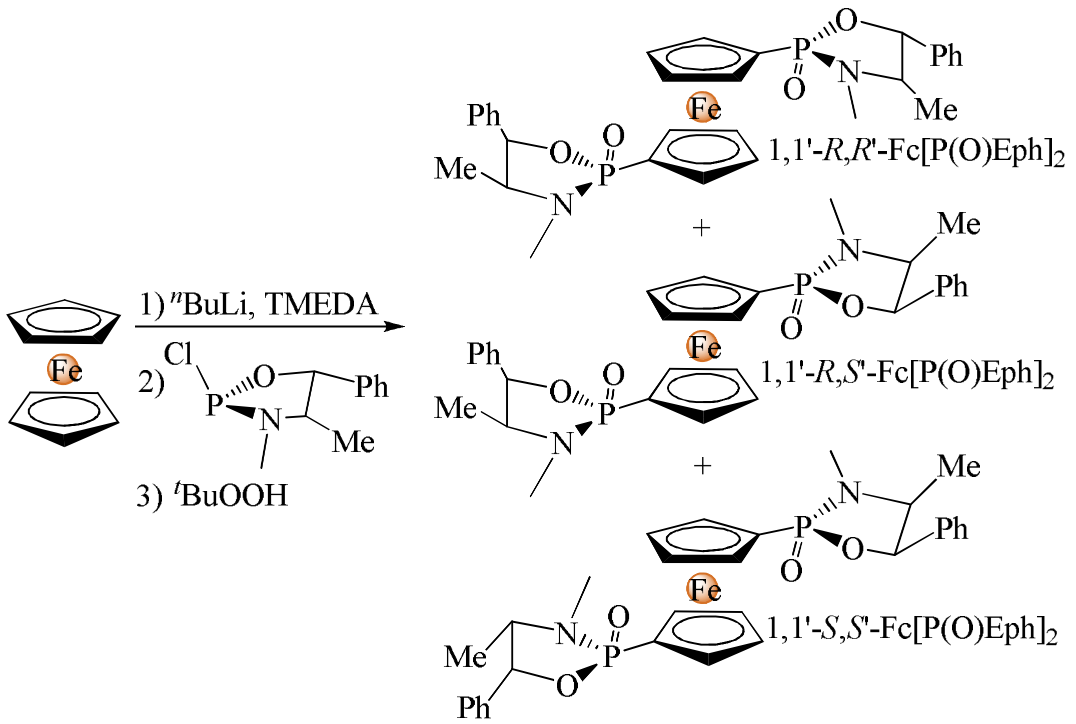
O primeiro passo da nossa investigação consistiu na síntese do cloreto de oxazafosfolidina, o qual foi obtido como um único diastereómero, de configuração *R*, *R*-ClPEph, segundo o esquema abaixo.



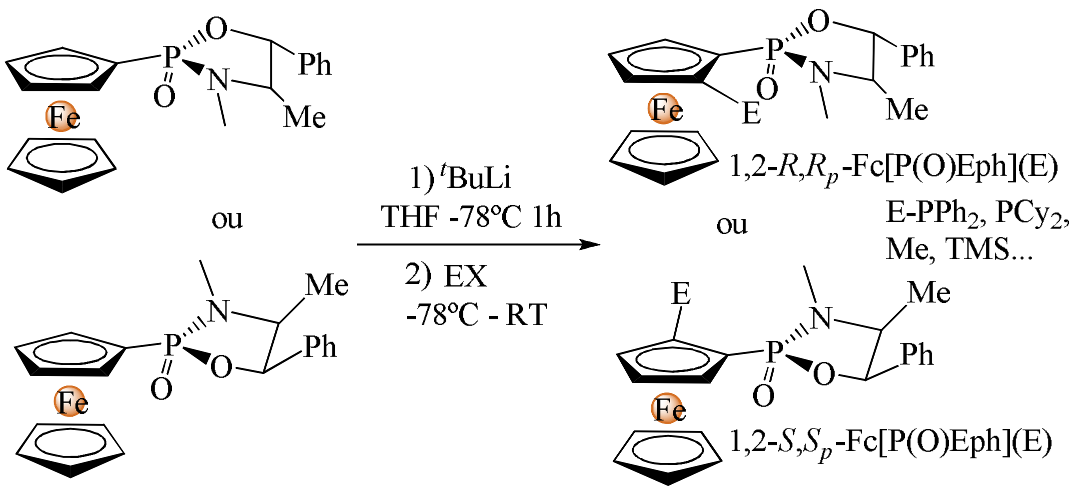
Por outro lado, ao utilizar este composto aquando da preparação do óxido de oxazafosfolidina ferroceno, o nosso material de partida, verificou-se a formação de dois P-epímeros, *R*-FcP(O)Eph e *S*-FcP(O)Eph, sendo que este último não havia sido previamente detectado. Ambos compostos representados abaixo, foram devidamente caracterizados, tendo-se analisado as suas estruturas de raio-X, tentando-se também racionalizar o rácio entre os P-epímeros.



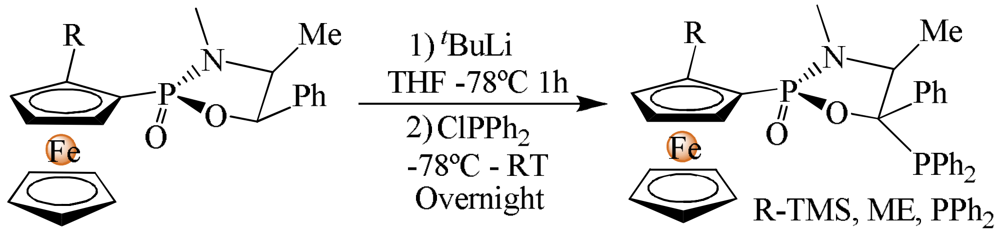
A di-litiação do ferroceno nas posições 1 e 1’ seguidas da reacção com o cloreto de oxazafosfolidina levou à formação de três ferrocenos 1,1’-di-substituídos. Como verificado no seguinte esquema os compostos distinguem-se pela configuração do átomo de fósforo nos grupos oxazafosfolidina ligados a cada anel ciclopentadienil, 1,1'-*R*,*R*'-Fc[P(O)Eph]$_2$, 1,1'-*R*,*S*'-Fc[P(O)Eph]$_2$ e 1,1'-*S*,*S*'-Fc[P(O)Eph]$_2$.



Face à existência de dois epímeros de óxido de oxazafosfolidina ferroceno colocou-se a hipótese de se formarem ferrocenos 1,2-di-substituídos com quiralidade planar de configuração oposta. Prosseguiu-se na investigação da *orto*-litiação e funcionalização do novo P-epímero, *S*-FcP(O)Eph. Este passo verificou-se régio-selectivo apresentando também elevada estéreo-selectividade, >99% e.d. Estruturas de raio-X de dois dos novos compostos formados revelaram de facto inversão na configuração do plano quiral, S_p. De acordo com o esquema abaixo, vários novos compostos foram por este meio preparados inclusive fosfinas contendo dois ferrocenos, demonstrando a flexibilidade, abrangência e reprodutibilidade da metodologia. A diastéreo-selectividade observada durante a litiação foi discutida tendo em mente os possíveis modos de coordenação entre o lítio e o grupo óxido de oxazafosfolidina.

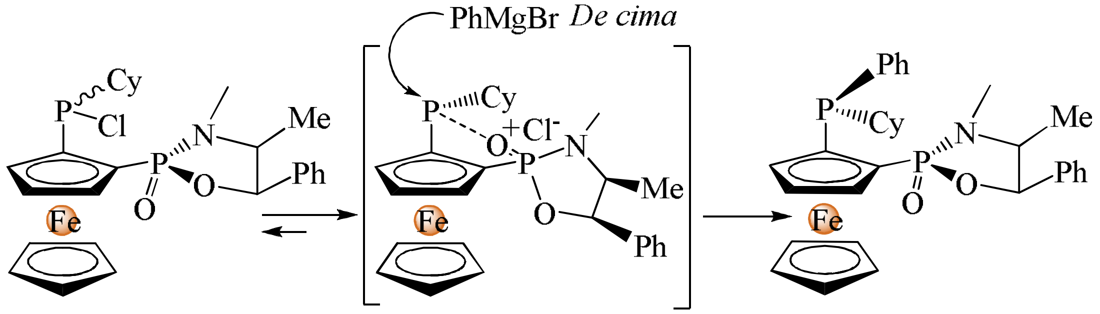


Sendo possível obter 1,2-ferrocenos com quiralidade P-central, no fósforo da oxazafosfolidina, e planar com configurações inversas, R,R_p e S,S_p, pretendeu-se investigar a possibilidade de obter os outros possíveis diastereómeros, R,S_p e S,R_p. Para tal tentou-se realizar uma segunda *orto*-litiação e funcionalização nos ferrocenos 1,2-di-substituídos anteriormente formados, nomeadamente visando a substituição do outro protão *orto* relativamente ao grupo oxazafosfolidina. Caso isto se verificasse possível, a utilização de um grupo removível aquando da primeira substituição, permitiria, após a segunda substituição e remoção do primeiro substituinte, a formação de um composto com quiralidade planar e P-central distintas. Aplicando-se a anterior metodologia de litiação e funcionalização verificou-se insucesso no objectivo pretendido. Na realidade constatou-se que os novos 1,2-ferrocenos, 1,2-*S*,*S*$_p$-Fc[P(O)Eph](E), sofriam substituição selectiva do protão CHPh existente no anel de oxazafosfolidina. Embora sem ser inicialmente pretendido formaram-se assim novos ligandos, mais especificamente as seguintes fosfinas invulgares, 1,2-*S*,*S*$_p$-Fc[P(O)(Eph'PPh$_2$)](R).



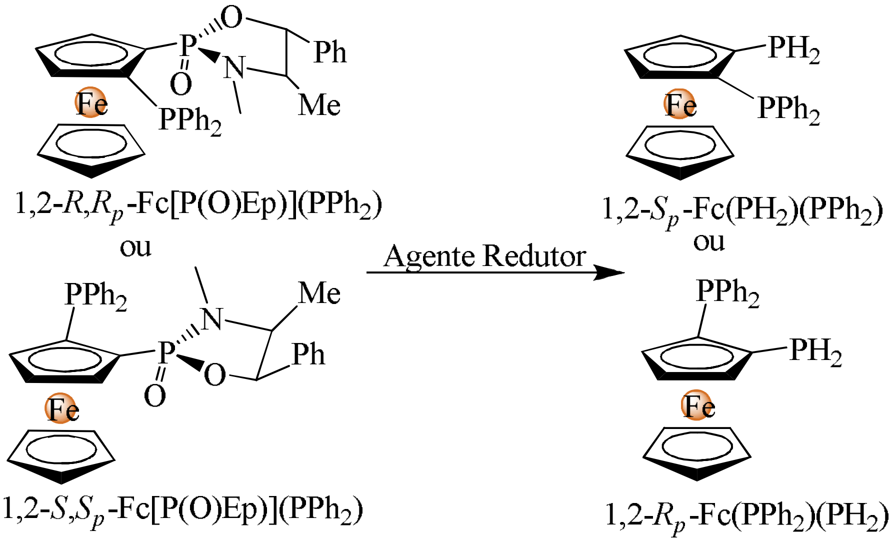
1,2-*S*,*S*$_p$-Fc[P(O)(Eph'PPh$_2$)](R)

Seguindo uma estratégia de *orto*-litiação e funcionalização ligeiramente diferente da original verificou-se a capacidade de indução estéreo-selectiva por parte do nosso GDQ na formação *in situ* de fosfinas estereogénicas. Novamente formaram-se ferrocenos 1,2 di-substituídos com quiralidade planar como o ligando 1,2-*S*,*S*$_p$-Fc[P(O)Eph](PPhCy). A diastéreo-selectividade demonstrada neste caso foi brevemente discutida. Segundo o seguinte esquema, é considerada a possível formação de um intermediário apresentando coordenação entre o fósforo da nova fosfina e o oxigénio do óxido de oxazafosfolidina.



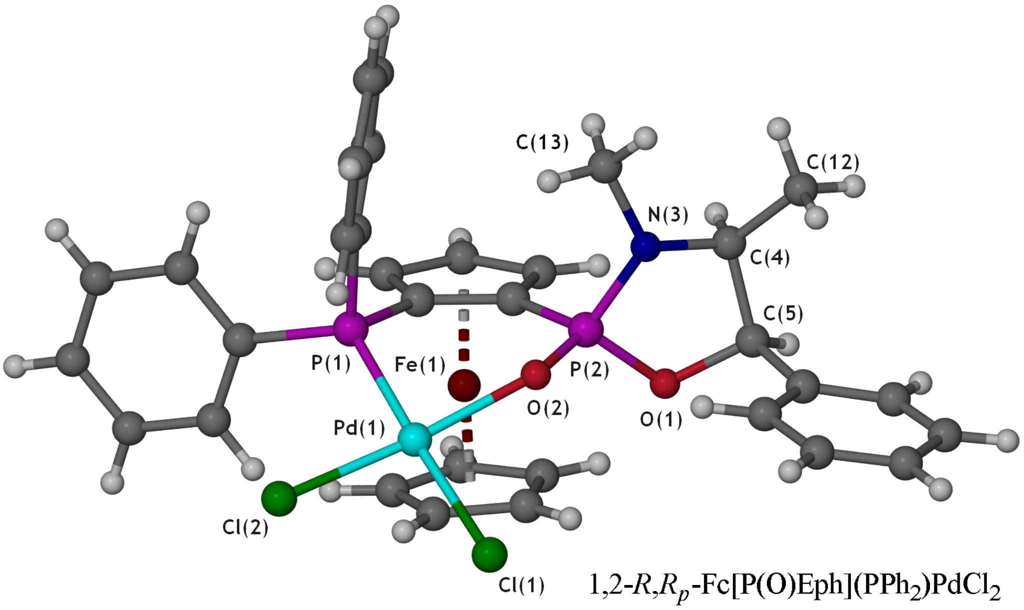
1,2-*S*,*S*$_p$-Fc[P(O)Eph](PPhCy)

Posteriormente à etapa de *orto*-litiação e funcionalização, a derivatização do GDQ poderá dar lugar a novos compostos com maior interesse. No nosso caso por razões já mencionadas pretendeu-se investigar a redução do grupo óxido de oxazafosfolidina. De facto verificou-se que a redução com triclorosilano, um agente tipicamente usado na redução de óxidos de fosfinas, não resulta na oxazafosfolidina livre. Antes constatou-se a remoção do fragmento de efedrina com a formação de fosfinas primárias, isto quer fossem usados ferrocenos mono ou di-substituídos. Sendo as fosfinas primárias importantes materiais de partida na preparação de ligandos, inclusive fosfinas pseudo-quirais, a reacção suscitou o nosso interesse. A ocorrência de compostos secundários na reacção impôs a exploração de diferentes agentes redutores. Testaram-se também diferentes procedimentos na purificação dos produtos, os quais são sensíveis ao ar e água, sendo a sua manipulação delicada. Apesar disto a reacção permitiu a formação de fosfinas primárias inseridas em ferrocenos contendo quiralidade planar com ambas as possíveis configurações. Acreditamos ainda não ter sido publicada a síntese de tais fosfinas primárias, 1,2-S_p-Fc(PH_2)(PPh_2) e 1,2-R_p-Fc(PPh_2)(PH_2), representadas abaixo.



Seguindo um capítulo de introdução geral à tese e um capítulo em que foram apresentadas a síntese, investigação e redução dos nossos óxidos de oxazafosfolidina ferrocenos, dedicamos um terceiro capítulo em que de forma breve abordamos a sua química de coordenação e a sua investigação em catálise química.

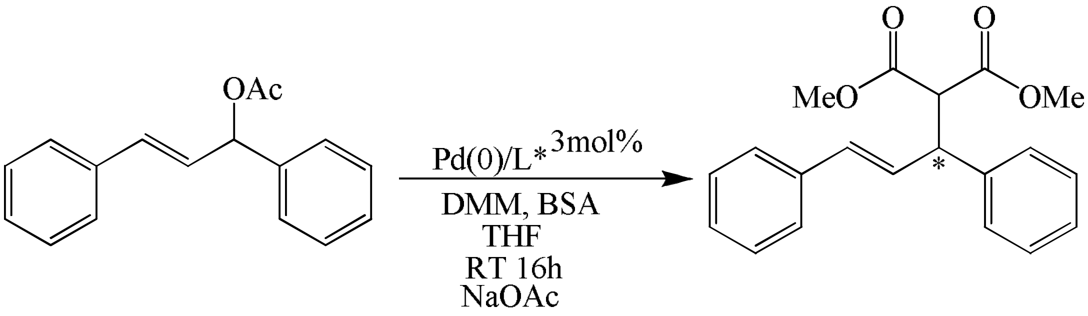
O grupo óxido de oxazafosfolidina apresenta vários átomos susceptíveis de coordenarem com um metal de transição. São eles o átomo de oxigénio no fosforilo, o azoto e o oxigénio no anel, estes últimos pertencentes ao fragmento de efedrina. No nosso caso, o complexo resultante da coordenação do metal com o ligando varia consoante o centro de coordenação com o qual a ligação é estabelecida. Cada um destes três possíveis complexos apresentará portanto propriedades espaciais e electrónicas particulares. A catálise química depende do catalisador utilizado sendo pois influenciada pelo modo de coordenação do ligando ao metal. Assim, num breve estudo fizeram-se reagir vários dos ligandos sintetizados neste trabalho com uma fonte de paládio, $PdCl_2(PhCN)_2$. De modo a tirar conclusões quanto aos modos de coordenação de cada composto formado compararam-se dados de RMN ^{31}P, das fosfinas livres e das fosfinas complexadas. Estas conclusões basearam-se sobretudo na seguinte estrutura de raio-X de um complexo de paládio formado com um dos nossos ligandos, 1,2-*R*,R_p-Fc[P(O)Eph](PPh_2)$PdCl_2$. Neste complexo 1:1 ligando/paládio, em cujo ligando 1,2-*R*,R_p-Fc[P(O)Ep)](PPh_2) apresenta uma fosfina livre para além do óxido de oxazafosfolidina, observou-se a coordenação do metal quer com a fosfina livre quer com o oxigénio do fosforilo.



1,2-*R*,R_p-Fc[P(O)Eph](PPh_2)$PdCl_2$

Efectivamente constatou-se que o óxido de oxazafosfolidina age como um grupo hemilábil que pode ou não coordenar com o metal de acordo com o seu grau de saturação por parte de outros centros de coordenação mais fortes, por exemplo fosfinas livres. De acordo com isto, dados de RMN ^{31}P sugerem que num ligando apresentando duas fosfinas livres para além do fosforilo, 1,2-*S*,S_p-Fc[P(O)(Eph'PPh_2)](PPh_2), o metal coordenou apenas com estas ao passo que o óxido permaneceu livre.

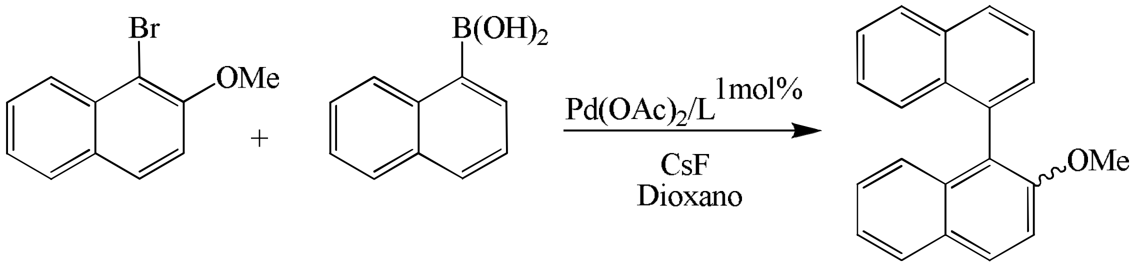
Tendo tirado algumas conclusões quanto à química de coordenação dos nossos ligandos pretendemos testá-los quanto à sua performance em catálise. Devido à importância da reacção de alquilação alílica assimétrica, os nossos ligandos foram testados neste tipo de reacção entre o 1,3-difenil-2-propenil acetato e o anião de dimetil malonato na presença de *N*,*O*-bis(trimetilsilil)acetamida, tal como visualizado no esquema seguinte.



Associados ao paládio, todos os ligandos utilizados permitiram óptimas conversões, demonstrando formar catalisadores com excelente actividade química nesta reacção específica. Por outro lado a enantio-selectividade variou bastante de ligando para ligando alcançando-se um valor máximo de 70% e.e. Embora não nos fosse permitido fazer um estudo separado em relação ao efeito da quiralidade planar e da quiralidade central no fósforo, julga-se que de facto a quiralidade planar afecta a indução quiral. Observou-se que os produtos formados apresentavam configuração idêntica à dos ligandos utilizados. Uma excepção teve lugar quando se utilizou um dos ferrocenos contendo duas fosfinas livres, 1,2-*S*,S_p-Fc[P(O)(Eph'PPh_2)](PPh_2), uma delas inserida no anel de oxazafosfolidina. Embora de configuração *S*,S_p, este ligando levou à formação de produto com configuração *R*.

Visto os ligandos de configurações opostas, 1,2-*S*,S_p-Fc[P(O)Eph](PPh$_2$) e 1,2-*R*,R_p-Fc[P(O)Eph](PPh$_2$), não serem imagens no espelho mas diastereómeros ou P-epímeros, poderíamos antever diferentes comportamentos. Na verdade estes levaram à formação de produtos com configurações opostas porém com enantio-selectividade dissimilar, sugerindo relevância por parte da quiralidade central nos ligandos. O melhor resultado na enantio-selectividade, demonstrado por parte de um ligando de configuração *R*,R_p, foi discutido tendo por base o arranjo tridimensional do espaço envolvendo o centro metálico. Julga-se que o facto deste último ligando 1,2-*R*,R_p-Fc[P(O)Eph](PPh$_2$) apresentar maior impedimento espacial junto do centro metálico imponha maior rigidez resultando em maior grau de enantio-selectividade na reacção.

De forma a melhor comparar a performance dos nossos ligandos em relação à sua actividade catalítica, testamo-los na importante reacção de acoplamento-cruzado de Suzuki-Miyaura. Procedeu-se pois ao acoplamento entre 2-metoxi-1-bromo-naftaleno e ácido naftil-borônico, catalisado por paládio.

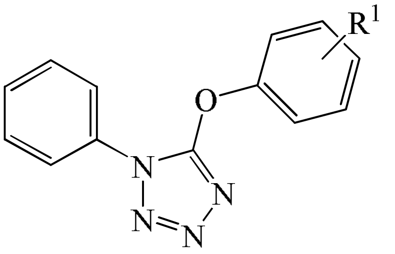


De forma geral foram observadas diferentes actividades por parte dos vários ligandos utilizados. Apesar disto entre ligandos P-epímeros um do outro, 1,2-*S*,S_p-Fc[P(O)Eph](PPh$_2$) e 1,2-*R*,R_p-Fc[P(O)Eph](PPh$_2$), observou-se semelhante actividade na reacção. Por outro lado a comparação de resultados obtidos aquando da utilização destes últimos ligandos, e de um ferroceno contendo a mesma fosfina livre (PPh$_2$) sem o grupo óxido de oxazafosfolidina, FcPPh$_2$, demonstrou que o óxido tem influência na reacção. Supostamente melhores resultados são obtidos devido à presença do óxido, o qual pode também ter um papel na estabilização do complexo metálico, sobretudo quando a proporção do ligando para com o metal é de 1 para 1. Os ligandos foram testados na reacção envolvendo outros brometos conduzindo a elevadas conversões.

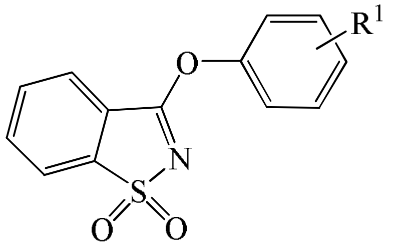
Em geral, na reacção de Suzuki, o passo determinante varia de acordo com o tipo de substrato utilizado, por exemplo brometos versus cloretos. Foram por isso realizados testes envolvendo o acoplamento entre a cloro-acetofenona e o ácido fenil-borônico. Comparando a acção dos mesmos três ligandos acima mencionados, o efeito do óxido de oxazafosfolidina na reacção é neste caso aparentemente menos positivo, levando a menor actividade quando comparado com o ferroceno sem este grupo. Tal facto poderá estar ligado à formação de um complexo demasiado estável o que poderá abrandar a velocidade da reacção.

O trabalho até agora mencionado envolveu a síntese e utilização de ligandos quirais com o intuito de contribuir em metodologias de síntese especialmente do ponto de vista da catálise assimétrica. Pretendendo contribuir com o desenvolvimento de novos métodos de síntese, agora mais do ponto de vista do substrato, realizou-se um estudo visando a utilização de éteres fenólicos hetero-aromáticos, derivados de tetrazol e benzisotiazol, na reacção de Suzuki.

O interesse nos fenóis relaciona-se sobretudo com a sua acessibilidade. No entanto a elevada força da ligação C-OH em fenóis coloca entraves à sua utilização directa na reacção de Suzuki. A sua derivatização com o enfraquecimento da dita ligação é pois indispensável. Apesar disto ser possível por meios de triflatos, ou outros agentes, estes em geral apresentam desvantagens sendo que continuam a ser necessárias melhores alternativas. Éteres fenólicos hetero-aromáticos preparados por meio de 5-cloro-1-fenil-1*H*-tetrazol ou de 3-cloro-1,2-benzisotiazole 1,1-dióxido apresentam várias vantagens atractivas. A sua estrutura revela o enfraquecimento da ligação C-O(H), existente no fenol original, sendo estes compostos usualmente cristalinos, relativamente estáveis e de fácil manuseamento. Estes podem ainda ser eficazmente utilizados como um meio indirecto de realizar a *ipso*-substituição do grupo hidroxilo em fenóis. Tais substituições realizando-se nomeadamente por meio de hidrogenações catalíticas com hidrogénio molecular ou dadores de hidrogénio, ou por meio de reacções de acoplamento catalítico com nucleófilos derivados de magnésio, estanho ou zinco. Assim primeiramente efectuou-se a síntese de alguns éteres fenólicos com diferentes substituintes, nomeadamente 5-aril-1-fenil-1*H*-tetrazol, **I**, e 3-aril-1,2-benzisotiazole 1,1-dióxido, **II**, representados abaixo.



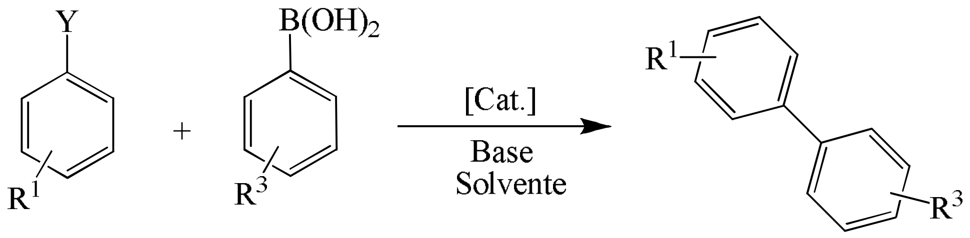
(I)



(II)

R^1-MeO, Me, H, Cl, F_3C...

De acordo com o esquema seguinte, seguiu-se um estudo da sua aplicação à reacção de Suzuki, ou seja no seu acoplamento com nucleófilos borônicos, neste caso catalisada por níquel ou paládio.



Y- OTet, OSac, Br, Cl

Vários parâmetros foram tidos em atenção tais como o sistema catalítico a ser utilizado, a base, o solvente, o substrato, o derivado de boro, entre outros. Embora os resultados preliminares obtidos não fossem favoráveis, conduzindo a baixas conversões, permitiram inferir algumas conclusões em relação à reacção. Por exemplo a hidrólise dos éteres, especialmente os benzisotiazolílicos, originando os fenóis originais, e a reacção de homocoupling por parte do ácido borônico demonstraram serem reacções secundárias indesejadas que competem com a reacção de acoplamento cruzado

pretendida. O acetato de paládio na ausência de ligandos permite a ocorrência da reacção, contudo o ciclo catalítico é interrompido desde cedo supostamente devido à instabilidade do catalisador. Por outro lado a utilização de fosfinas anteriormente tipicamente utilizadas na reacção, tais como trifenilfosfina ou dppf, quando associadas ao metal de transição não conduzem à formação de catalisadores suficientemente activos.

Tendo em conta as observações anteriores decidimos utilizar ligandos electronicamente ricos e espacialmente impedidos com vista a formar catalisadores mais activos e a favorecer o ciclo catalítico. Num breve estudo a triciclohexilfosfina e um dos nossos ferrocenos contendo o grupo difenilfosfina foram utilizados na reacção de Suzuki com éteres tetrazolílicos e benzisotiazolílicos. Esta estratégia positiva resultou em conversões mais elevadas até ligeiramente abaixo de 50%, desvendando potencial especialmente por parte dos éteres tetrazolílicos na sua aplicação à reacção de Suzuki.

Em suma, o trabalho efectuado nesta tese demonstra a versatilidade do grupo óxido de oxazafosfolidina na construção de uma família de novos ligandos derivados de ferroceno apresentando quiralidade planar com as duas configurações possíveis. Entre as várias estruturas contam-se 1,2-ferrocenos apresentando diferentes grupos orgânicos, inclusive fosfinas estereogénicas e fosfinas primárias, estas últimas passíveis de serem derivatizadas. Ao serem testados, estes ligandos revelaram-se promissores, tendo demonstrado elevada actividade catalítica na reacção de Suzuki-Miyaura e na alquilação alílica assimétrica. Nesta ultima reacção a sua capacidade de indução estéreo-selectiva foi testada levando a moderados excessos enantioméricos, sendo que ambas a quiralidade planar como a central desempenham um papel importante.

O estudo envolvendo éteres fenólicos tetrazolílicos e benzisotiazolílicos no acoplamento de Suzuki confirma a aplicabilidade dos primeiros à reacção.

Palavras-chave: Óxido de oxazafosfolidina ferroceno; grupo *orto*-director quiral, quiralidade planar; redução; catálise assimétrica; éteres fenólicos tetrazolílicos e benzisotiazolílicos.

Acknowledgements

Often the human language is inadequate to express what one may have in his mind and heart. Yet I would like to utter a few words as a token of gratitude and appreciation for the gift of life and for what so many people have meant to me throughout the course of this PhD work.

Professor Amadeu Brigas you have received me as your student since the beginning and have endured with me until the end. Without your help I wouldn’t be able to take this project forward. What's more you sought to teach me other than chemistry; persevering to do what is right. Professor Jianliang Xiao you have gladly welcomed me as a member of your group, respecting my beliefs and helping me in all challenges. In your group I was able to contemplate chemistry being done in a very enthusiastic and spirited fashion, being in contact with different cultures and people. I feel privileged for having had such opportunity. Indeed I am glad for the many friends I have met and for the lessons learned with them. My appreciation goes to my lab mates, namely Colin, Jun Mo, Richard, Daniele, Nuno, Ourida, Xiaofeng, Zeyn, Matthew, Shifang, Jiwu, Li, Xiaohong, Chao, Yunfei, Barbara and all members of JX group. I would also like to mention friends from the department such as J.-B., Valerie, Maria and Chi, as well as the sport guys and others. Still from the chemistry department I thank all the technicians, especially Sandra and Paul (NMR), Allan and Moya (mass spectrometry), Steve (elemental analysis), John (X-ray), and Paul (glassblower).

My gratitude goes as well to other friends, mostly at Liverpool, with whom I was privileged to share special moments during my PhD: Esther, Filipa, Maria, Raquel, Luís, Emanuel, Pat, Kawa, Sérgio, Hugo, Steff, Mariana, Edite, Becas, Nuna, Rui, Barroca, Rita, Susete, Rosie, Natalia and others - (Edite and Rui many thanks for the analyses you have provided while I was still in the Algarve). I really was blessed with our Portuguese group in which I could find friendship, support and feel closer to home. Ory, I must thank you again; you are a special friend always showing great willingness and heart. Vera and Ricardo, you have lent a hand to me in one of the darkest moments of my life being like angels sent from God. Liverpool SDA church, you have been my spiritual family in Liverpool. My gratefulness to the Rey clan, Michelle, Mwiya, Merlvin, Gershom, Tiphaine, Kia, Pat, Sister White, Cheryl, Sinda, Peris, Manuel, family da Silva, all the families and everyone.

In the Algarve I could benefit from fellowship, advices and help of friends, colleagues, staff, and professors, so among others my recognition goes to David, Frija, Marisa, Rute, Daniela, Carla, Teresa, Rosário, Catarina, and to professors Vasco, Américo, João, Conceição, André, José, Lurdes and Ana. I am in debt to my spiritual family in Faro, especially to those that hold me up with much care, Fátima, Jomim, Telma, Neemias, Simoni and Catarina.

I would like to thank the Universidade do Algarve and the University of Liverpool for receiving me as their student, and the Fundação para a Ciência e Tecnologia for two vital PhD grants. In a more general way I am thankful to the Portuguese society and those that contributed with taxes allowing my studies, and to all those, teachers, colleagues and others, that someway have contributed to my life as a student, since I first started to attend school back in France until this day. Many thanks to those at the Universidade do Algarve which, in all possible manners, contributed to the completion of this project.

Special recognition goes as well to dear friends for their encouragement, and shared moments in Publicadora Servir, Luanda, Kajiado, and others places. My gratitude goes to Hélio and Laura, Patrícia, Luís, Rute and Rony, Carol, Sandra Silva, and to so many others. In addition I think of more recent friends that have kept me in prayer, Miriam, Rute Mónica, Sandra and Paula.

There are no words to describe the great love revealed by my family in these last years of challenge and trial. Despite all the suffering I somewhat caused you to go through you have consistently and unconditionally loved and supported me... my heart is overwhelmed. Sincerely, while following my conscience, I whish to be able to bring you as much joy as possible.

To the One that gives life and sustains the worlds, what can I but say: ” *Lord, thou knowest all things*…”

Preface

This thesis is based on research work carried out in two different research centres, namely at “Universidade do Algarve - Faculdade de Ciências e Tecnologia” and at “The University of Liverpool - Centre for Materials and Catalysis”. A common notion that permeated our research was to explore and manipulate the structure of molecules as a means to contribute for the improvement of synthetic methods.

Parts of this thesis have appeared in the following articles:

Ferrocenyl phosphine-oxazaphospholidine oxide ligands for the Suzuki-Miyaura coupling of hindered aryl bromides and chlorides.

Vinci, D.; Martins, N.; Saidi, O.; Bacsa, J.; Brigas, A.; Xiao, J., *Can. J.* Chem., **2009**, *87* (*1*), 171-175.

Another Side of the Oxazaphospholidine Oxide Chiral *ortho*-Directing Group.

Martins, N.; Mateus, N.; Vinci, D.; Saidi, O.; Brigas, A.; Bacsa, J.; Xiao, J., *Org. Biomol. Chem.*, **2012**, *in press.*

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Abbreviations

AAA	acetamidoacrylic acid
Ac	acetyl
ACA	acetamidocinnamic acid
Ar	aryl
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphtyl
BINOL	1,1’-bi-2,2’-naphtol
Bn	benzyl
BPMO	bisphosphine monoxide
BPPFA	α-[1’,2-bis(diphenylphosphino)ferrocenyl]ethyldimethylamine
BSA	*N*,*O*-bis-(trimethylsilyl)acetamide
Bu	butyl
COD	*cis*-1,5-cyclooctadiene
Cp	cyclopentadienyl
Cy	cyclohexyl
Dba	dibenzylideneacetone
DCM	dichloromethane
De	diastereomeric excess
DET	diethyl tartrate
DIBAL-H	diisobutylaluminium hydride
DIOP	2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPAMP	bis[(2-methoxyphenyl)phenylphosphino]ethane
DMIT	dimetyl itaconate
DMM	dimethyl malonato
EA	elemental analysis
Ee	enantiomeric excess
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
Fc	ferrocenyl
FcPN	1-dimethylaminomethyl-2-(diphenylphosphino)ferrocene
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
HPLC	high-performance liquid chromatography
ITA	itaconic acid
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LiDBB	lithium di-*tert*-butylbiphenylide
MAA	methyl 2-acetamidoacrylate

MAC	α-methyl acetamidocinnamate
Me	methyl
Ms	methanesulfonyl
Naph	naphthyl
NMO	*N*-morpholine oxide
NMR	nuclear magnetic resonance
TADDOLS	α,α,α',α'-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol
THF	tetrahydrofurane
MeOH	methanol
MMPP	magnesium monoperoxyphthalate
o-DPPFA	2-(diphenylphosphanyl)ferrocene carboxylic acid
Ph	phenyl
Phox	phosphino-oxazolines
PPFA	α-(2-diphenylphosphinoferrocenyl)ethyldimethylamine
Ppm	parts per million
Pr	propil
Sac	1,1-dioxo-1,2-benzisothiazol-3-yl
TES	triethylsilyl
Tet	1-phenyl-1*H*-tetrazole-5-yl
Tf	trifluoromethanesulphonyl
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	trimethylsilyl
Tol	tolyl
TPAB	tetrapropylammonium bromide
TRAP	2,2'-bis[1-(diarylphosphino)ethyl]-1,1'-biferrocene
Ts	*p*-toluenesulfonyl

1

Introduction

The development of new effective chiral ligands for asymmetric catalysis, as a means to meet the ever increasing demand for enantio-enriched compounds, remains a theme worthy of attention.

In addition to disclosing the scope of this thesis one desires to set the stage and background that led to carry out this work. In a general introduction relevant notions and facts that converge to the purpose of this thesis will be approached in order to facilitate its comprehension.

Chapter *1*

1.1 GENERAL OVERVIEW

1.1.1 A POINT OF VIEW ON SCIENCE TOWARDS SOCIETY

In his quest to survive and answer to the everyday problems that persist to crop up along the journey, man has evermore tried to discover solutions, and to attain a better understanding of his surroundings and of himself. Moreover, the “book of nature” has always intrigued us with its endless mysteries and mind bugging intricacies. In effect the increasing want for new solutions and the innate curiosity of man has acted as a powerful, self growing, gravitational force driving us to relentlessly search for new ways of facing life, and all the challenges that it entails. This is especially so in this young but complex 21st century. Never a society had so much and at the same time wanted so much. The arising demands are great and encompass many aspects of man’s life, physical, mental and spiritual. Within its scope of action, more than ever science could play an important role. The answers to be given must go well beyond the strain of materialism, ensuing in the increasing development of new materials and technologies. Solutions for energy concerns, waste problems and pollution, global warming, scarce production of food in certain areas of the globe, new diseases, the call for new medicines, et cetera, all need to be tackled. Inevitably the “hand of science” needs to be led in the right direction.

1.1.2 THE ROLE OF CHEMISTRY AND CATALYSIS IN DAILY LIFE

Far from being able to solve all society’s problems, chemistry is an important tool in the hands of scientists and ought always to be at man’s service. For instance, catalysis may be highlighted for significant contributions in our day-to-day life, providing fuels, polymers, fine and commodity chemicals, pharmaceuticals, and tools to better safeguard the environment.[1-4]

1.1.3 ASYMMETRIC CATALYSIS VERSUS THE DEMAND FOR ENANTIO-ENRICHED COMPOUNDS

In the last few years asymmetric catalysis has been experiencing a great expansion.[5,6] There is an increasing demand for enantio-enriched and enantio-pure compounds widely applied in our life. Pharmaceuticals, agrochemicals, fungicides, animal health products, pheromones, fragrances, flavors, and materials like chiral polymers and liquid crystals are examples.[7,8] Plus, with great impact to the pharmaceutical industry's trends, the FDA (U.S. Food and Drug Administration) stated a policy[9] in 1992 that shifted the drug production from less and less racemates into more and more single-enantiomer drugs.[10,11]

Although enantiomerically enriched compounds have been, and still are, obtained by transformation of available chiral compounds from nature some drawbacks are implied. For instance the dependence on the commercial availability of such chiral building blocks from chiral pool and the fact that stoichiometric amounts of those same chiral materials are required. As well, frequently used is the classical resolution of racemic mixtures of two enantiomers which nonetheless implies yields that can not go higher than 50% of the desired enantiomer.[8,10] Asymmetric synthesis has therefore gained widespread recognition amongst chemists from several different areas. Organic synthesis, natural products chemistry, medicinal chemistry, agricultural and pharmaceutical industries are among such areas.[6] Often because of waste, economic and efficiency reasons, the use of stoichiometric amounts of chiral reagents, or chiral auxiliaries, is not attractive in asymmetric synthesis. Catalytic asymmetric synthesis is thus more attractive since it involves stereoselective reactions based on chiral catalysts.[5-7]

1.1.4 THE CHIRAL CATALYST: IMPORTANCE, POTENTIAL AND DEMAND FOR

Because of its ability of being continuously regenerated one single molecule of chiral catalyst in the asymmetric catalysis yields many molecules of chiral product.[6,8] This aptitude to mimic nature, or to transfer chirality as enzymic catalysts do in biological systems, is certainly what makes asymmetric catalysis so desired and at the same time so challenging.[6] In fact, as early perceived,[12-15] man-made catalysts can show greater generality when compared with enzymes, which are limited by a single-handed lock and key specifity.[7] Though man-made catalysts permit the use of a wider array of substrates, there is still a need to increase the number of really useful enantioselective catalysts. In fact among a number of catalysts few have found applications in the industry which has set the trend to patent new chiral ligands and catalysts.[5,10] Only matured applications of asymmetric catalysis such as asymmetric hydrogenation have more catalytic systems available.[11]

The majority of catalysts used in asymmetric catalysis are transition-metal complexes containing chiral organic ligands. As a consequence much attention has been placed on chiral ligand design.[5] In reality, the development of a new catalyst is intrinsically dependent on the choice of the appropriate chiral ligand, and despite the tendency to rationalize catalyst design the approach remains generally more empirical.[5]

Having introduced the reader to the context in which this work was developed we will now expand on it and approach some important concepts and notions that are relevant to this work.

1.2 CHIRALITY

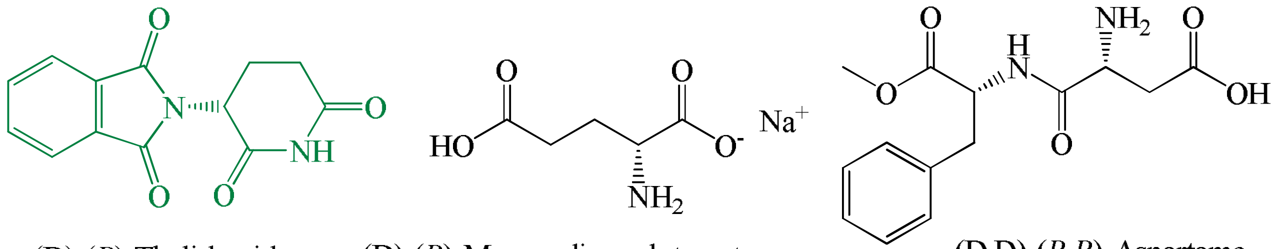
1.2.1 FACTS AND NOTIONS ON CHIRALITY

The term and concept of chirality, and several other related terms, find their birth not limited to the field of chemistry but permeate other domains like the ones of art, mathematic and philosophy.[16] At a molecular level the notion of chirality and of non-superimposable mirror images can be described by a tetrahedral carbon connected to four different groups. In this case chirality is based on a tetrahedral skeleton, a chiral centre, and is known as central chirality.[19] Other molecules may also display the property of handedness. For example if presenting a chiral axis, such as in the case of atropisomeric biaryls, or a chiral plane such as in the case of paracyclophanes.[19] As a matter of fact some molecules may present more than one element of chirality. For such cases Cahn, Ingold and Prelog have settled a useful rule, CIP, to apply when assigning their right configuration. The rule states that central chirality should come first followed respectively by axial chirality and planar chirality.[19]

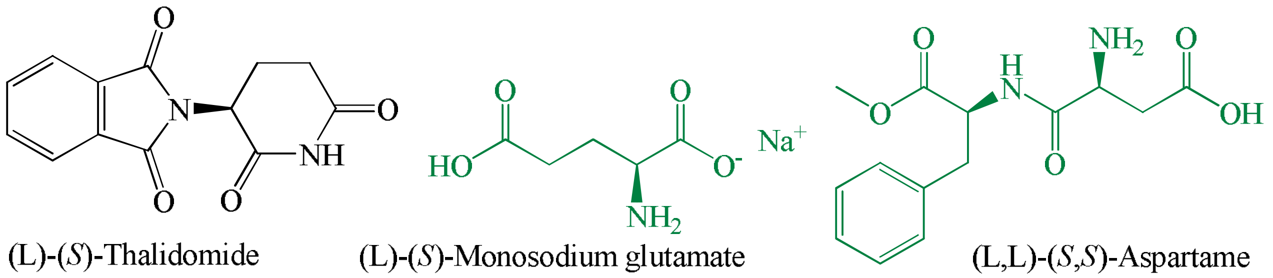
1.2.2 IMPORTANCE OF CHIRALITY IN NATURE

Chirality is a pervading feature in nature, one among others that at least to the author talk of a Great CREATOR. Near 50% of molecules in living organisms are chiral with biological systems being homochiral, L or D, all through the biosphere.[20-23] Inevitably this homochirality leads to an important question, with profound implications, as raised by L. Barron:” *If living matter evolved in prebiotic times from chiral molecules formed out of simple achiral precursors, how did this resolution appear?...*”.[21]

Owing to homochirality, biological systems are able to discriminate enantiomeric compounds frequently educing dissimilar responses in living organisms.[6,7,20,22-24] Insect pheromones, plant growth regulators, pesticides, and drugs, are among some of these natural or anthropogenic compounds.[20] For example enantiomers of chiral compounds may show differences in odour or in taste.[23] *N*-(L-α-Aspartyl)-L-phenylalanine,1-methyl ester, commercially known as aspartame, is perceived by us as having a very sweet taste, whereas the DD enantiomer as being bitter. Also widely used in food industry, monosodium L-glutamate, MSG, presents a characteristic umami taste, while the D enantiomer does not.[23] Regarding drugs, an enantiomeric substance may exhibit highly beneficial therapeutic effect, while its mirror image compound can be toxic or even mutagenic.[18,20] This is due to precise molecular recognition characteristic of natural binding sites in protein enzymes, receptors, transport systems and so on.[20] Widely known is the case of thalidomide, of which the enantiomers have different properties, pharmacodynamic and pharmacokinetic.[25,26] While the D form of the drug is a mild analgesic the L form is a powerful teratogen. Tragic consequences are linked with its use in 46 countries. Thousands of babies, whose mothers had taken thalidomide while pregnant, were born with external and internal deformities such as phocomelia, manifested by short limbs, and amelia, manifested by the absence of limbs. Also ear, eye, heart, gastrointestinal, uterine and vaginal abnormalities were reported.[25,26] The enantiomers of thalidomide, monosodium glutamate and aspartame are presented in the **Figure** below.



(D)-(*R*)-Thalidomide (D)-(*R*)-Monosodium glutamate (D,D)-(*R*,*R*)-Aspartame



(L)-(*S*)-Thalidomide (L)-(*S*)-Monosodium glutamate (L,L)-(*S*,*S*)-Aspartame

Figure 1 - The enantiomers of thalidomide, monosodium glutamate and aspartame. The structures in green are the ones that display the desired effect mentioned above.

1.2.3 THE SCIENTIST'S ATTITUDE TOWARDS CHIRALITY

The heart-rending case involving the use of thalidomide between the 1950's and 60's led to changes in the way chemists and other scientists view their responsibility and role. Some have mentioned the thalidomide episode as *"a turning point, an end of innocence and the beginning of a new and greater sense of responsibility in clinical pharmacology, in clinical investigation and in medicolegal relationships (Curran 1971). It also had profound effect on the drug regulatory process (Kelsey 1988)".*[26] In his book *Catalytic Asymmetric Synthesis* Iwao Ojima states: *"It is the responsibility of synthetic chemists to provide highly efficient and reliable methods for the synthesis of desired compounds in an enantiomerically pure state, that is, with 100% enantiomeric excess (% ee), so that we shall not repeat the thalidomide tragedy".*[6]

The book "Through the Looking-Glass" by Lewis Carroll makes us also ponder about another issue that scientists are now considering more, i.e., the chiral safety of the biosphere. The question posed by Alice to Kitty, her cat, may well be posed to ourselves: *"How would you like to live in a looking-glass house, Kitty? ... Perhaps looking-glass milk isn't good to drink".*[16] This excerpt gains additional meaning in today's world in which the chiral purity in nature is threatened by chiral xenobiotic compounds. In reality nature normally only accomplishes degradation of one stereoisomer, reason why the lack of a biodegradation route for the other stereoisomer may well impose an environmental problem.[20] Part of the solution to it may be strong consciousness and responsibility towards the issues involving chirality and biosphere. Inevitably other part is the development of methods that will allow effective stereocontrol in the synthesis of chiral compounds. Asymmetric catalysis can contribute for that matter.

1.3 ASYMMETRIC CATALYSIS

1.3.1 HISTORICAL FACTS ON CATALYSIS

Catalytic processes have been a part of our lives since very early times, for instance enzymatic catalysis have been widely used in the fermentation of wine and beer.[1] However, one of the first scientists to recognize a catalytic reaction was Kirchoff in 1814, when working on the acid-catalysed hydrolysis of starch to glucose. Later Sir Humphry Davy worked with heterogeneous catalysis on the oxidation of coal gas on platinum. Only in 1835 would Baron Berzelius coin the terms catalysis and catalytic, referring to processes that involve small amounts of a foreign agent, causing chemical change in a great manner without consuming that same agent.[27]

1.3.2 THE CATALYST

The agent that we just mentioned above is known as the catalyst which normally is responsible for allowing or accelerating a specific reaction by reducing its overall activation energy.[28] Frequently the catalytic process involves more steps, and of considerably lower energy-barriers, than the non-catalytic one.[28] Among important classes of catalysts we find enzymes, non-transition metal acids and bases, and thirdly compounds containing transition metals. The first class is responsible for enzymatic catalysis, while the two last ones are responsible for both homogeneous and heterogeneous catalysis.[29]

1.3.3 TRANSITION METAL CATALYSTS

Catalysts based on transition metals have been increasingly and successfully used in the last decades showing very useful properties that are associated with the metal's presence in the compound.[29] By virtue of their *d*-orbitals, transition metals are electronically able to stabilize or activate molecules or ions that coordinate with them.

In this way metals can control reactions occurring on the coordination sphere acting as templates.[24] In fact filled nonbonding orbitals and empty low-lying orbitals are made available by the metal, which therefore provides effective frontier orbitals, HOMO and LUMO. This fact allows concerted and synergistic interactions and subsequently transformations with low activation energies. Transition metals catalysts can also reversibly change their oxidation state, without need to change the reaction conditions.[29]

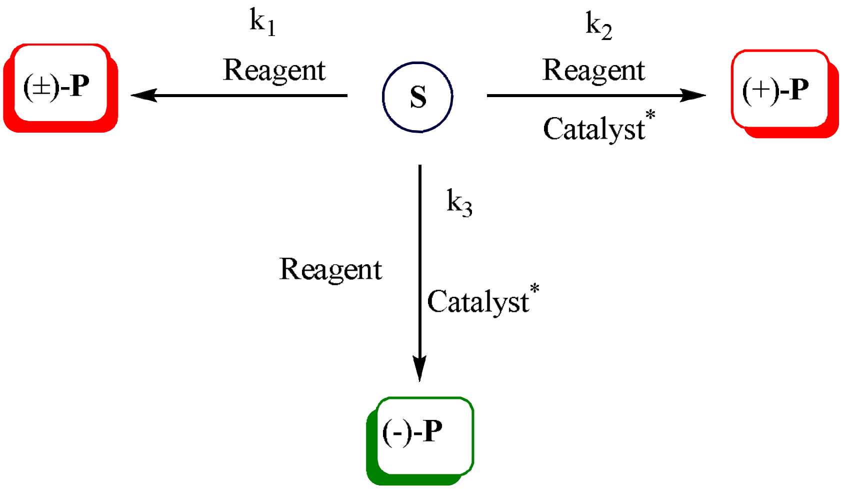
1.3.4 HOMOGENEOUS CATALYSTS VERSUS HETEROGENEOUS CATALYSTS

Catalysts based on transition metals can be homogeneous or heterogeneous, both presenting advantages and disadvantages. Heterogeneous catalysts often display higher activity, tolerate their use under vigorous reaction conditions, and lead to more effective separations from the products.[2] On the other hand homogeneous catalysts, which opposite to the heterogeneous ones are in the same phase as the reactants, are not affected by physical surface effects usually presenting better reproducibility.[2] Theoretically in the homogeneous catalyst all metal atoms can be used, consequently this fact might have some economical impact especially when one considers the use of expensive metals in large scale catalysis.[2] Homogeneous catalysts allow easier kinetic and mechanistic studies, in certain cases it is even possible to isolate key intermediates. Often one may also tailor the catalyst by modifying its structure, for example by adding or changing cations or anions in the catalyst, by adding ligands or changing the ligand to metal ratio. Especially the steric and electronic properties on the ligand may be changed. Finally homogeneous catalysts are also attractive because of higher selectivities normally involved in their use. This factor is relevant in the manufacture of fine chemicals, especially in asymmetric catalysis.[2] Indeed the use of homogeneous catalysts, namely chiral transition metals complexes, is often one of the most effective choices in asymmetric catalysis.[5,24] Ideally one single molecule of chiral catalyst can lead to the generation of millions of chiral product molecules, in the same fashion as enzymic catalysts do in the biosphere.[5,6]

1.3.5 REQUIREMENTS FOR EFFECTIVE ASYMMETRIC CATALYSIS

Asymmetric catalysis depends on suitable kinetics in order to efficiently multiply chirality.[24] For instance, having in mind a prochiral substrate **S** reacting with a nonchiral reagent in the presence of the chiral catalyst, one can anticipate three major pathways for the reaction. One of them will be the direct reaction, non-catalytic, of the nonchiral reagent with the substrate which will lead to the formation of a racemate (±)-**P**. In the other two the substrate will react with the reagent/catalyst complex resulting in the formation of the single enantiomer (+)-**P**, or in a separated pathway that same substrate and reagent/catalyst complex will give rise to the other enantiomer (-)-**P**. Assuming that our desired product is this last enantiomer, (-)-**P,** then the other pathways are competing pathways that will decrease the product's enantiomeric purity. Hence it is important to guarantee that the kinetic constant for the reaction that leads to our desired compound, k_3, is sufficiently higher than the ones corresponding to the undesired reactions, k_1 and k_2. This will guarantee high enantioselectivity, $k_3 >> k_1$ and $k_3 >> k_2$ according with **Scheme** 1.[10]

Scheme 1 - Possible pathways occurring during asymmetric catalysis.



As we can perceive from **Scheme** 1, the reagent/catalyst complex needs to be more reactive towards the substrate than the reagent itself,[10] for this implies that the catalytic pathways will occur preferentially in comparison with the non-catalytic one. Nevertheless the insurance that only one of the two possible catalytic pathways will occur is still needed in order to achieve an enantiopurity that is shifted from the nonselective values, 50:50, to the perfectly selective ones, 100:0. Theoretically the first case occurs when both catalytic reactions take place at the same rate and to the same extent while the second scenario entails that the desired reaction is the only one occurring. Indeed enantioselectivity requires that the catalyst is able to precisely differentiate between enantiotopic faces, groups or atoms, in achiral molecules.[7,24]

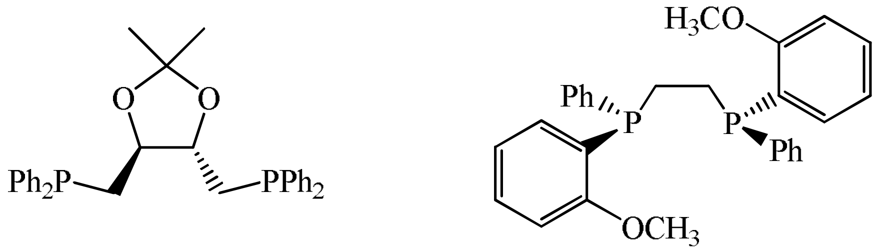
At this stage it is not difficult to perceive that a set of requirements need to be met by the chiral catalyst, under optimal reaction conditions, so that its function will be effective. Indeed an ideal combination of three-dimensional structure and suitable kinetics is needed in order to achieve optimal efficiency in asymmetric catalysis.[24] In effect an ideal catalyst should be designed in such a way that it would lead to high turnover number (TON) and turnover frequency (TOF) as well as high stereoselectivity and reproducibility. While doing this the catalyst should be easily accessible, allow a wide scope of applications and be tolerant of many functional groups. Also it should perform under such conditions that would imply simple operational procedures, low-energy consumption and atom economy, with low overall costs and minimal environmental impact.[5,7]

Despite the many challenges and need for the development of more effective chiral catalysts, especially at an industrial level, in the past recent years big progress has been made.[5,10] Indeed some catalysts have been shaped in such a way that not only are they capable to increase the reaction speed over and over, but also to discriminate among transition states with a precision of 10 $kJmol^{-1}$.[7,24] For these properties, including their size that is no bigger than 20 Å in length or diameter, these catalysts are very attractive tools to apply in the synthesis of enantiomeric pure compounds.[7,24] Furthermore the fact that transition metals exert a variety of catalytic activities combined with the numerous structural motifs that organic ligands may present imply enormous opportunities and potential still to be explored in asymmetric catalysis.[7,24]

1.3.6 FROM AN IDEALIZED GOAL TO SUCCESSFUL ASYMMETRIC CATALYSIS

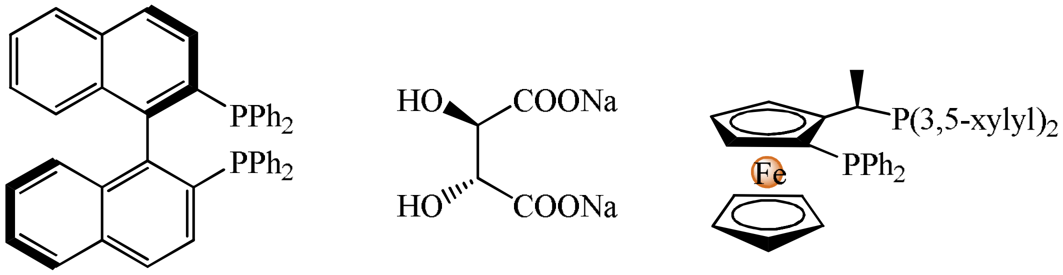
In 1966 Wilkinson et al. showed that alkenes could undergo homogeneous hydrogenation when a rhodium complex with a phosphine ligand, triphenylphosphine, was used.[30] Until then activation and transference of molecular hydrogen to alkenes had been believed to be possible only when involving the use of metallic surfaces.[5] However the knowledge that hydrogen activation could be achieved by Wilkinson's catalyst led several chemists to consider asymmetric hydrogenation as an attainable goal. The envisaged strategy was to use chiral ligands instead of non-chiral ones.[5] With this objective in mind the two distinct groups from Knowles et al. and from Horner et al. reported the first asymmetric hydrogenation reactions by using P-chiral monophosphines as chiral ligands.[12,31,32] Although these first results reflected poor enantioselectivities[12,31,32] Kagan's work from 1971 revealed that their new C_2-symmetric diphosphine ligand, DIOP **1**, was able to induce high enantioselectivity.[14] In 1974, also using a C_2-symmetric chiral ligand, DIPAMP **2**, Knowles' group was able to develop the well known Monsanto process. Indeed the commercial synthesis of the anti-Parkinson drug L-DOPA by Rh(I)-catalysed enantioselective hydrogenation is widely considered as being a major advance and source of inspiration in the field of asymmetric catalysis.[2,5,6,7,28]

Other catalytic systems have since past the ultimate test of practicability, i.e., commercialization. Noyori's BINAP **3** was used in significant rhodium catalysed asymmetric hydrogenation of olefins and ketones. Also, to prepare (L)-menthol in the Takasago process via rhodium catalysed asymmetric isomerisation of allylic amines into enamines.[5,7] Another instance is the Arco process for the synthesis of *S* and *R*-glycidol involving Sharpless epoxidation[15] of allylic alcohols with tartrate **4** and titanium.[2,24] Really, this work developed by Sharpless together with the aforementioned work on asymmetric hydrogenation developed by Knowles and Noyori represent some of the most successful applications of asymmetric catalysis. Such work granted them the Nobel chemistry prize from 2001.[7,15,31] In a more recent case of great success in asymmetric catalysis the CIBA-Geigy process involves iridium catalyzed asymmetric imine hydrogenation to produce S-metolachlor, an extensively used herbicide for maize. This process, which makes use of the ferrocenyl type ligand Xyliphos **5**, is the largest-scale asymmetric catalysis process in industry.[33-35] **Figure** 2 displays the above ligands.



(1)
DIOP

(2)
DIPAMP



(3)
BINAP

(4)
Sodium Tartrate

(5)
XYLIPHOS

Figure 2 - Selection of ligands with important applications in asymmetric catalysis.

1.4 THE LIGAND IN ASYMMETRIC CATALYSIS

1.4.1 ROLE AND IMPORTANCE OF THE CHIRAL LIGAND

The majority of enantioselective catalysts used in asymmetric catalysis are organometallic compounds, consisting of metal complexes containing chiral organic ligands.[5,7,36] Furthermore, chiral ligands have been designated as the *"foundation upon which metal-catalysed asymmetric reactions are based."*[37] In reality within the catalyst, the ligand is the one responsible for controlling chirality; hence the development of a new catalyst requires the selection of an appropriate ligand.[5] In order to be effective, the chiral ligand must create an asymmetric site in the catalyst. For instance supposing that in a specific reaction the substrate is a prochiral olefin, there must be a favoured conformation in which the olefin will bind to the catalyst. In this manner the formation of one enantiomeric product, among the two possible ones, will be privileged.[2,36] This asymmetric discrimination should be rendered by the ligand's action upon the metal. In other words, by coordinating to the metal the chiral ligand originates a chiral hole within the coordination sphere.[2] Actually the chiral ligand has such a critical role because it is able to modify both selectivity and reactivity in the catalyst.[36]

1.4.2 DESIRED FEATURES ON THE CHIRAL LIGAND

Someone might ask himself about which features make up an efficient chiral ligand. The fact is that ligand rational design is still a rather demanding task which due to lack of satisfactory mechanistically insight leads to a more empirical approach. Accordingly, ligand design relies on some degree of instinct, perseverance, systematic screening and even providence.[5,36,38] Nevertheless an analysis to some of the most efficient ligands, the so called *"privileged ligands"*,[38] brings forth some general guide lines. These should allow the ligand to have enough flexibility, in order to bear high activity, at the same time that the rigidity is also adequate for optimal stereoregulation:[39]

- Preferably the ligand should be readily prepared.[5]
- In principal bidentade ligands lead to higher enantioselectivity, especially those that are more rigid.[39]
- Ligands that have C_2-symmetry like DIOP, or that are strongly unsymmetrical like JOSIPHOS type ligands, both being used in asymmetric hydrogenations, are able to decrease the number of substrate catalyst arrangements. This feature is predictably related to high enantioselectivity induction displayed by these ligands in asymmetric hydrogenation.[5,39]
- Considering their optimal scope of action, ligands are somehow limited to a certain number of substrates and catalytic processes. A way to tackle this drawback is to try to develop ligands with a framework that is likely to be systematically modified. The thought is to have a ligand that can easily undergo fine tuning of its electronic and steric properties and thus being tailored for a specific reaction and substrate. In truth the research and development for these modular ligands, ideally from simple precursors, has become a trend.[5,36,39]
- The presence of chiral elements that are in the immediate proximity from the adsorbed substrate such as a stereogenic P atom[39] can lead to a more effective chirality induction.
- Introducing the P atom in a ring that has at least one stereogenic centre has also proved to be efficient.[39]
- The orientation control of the incoming substrate is supposedly improved by secondary interactions caused by additional functional groups incorporated in the ligand. Also bridges or extra substituents could restrict conformational flexibility and therefore play a positive role in regards to enantioselectivity.[39]

- Phosphorus ligands containing three binding sites that include bonds such as P-N, P-O or P-C have demonstrated to be active and stereoselective.[39]
- Ligands with axial and planar chirality other than central chirality have also proved to be effective.[39]

Although these features have allowed some ligands to yield good results it is important to have in mind that they do not guarantee that a ligand would be effective and in fact in some cases ligands that do not obey to these guide lines are as effective.[39]

1.4.3 PHOSPHINES AND OTHER PRIVILEGED CHIRAL LIGANDS

Taking into account the types of chiral ligands that have found application in the field of asymmetric catalysis one will notice that the big majority of them are phosphine ligands.[5,6,37,40] Although monophosphines were the first chiral catalysts to be developed,[12,31,40] diphosphines have been more widely used.[2,5,6] Nevertheless, despite this tendency a large number of ligands containing coordinating atoms such as N, O, and others apart from P, have been used. For example bi- and multidentade monophosphines such as P,N, P,O, etc.[5,6,36]

Interestingly enough only a few structural classes of ligands are represented by the most efficient ligands. For instance the C_2-symmetric ligands, BINAP **3**, BINOL **6**, and other binaphthyl and biaryl derivatives, bisoxazolines, or BOX, salens, and tartrate derivatives TADDOLS.[5,38] Furthermore non-symmetric ligands are also included as efficient ligands being represented by important classes, amongst them cinchona alkaloid derivatives **7**, phosphinooxazolines or PHOX, and ferrocenylphosphines.[5,38] Indeed nonsymmetrical ligands have in certain reactions yielded better results than the best C_2-symmetric ligands.[36] As an example, by desymmetrizing DIOP Achiwa's group was able to obtain appreciably higher enantioselectivity and activity.[36,41] XYLIPHOS is by itself another excellent example of how nonsymmetrical ligands can be rather efficient.[36] Finally nonsymmetrical heterobidentade ligands, such as PHOX ligands to cite one example, have also shown to be capable to educe good results. It is believed that the two sterically and electronically dissimilar coordinating groups that are present in the structure of heterobidentade ligands lead to good enantiocontrol.[36] **Figure** 3 presents a selection of the aforementioned privileged ligands.

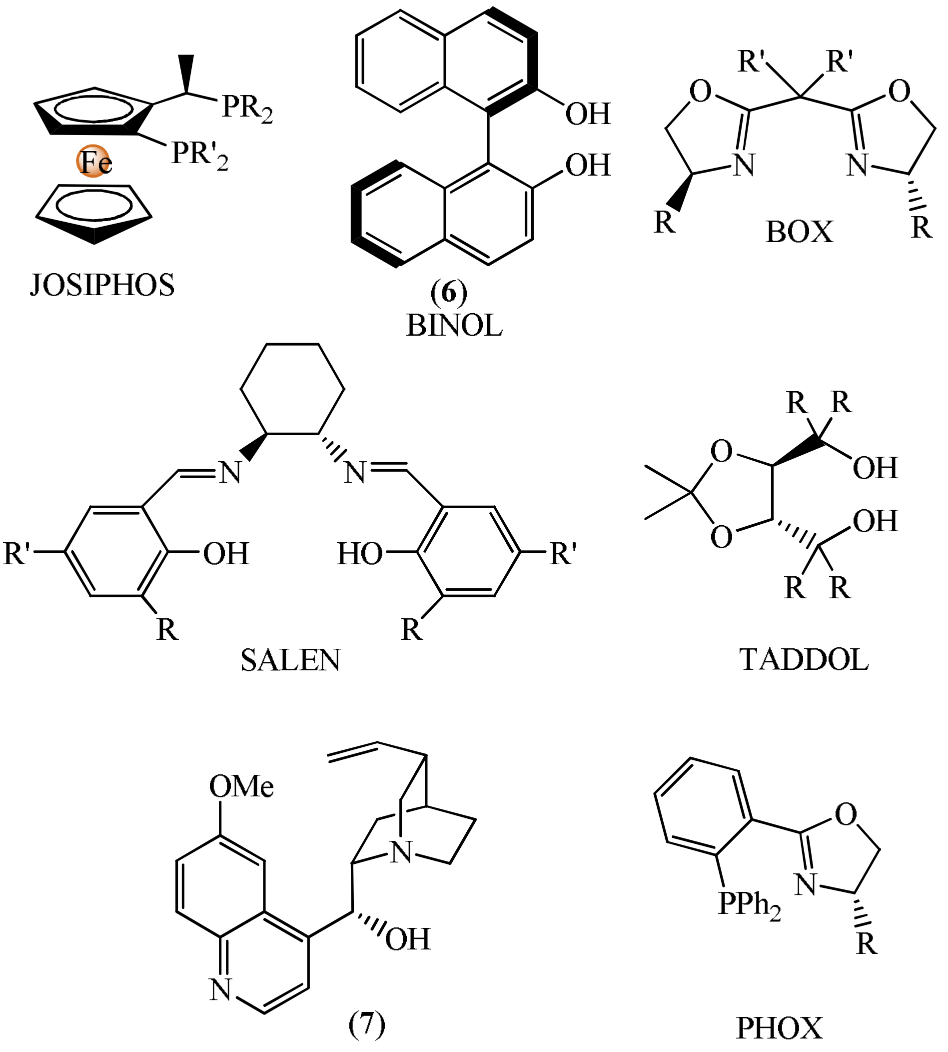


Figure 3 - Selection of some of the so called privileged ligands used in asymmetric catalysis.

1.5 FERROCENE, AN EXCELLENT BACKBONE STRUCTURE FOR CHIRAL LIGANDS

1.5.1 HISTORICAL FACTS AND APPLICATIONS OF FERROCENE

Since it was first discovered in the early fifties by Kealy and Pauson[42] and also independently and previously by Miller, Tebboth and Tremaine,[43] ferrocene has seized the attention of scientists from several areas. It has played, and still plays, a considerably important role in chemistry, especially in the development of organometallic chemistry.[44,45] Indeed the importance given to the discovery of this molecule and the understanding of it's structure and properties[46-51] is well perceived in the attribution of the 1973 chemistry Nobel prize to Fisher[52] and Wilkinson.[53]

The several and varied applications involving ferrocenes go beyond organic chemistry and other fields.[35,44,45,54] One may mention bioorganometallic chemistry[55] with derivatives presenting cytotoxic activity used in cases of breast cancer.[56] In some instances, by replacing certain functionalities in a medicine by ferrocene one may gain an advantage. This is illustrated by ferroquine which has solved the problem of drug resistance exhibited by some malaria strains towards chloroquine.[56] Ferrocenes have also been used as precursors for radiopharmaceuticals and to label peptide nucleic acids for the detection of biomolecules.[56] Moreover the molecule of ferrocene has also a place in materials chemistry.[45] It has been introduced in the structure of atypical polymers that display desirable properties. These include optical, electrical and magnetic, as shown by liquid crystalline and charge-transfer materials.[45]

1.5.2 FERROCENE'S DESIRABLE FEATURES AS A STRUCTURAL MOTIF

Iron biscyclopentadienyl, or ferrocene as it was named by Woodward[57] in 1952, has a unique structure that in a way resembles a sandwich, "the iron sandwich" as first remarked by Wilkinson.[58] As such, ferrocene represented by the formula $Fe(C_5H_5)_2$ is a metallocene. It is the first of a kind among many other metallocenes with the general formula $M(\eta_5C_5R_5)_2$, which have been found ever since the serendipitous discovery of ferrocene.[45] This molecule's structure displays adequate rigidity. When used as a scaffold for the synthesis of chiral ligands it allows them to exhibit suitable chiral environments. In fact, ring compounds that are not too flexible and thus present reasonable rigidity are frequently used as backbones in ligand synthesis.[59] Simultaneously, because of its steric bulkiness, ferrocene acts as a shield which may provide an adequate steric environment. Again, it possibly contributes for a more effective stereo and enantioselectivity control.[59] Because the cyclopentadienyl (Cp) rings in ferrocene have a partial negative charge, ferrocene presents a behaviour characteristic of electron-rich aromatic compounds.[35,57,59] Actually, it reacts $3x10^6$ times faster than benzene being easily derivatized.[59] It undergoes facile lithiation either at one Cp ring or at both, 1,1'-position, being prone to undergo electrophilic substitution reactions, allowing the incorporation of various donor groups in the molecule.[35,59] Still from a stereo and electronic point of view, ferrocene has donor ability being able to stabilize carbocations at the benzyliclike position.[35] Also as an example, ferrocene carboxylic acid is less acidic than benzoic acid, and ferrocene amine is more basic than aniline.[59] Moreover, when in a transition metal-complex catalyst, it is possible for the ferrocenyl iron atom to interact with the other transition metal atom.[59]

Another attractive and important aspect of this framework is its thermal stability and tolerance to oxygen, moisture, and several other types of reagents.[35,45,59] Ferrocene is also easy to prepare, readily available, and inexpensive (US $ 0.19/g for 500 g - Aldrich).[35,45,59,60]

1.5.3 PLANAR CHIRALITY ON FERROCENE DERIVATIVES

The "iron sandwich" presents a further key attractive quality associated with its plane of symmetry. It has the ability to become a planar chiral structure upon insertion of two different functionalities in the same Cp ring,[35,59] in other words, by breaking the plane of symmetry.[61] Accordingly with **Figure** 4, by looking at the right ferrocenyl structure from the upper ring down, assuming A as the higher substituent in priority, then the priority decreases counter-clockwise and the configuration is assigned as *S* in agreement with the CIP rule.[19,61]

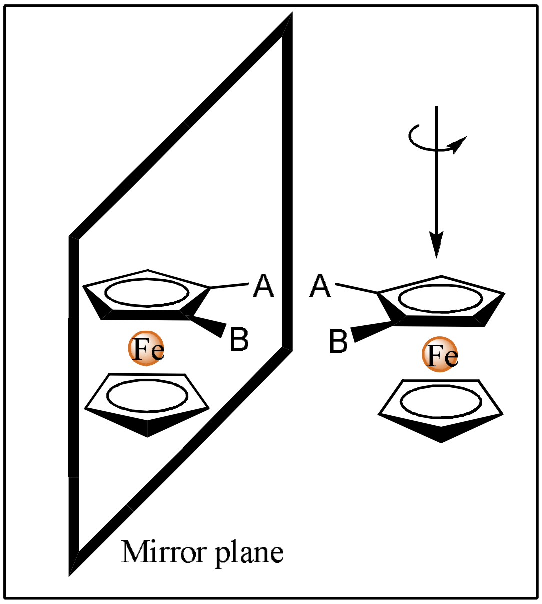


Figure 4 - Planar chirality on ferrocene.

With respect to the importance of planar chirality it is worth mentioning that it is not submitted to racemisation, which per se is an important advantage of this element of chirality.[61] Nevertheless, the subject pertaining to the role of planar chirality has for some time transpired as being a fairly unclear one.[59,62] Indeed in the last years several different studies have been conducted by different research groups with the purpose of bringing some insight and reasoning into this matter. Different catalytic systems and ligands have thus been studied in diverse reaction types, regarding the role of planar chirality in asymmetric catalysis.[59,61-63] To some extent the conclusions might be intriguing. Some results regarding ligands presenting both central and planar chirality have suggested that planar chirality had little effect, whereas in other cases it had decisive influence on the overall enantioselectivity.[59,61-63] Kumada and Hayashi studied the performance of (R,S_p)-PPFA **8** and (R,R_p)-PPFA **9**, planar and central chiral, and an analogous ligand (S_p)-FcPN **10**, only planar chiral. They pointed to planar chirality as exerting critical influence in the absolute configuration and enantiomeric excess of the products formed in coupling reactions.[64] In contrast, working in diethylzinc addition reactions, Bolm et al. observed that removing central chirality on an 1,2-hydroxy-oxazolinyl ferrocene ligand **11** would reduce the enantiomeric excess.[65,66]

Ligands possessing a chiral plane as their sole source of chirality are pertinent to ascertain whether this element is by it self capable to educe chirality. To this matter one can mention Ikeda's work on the synthesis of ferrocenyl C_2-symmetric diphosphine ligands **12-16**, which afforded excellent enantioselectivity in palladium-catalyzed allylic alkylation reactions.[67] Kagan's ferrocene based 1,2-bis(phosphanes)[68] **17-18** and 1,3-bis(phosphanes)[69] **19-23** also led to excellent results, in the rhodium catalyzed asymmetric hydrogenation. Fu and co-workers have as well shown ferrocenyl type ligands **24**, exclusively planar chiral, to be effective.[22,70] The chiral ligands mentioned above are presented in the following **Figure**.

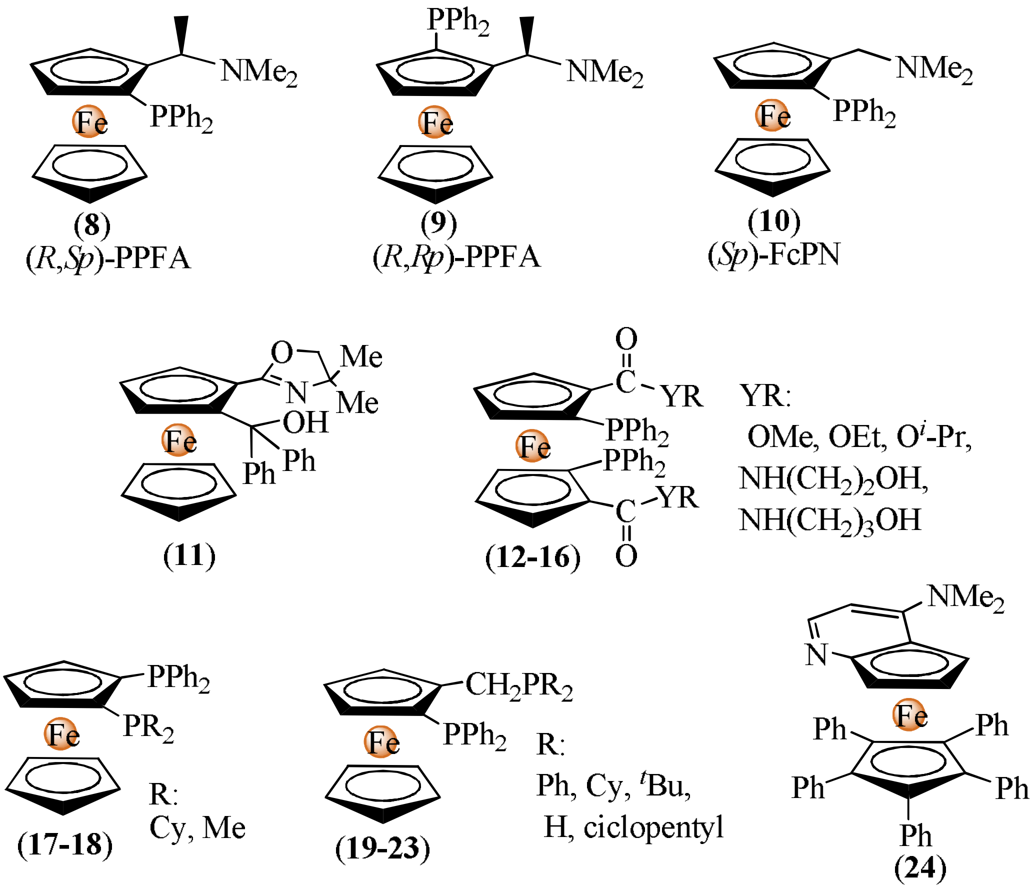


Figure 5 - Selection of ligands containing planar chirality and in some cases central chirality as well.

Usually chiral 1,2-dissubstituted ferrocenyl ligands possess both planar and central chirality.[59,61] It is therefore important to understand that planar chirality may exert a significant influence in the enantioselectivity of the reaction even as in most cases matching of both chiral elements are vital to convey an optimal result.[62,71] In effect, ferrocene's aptitude to be derivatized into a planar chiral structure, all together with the supra-stated features, has contributed to make it a scaffold of election. It is used not only for the synthesis of achiral functionalized ferrocenes, but also for the synthesis of planar chiral derivatives, especially in the design of chiral ligands, one of ferrocene's major applications.[35,44,45,59]

1.6 SCOPE OF THIS THESIS

According with the above perspectives, the present work has been mainly focused in the design and synthesis of new ferrocenyl chiral ligands, having in mind their future application in asymmetric catalysis. The use, further development and exploration of a “homegrown” *ortho*-directing group and its structural features have been the key motivating force and building block around which the efforts of this project have revolved. As a matter of fact one did not have in mind the bringing forth of new ligands just for the sake of it. Indeed the need for effective solutions for the manufacture of enantiomerically pure compounds remains a concern to the chemist pushing research into the further development of existing methodologies, and in conceiving new synthetic strategies. As such, whether it might be expanding the scope of a specific type of reaction, or bringing it to become asymmetric or “greener”, in sum, the purpose is to step further in reaching superior useful knowledge in the area and finding reliable tools for chemistry. The pursue for this goal has been present in the work we have conducted even if at times, as would be expected in research, the routes that were formerly envisaged couldn’t be strictly followed.

An ideal catalytic system such that would be general, regarding types of reactions and substrates, and that would yield high activity and enantioselectivity, is yet to be discovered. In face to this fact one finds that a reasonable approach relies on developing catalytic systems that are subject to fine tuning in order to be adapted to the specific demands of a certain reaction and substrate. This last concept of modularity is present in the development of families of chiral ligands that allow ease of synthesis and adjustment of electronic and steric properties. In a way the family of ligands should “become” the ideal general catalyst that we mentioned. In this thesis we have purposed to explore a practical synthetic route that would open the way for a family of chiral ferrocenyl ligands, where possible, with potential to be modulated. Also we aimed for a brief trial on the applicability of the ligands to catalysis, all being done having in mind to positively contribute for the research in the field of ligand design and synthesis of chiral ligands for asymmetric catalysis.

The possibility to expand the scope of an important catalytic coupling reaction was also probed in this thesis.

The description that follows this general introduction will present and discuss the work that has been done in the thesis not in a chronological order but in a thematic one, aiming to be more logical. Hence, **Chapter *2*** will focus on the ligands' synthesis and on some of their structural aspects, whereas **Chapter *3*** will rest upon surveying their coordination chemistry and use in catalytic reactions. **Chapter *4*** will focus on the trial of phenolic heteroaromatic ethers for the Suzuki-Miyaura cross-coupling reaction. **Chapter *5*** will present the experimental details involved in the synthesis and characterization of the compounds synthesized herein. At last we will conclude with some ***Final Remarks*** on the overall thesis.

Synthesis of Chiral Ferrocenyl Ligands - Further Exploiting the Oxazaphospholidine Oxide Moiety as a Chiral *ortho*-Directing Group

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The synthesis of new and previous ferrocenyl oxazaphospholidine oxide ligands and the study of their possible conversion into new structures including planar and/or central chirality will be exposed. In order to better contextualize our work an introduction regarding the synthesis of other older but relevant ferrocenyl ligands will be made mostly based on a synthetic point of view and of their importance in the field of asymmetric catalysis.

Chapter 2

2.1 INTRODUCTION

The account behind the synthesis of chiral ferrocenyl ligands depicts how important and prolific this area of research has been for scientists.[22,35,44,45,59,61,72-76] In 1970 Ugi et al. laid down the goal of developing a method "*for the reliable preparation of optically pure ferrocene derivatives*", namely 1,2-disubstituted ones. He published a paper[77] that would clearly open the way for many chemists into the development of new chiral ferrocenyl ligands. Indeed building on top of Ugi's work, Hayashi and Kumada gave, in 1974, another important step in this area by synthesizing the first example of a planar chiral ferrocenyl phosphine, PPFA **8** and **9**.[78] The 1990 decade was also a very fruitful one with three different major contributions in the development of chiral ferrocenyl ligands.[35] Namely Togni's Josiphos bisphosphines,[79] the phosphino-oxazolines Fc-Phox, independently developed by Richards',[80] Sammakia's[81] and Uemura's[82] groups, and Knochel et al. work on the 1,5-bisphophine ligands Taniaphos.[83]

In effect, one would be amazed by the broad diversity of structural motifs represented by various families of chiral ferrocenyl ligands. These include 1-substituted, 1,1'-disubstituted, 1,2-disubstituted, 1,2,1'-trisubstituted and 1,2,1',2'-tetrasubstituted ferrocenes. Also included are other polisubstituted ferrocenes, bisferrocenes, and ferrocenyl-like planar-chiral heterocycles. Furthermore the substituents also comprise varied metal coordinating sites namely bearing phosphorus, nitrogen, sulphur and oxygen atoms. Among these variants, bidentade P,P and P,N ligands occur more often, nevertheless P,S and P,O ligands are also reasonably known, as well as some important mono and tridentade ones.[35] In effect among this great multitude of ferrocenyl chiral ligands, that have been synthesized, 1,2-heterosubstituted ones transpire quite frequently due to relatively higher ease of synthesis[84] and to inbuilt planar chirality.[35]

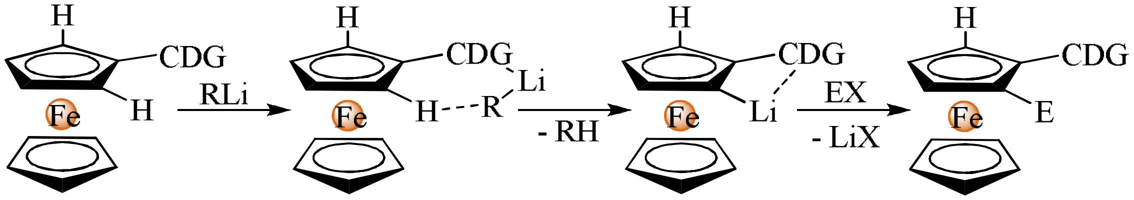
2.2 SYNTHETIC APPROACHES TO PLANAR CHIRAL 1,2-DISUBSTITUTED FERROCENYL LIGANDS AND DERIVATIVES

Following we intend to present several methods used for the synthesis of 1,2-disubstituted ferrocenyl derivatives, especially focusing on those that have found wider application in the preparation of planar chiral ligands.

2.2.1 DIASTEREOSELECTIVE *ORTHO*-LITHIATION AND FUNCTIONALIZATION

Among several strategies that have been developed for the manufacture of planar chiral 1,2-disubstituted ferrocenyl ligands,[35,85] diastereoselective direct *ortho*-metalation (D*o*M) has become mostly prominent.[35,84,85-87] In fact the majority of planar chiral 1,2-disubstituted, and even 1,2,3-trisubstituted ferrocenes, have been synthesized via *ortho*-lithiation of monosubstituted ferrocenes containing a suitable chiral *ortho*-directing group (CDG). This diastereoselective metalation step gives rise to a carbanion which by undergoing subsequent *in situ* trapping with an appropriate electrophile originates the 1,2-disubstituted derivative,[35,84,86,87] as presented in **Scheme** 2.

Scheme 2 - Diastereoselective *ortho*-lithiation induced by a chiral directing group.



The pioneering work of Ugi et al.[77,78] led to the development of a series of other chiral *ortho*-directing groups in addition to Ugi's amine **25**.[77] Namely, sulfoxides, [88,89] acetal **26**,[90-92] oxazolines,[80-82] azepine **27**,[93] pyrrolidine **28**,[94-96] hydrazones,[97,98] sulfoximine **29**,[99] phosphine oxides,[100] *O*-methyl ephedrine derivative **30**,[101] imidazolines,[102] oxazaphospholidine oxide **31**,[103] methoxy-imino auxiliaries[84] and of late free alcohols.[104] A selection of ferrocenes containing a CDG is presented in the **Figure** below.

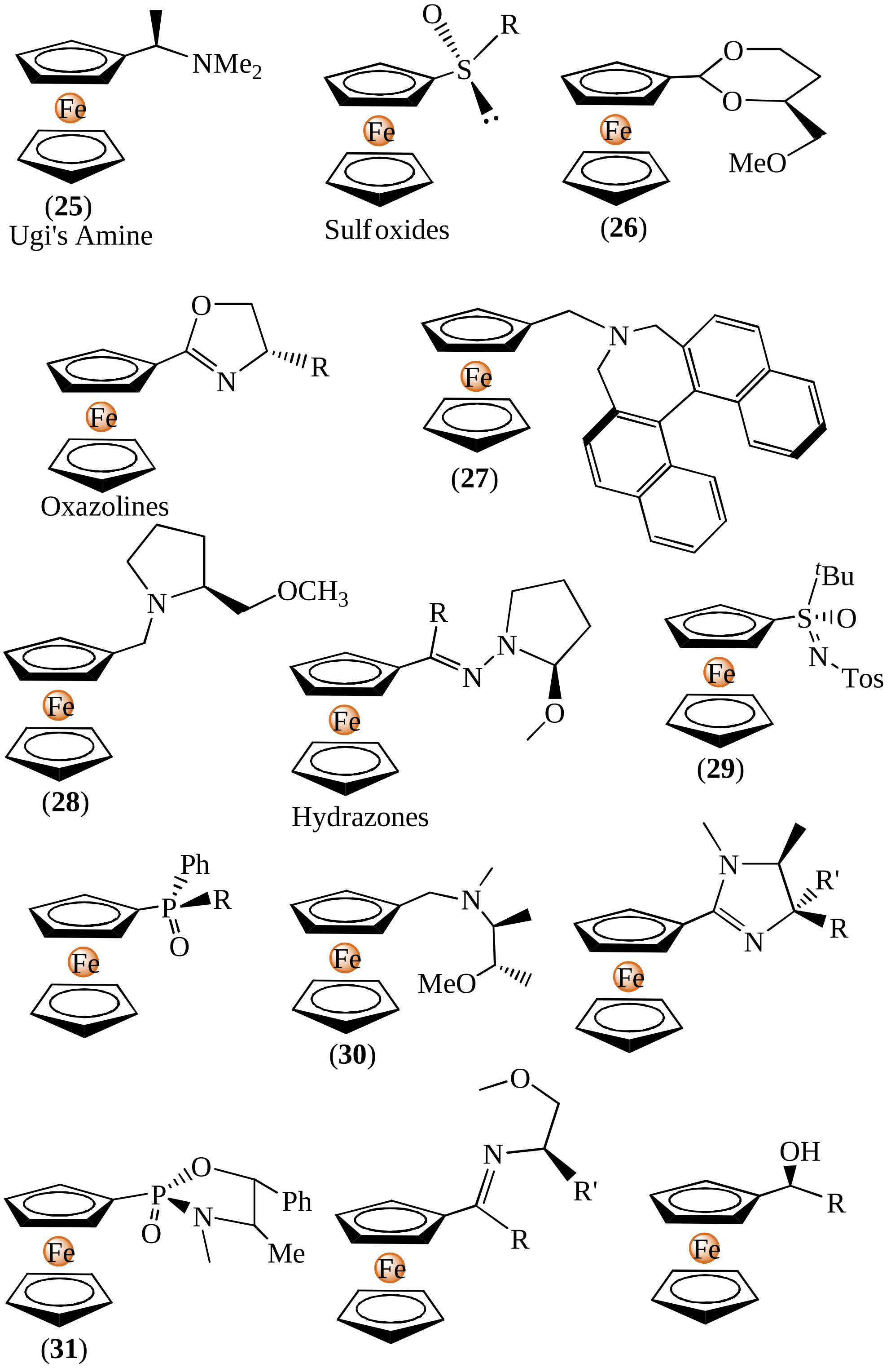


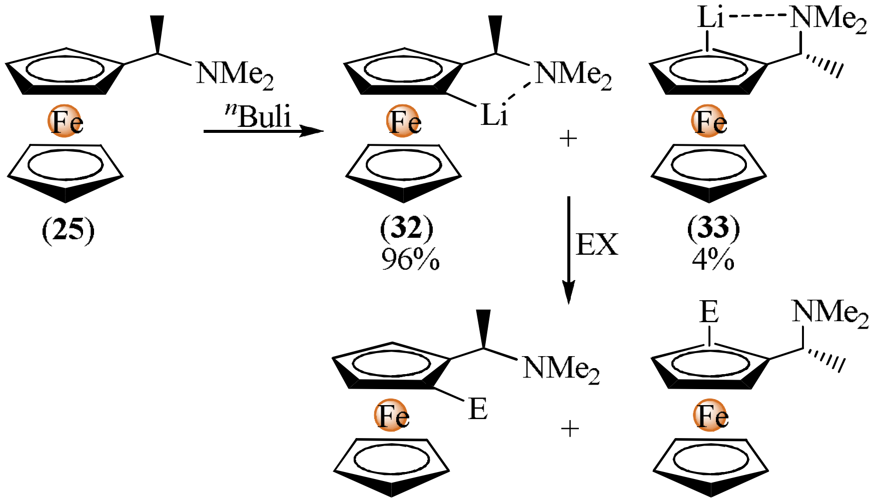
Figure 6 - Monosubstituted ferrocenes containing a chiral *ortho*-directing group.

Next we will consider a number of aspects relating to some of the chief CDG’s, having in mind that each system presents its own advantages and that all together they complement each other allowing the synthesis of planar chiral derivatives with different oxidation states.[98] Also, from a structural point of view, we will mention several ligand families that have thus been originated.

2.2.1.1 Ugi’s Amine

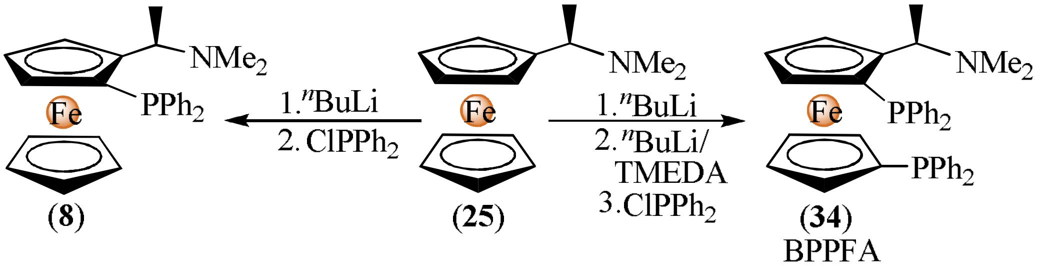
N,*N*-dimethyl-1-ferrocenylethylamine **25**, nowadays known as Ugi’s amine, was first prepared via treatment of 1-ferrocenylethanol with phosgene and subsequently with dimethylamine. The product was obtained as a racemate which permitted both enantiomers to be resolved with (*R*)-(+)-tartaric acid. Metalation of the *R* isomer, with butyllithium, followed by quenching with an electrofile would prove to be highly stereoselective, presenting a diastereomer ratio of 96:4,[77]as presented in **Scheme** 3.

Scheme 3 - Sequential diastereoselective *ortho*-lithiation and trapping of Ugi’s amine.



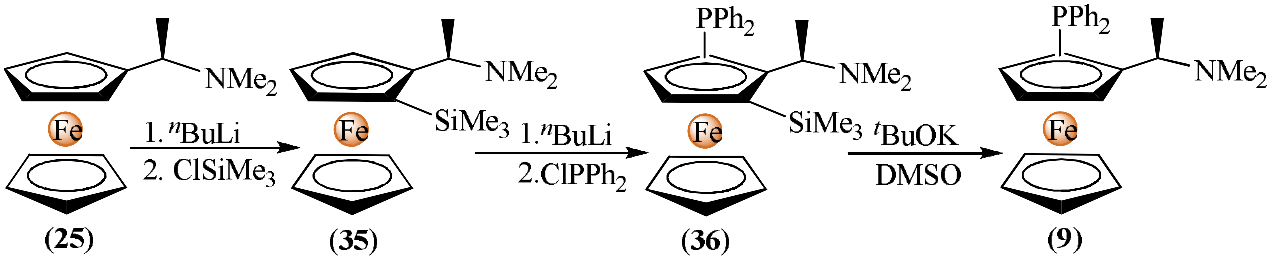
By using clorodiphenylphosphine ($ClPPh_2$) as the electrofile, Hayashi and Kumada, applied this methodology to afford PPFA **8**.[78] Carrying their studies they confirmed that planar chiral ferrocenylphosphines bearing two phosphine groups, one in each Cp ring, namely BPPFA **34** could be prepared. This preparation was based on the dilithiation of ferrocene with *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA). Following this stepwise lithiation of Ugi's amine, with BuLi and then with BuLi/TMEDA, trapping with $ClPPh_2$ was done according with **Scheme** 4.[105]

Scheme 4 - Diastereoselective mono- and dilithiation of Ugi's amine with subsequent formation of PPFA and BPPFA respectively.



Moreover, the fact that both optical antipodes of Ugi's amine are synthetically available is an advantage of this methodology.[35,77] Indeed Hayashi and Kumada profited of it in order to readily obtain (S,R_p)-PPFA and (R,S_p)-PPFA. Nevertheless being highly stereoselective the *ortho*-metalation step only provided small amounts of (S,S_p)-PPFA and (R,R_p)-PPFA. As a means to bypass this drawback they sought to protect the more reactive hydrogen atom, towards lithiation, with a trimethylsilyl group. This would allow a second lithiation step at the other, less reactive, hydrogen atom also vicinal to the 1-dimethylamino-ethyl group, the CDG. Quenching of the lithium compound with $ClPPh_2$ would result in a 1,2,3-trisubstituted planar chiral ferrocene which by desilylating provided the 1,2-substituted derivative with the desired planar chirality, (R,R_p)-PPFA.[105] In other words, although it wasn't their main goal, they proved Ugi's amine to be effective in the synthesis of 1,2,3-trisubstituted planar chiral ferrocenes. Also they unveiled the likelihood to form all four possible diastereomers corresponding to a compound possessing planar and central chirality together, as PPFA does. The strategy used by Hayashi and Kumada is presented in **Scheme** 5.

Scheme 5 - Synthesis of (R,R_p)-PPFA via the use of a blocking trimethylsilyl group.



Another one of the major advantages of Ugi's amine is its propensity to undergo S_N1 type nucleophilic substitution of the dimethylamine group (NMe_2), which occurs with retention of configuration. Therefore, once the *ortho*-lithiation step has been accomplished, with the introduction of a new substituent at the C2 on the ciclopentadienil ring (Cp), the CDG can be modified leading to the synthesis of several different classes of ligands.[35,61]

With this purpose, using secondary phosphines (R_2PH) or pyrazoles, in acetic acid (AcOH), Togni has replaced the NMe_2 group by phosphines, affording Josiphos[79] type ligands, the bisferrocenes Pigiphos[106] and others,[107] and by pyrazoles.[108] Ito, first using excess methyl iodide (MeI) followed by a secondary phosphine oxide ($R_2P(O)H$) and BuLi, has prepared C_2-symmetric *trans*-chelating bisferrocenes, TRAP.[109] Boaz made use of acetic anhydride (Ac_2O) subsequently reacting the acetyl derivative with a primary amine (H_2NR) and a diphosphine chloride ($ClPR_2$) in order to afford new phosphine-aminophosphine type ligands BoPhoz.[110]. Finally, also via reaction of the NMe_2 group with R_2PH in AcOH, Weissensteiner developed Walphos ligands.[111] The Ugi's amine derivatives mentioned above are displayed in **Figure** 7.

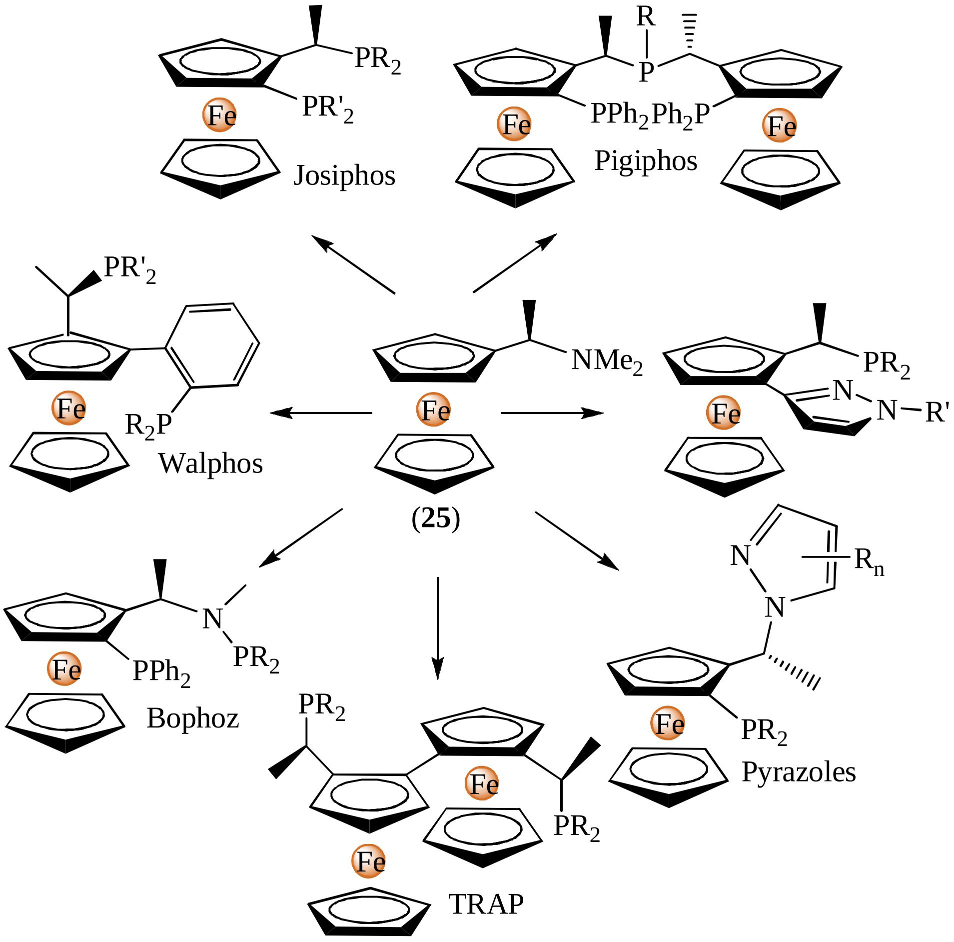
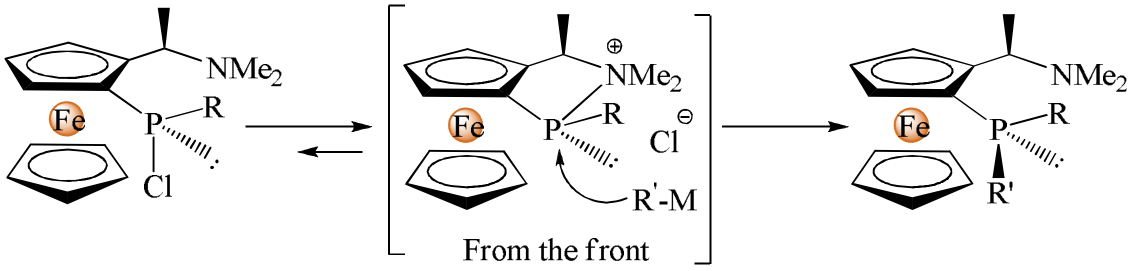


Figure 7- Selection of ligand families originated by modification of the NMe_2 group on Ugi's amine.

As one may notice, a common feature to the majority of ligands derived from Ugi's amine is that they normally present both planar and central chirality, this last element being usually a stereogenic carbon attached to C1 and containing a methyl group.[35]

More recently, Chen and Roberts set the purpose of building a stereogenic phosphorus at the C2 carbon belonging to a ferrocene derivative containing a CDG. For that they started by reacting *ortho*-lithiated Ugi's amine, with a phosphine dichloride (Cl_2PR) followed by reaction with another organometallic reagent (R'M). This strategy led to the serendipitous discovery that only one epimer was formed.[112] Indeed they found the strategy to be highly stereoselective as well as modular. Different phosphine dichlorides and Lithium or Grignard organometallic reagents could be used affording both diastereomers simply by switching R and R’ in the reagents. An explanation to this interesting result is based on a five-membered ring quaternary ammonium salt intermediate which reduces the possible orientations for the next nucleophilic attack by R’M as shown in **Scheme** 6.[112]

Scheme 6 - Formation of P-chiral ligands via Ugi’s amine induced diastereoselective nucleophilic attack at the phosphine chloride.



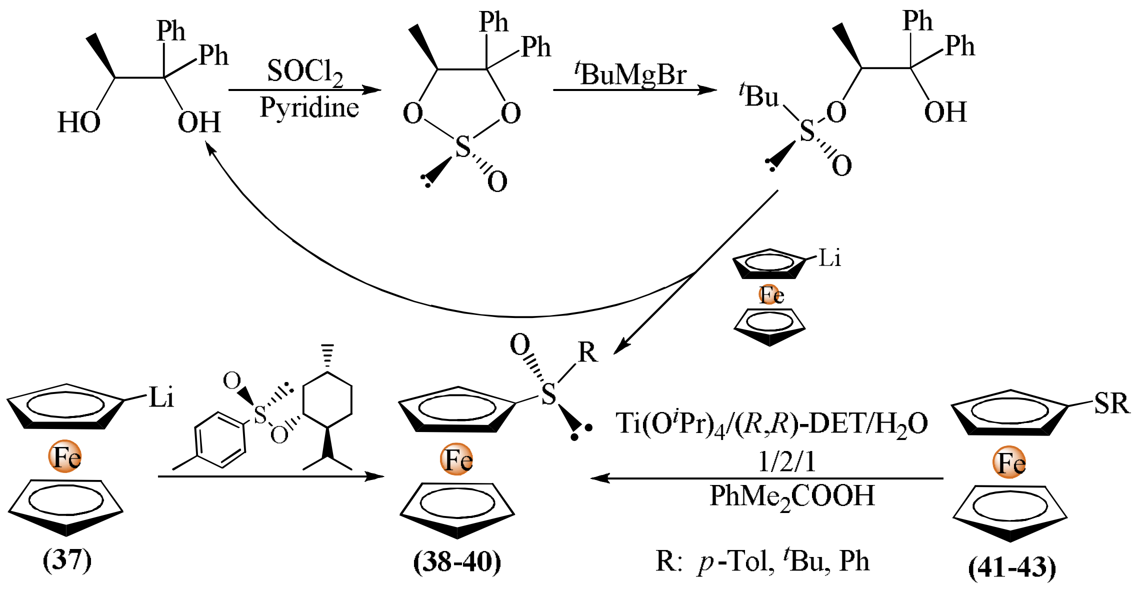
In sum Ugi’s amine has revealed it self to be a resourceful CDG with important applications in the synthesis of several ligand families.[35]

2.2.1.2 Sulfoxides

Ferrocenyl sulfoxides were initially brought forth by Kagan and his co-workers in the early 1990’s.[88] Though following a strategy inspired by Ugi’s diastereoselective *ortho*-lithiation, they wanted to avoid resolution methods, while preparing new chiral ligands for asymmetric catalysis. Envisioning that the CDG should be removable, and preferentially reusable, they approached the possibility of using a sulfoxide group.[73] Thus two approaches were employed to prepare the ferrocenyl sulfoxides. A first one based on two consecutives nucleophilic substitutions, at the sulfur atom of a chiral sulfite, using *tert*-butylmagnesium bromide (^{t}BuMgBr) and ferrocene lithium (FcLi) respectively, involving high enantioselectivity, >99%. Alternatively Andersen´s sulfinate,[113] (+)-(R_s,1S)-menthyl *p*-toluenesulfinate, and FcLi were used to afford a *p*-

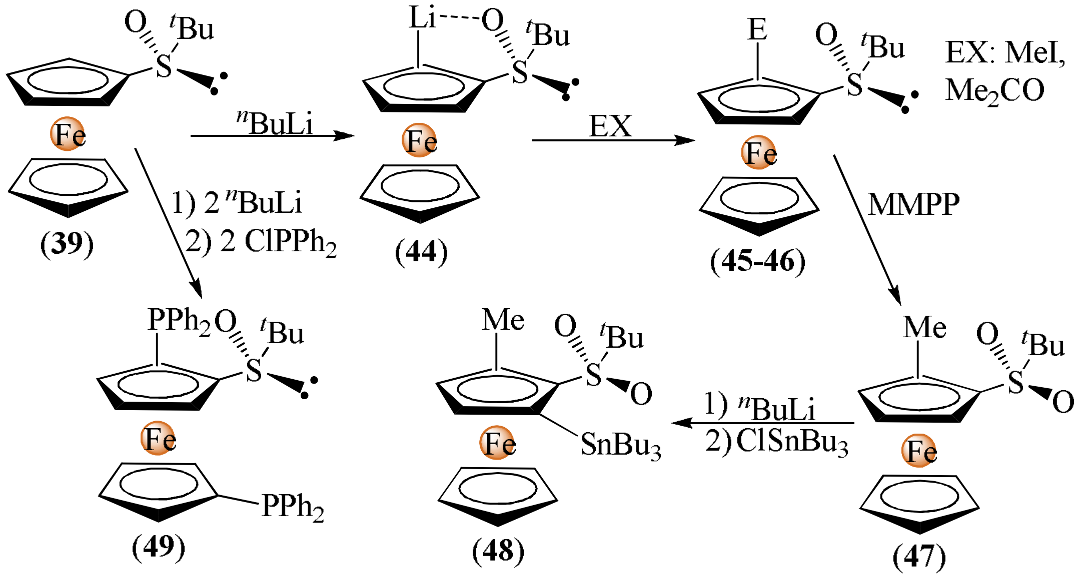
tolyl sulfoxide with ee's between 10 and 90%. The second approach was based on the asymmetric oxidation of ferrocenyl sulfides. This was achieved with hydroperoxides in the presence of stoichiometric amounts of a chiral titanium complex with diethyl tartrate (DET) as the chiral ligand providing ee's up to 99%.[73,88] The two approaches are presented in the **Scheme** below.

Scheme 7 - Formation of ferrocenyl chiral sulfoxides.



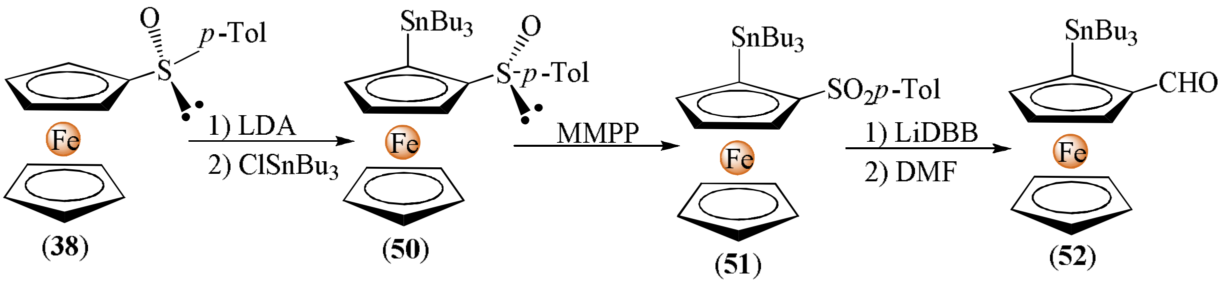
The sulfoxides' deprotonation followed by quenching with an electrophile proved to be highly diastereoselective. The *tert*-butyl derivative was lithiated with BuLi in 96% de, while the *p*-tolyl one with lithium diisopropylamide (LDA) in 98% de.[73,88] Besides affording planar chiral 1,2-disubstituted ferrocenyl sulfoxides, 1,2,1'-derivatives could also be synthesized just by using two equivalents of ^{n}BuLi followed by two equivalents of electrofile. Moreover, planar chiral 1,2,3-derivatives could also be afforded. For that the 1,2-disubstituted ferrocenyl sulfoxide was first converted into a sulfone via oxidation with magnesium monoperoxyphthalate (MMPP). The sulfone could then undergo a second *ortho*-lithiation step.[88] **Scheme** 8 exhibits the mentioned derivatives.

Scheme 8 - Diastereoselective lithiation of chiral sulfoxides to afford 1,2-, 1,2,3- and 1,2,1'-derivatives.



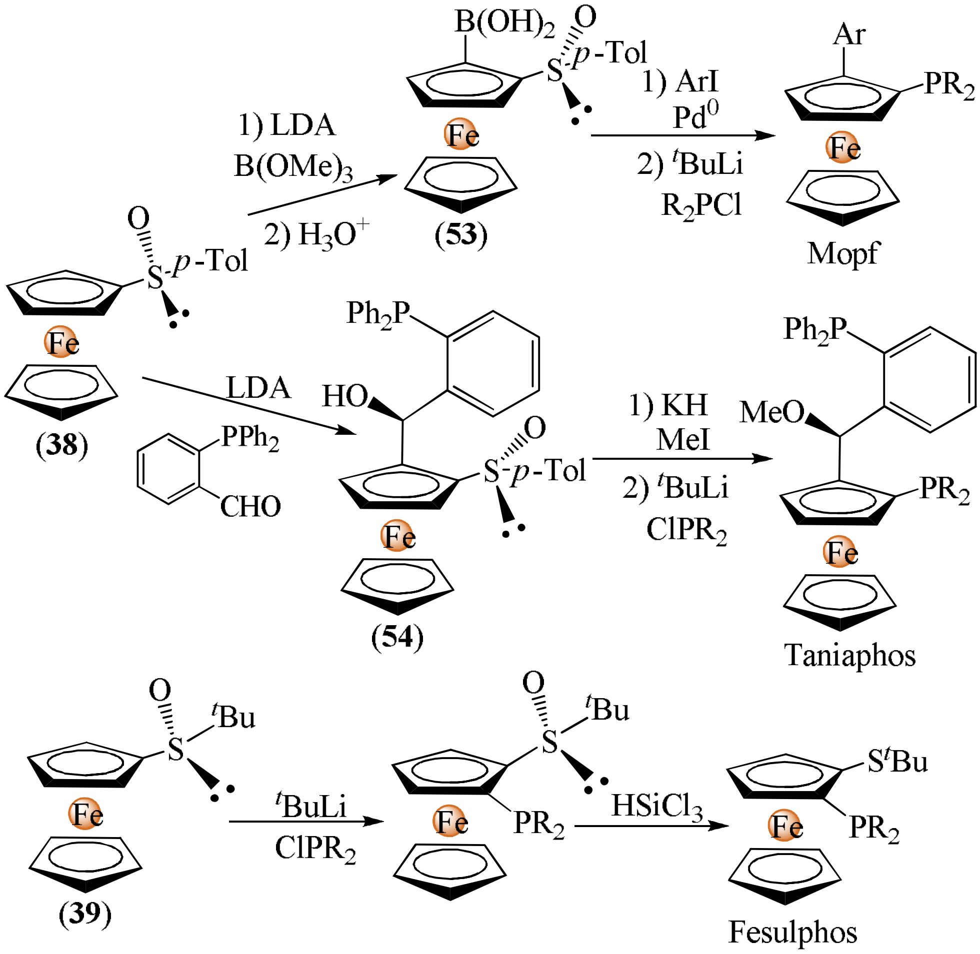
Replacement of the *p*-tolyl sulfoxide group in a 1,2-disubstituted ferrocenyl sulfoxide, was also shown by Kagan. Sulfoxide oxidation, successive lithiation, with lithium di-*tert*-butylbiphenylide (LiDBB), and trapping with DMF afforded a new planar chiral ferrocenyl aldehyde, as presented in **Scheme** 9.[73]

Scheme 9 - Sequential diastereoselective *ortho*-lithiation, quenching and substitution of ferrocenyl *p*-tolyl sulfoxide.



Developments into the exploration and optimization of the sulfoxide group as a CDG have ever since been carried out, with important applications.[114,35] For instance, Lagneau and Kagan groups have both expanded the number of electrophiles used in the quenching of the *ortho*-lithiated sulfoxides. Also the first group demonstrated addition of Grignard reagents to an aldehyde 1,2-disubstituted ferrocenyl sulfoxide to be completely stereoselective under chelation control.[89,115] The second group made use of sulfoxide-lithium exchange for the synthesis of enantiopure 1,2-disubstituted ferrocenes, including diphosphine ligands.[116,68] In effect, in recent times, due to their versatility sulfoxide ferrocenes are becoming important starting materials for the synthesis of 1,2-disubstituted and even polisubstituted ferrocenes. Sulfoxides can undergo diastereoselective *ortho*-metalation/functionalization, reduction into thioethers and oxidation into sulfones. They can also suffer sulfoxide-lithium exchange, a ^{t}BuLi promoted C-S cleavage, which can be followed by quenching with an electrophile.[35,114] As such the strategy on **Scheme** 10 has been applied for the synthesis of important ligands such as Taniaphos-type ligands,[117] Fesulphos,[118] aryl-Mopf,[119] and others.[35,114]

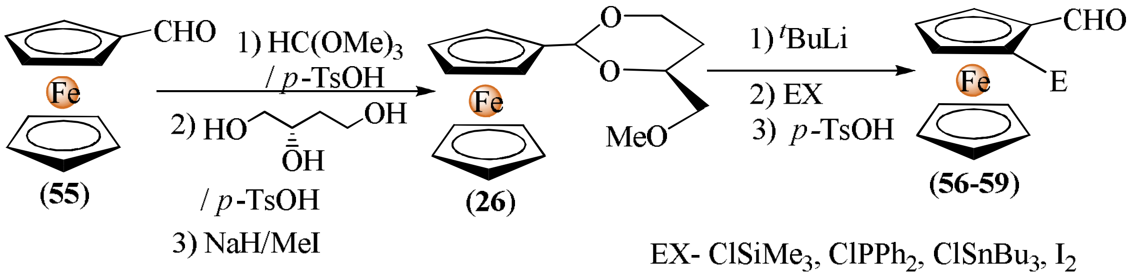
Scheme 10 - Employing sulfoxides in the formation of Mopf, Taniaphos and Fesulphos.



2.2.1.3 Acetals

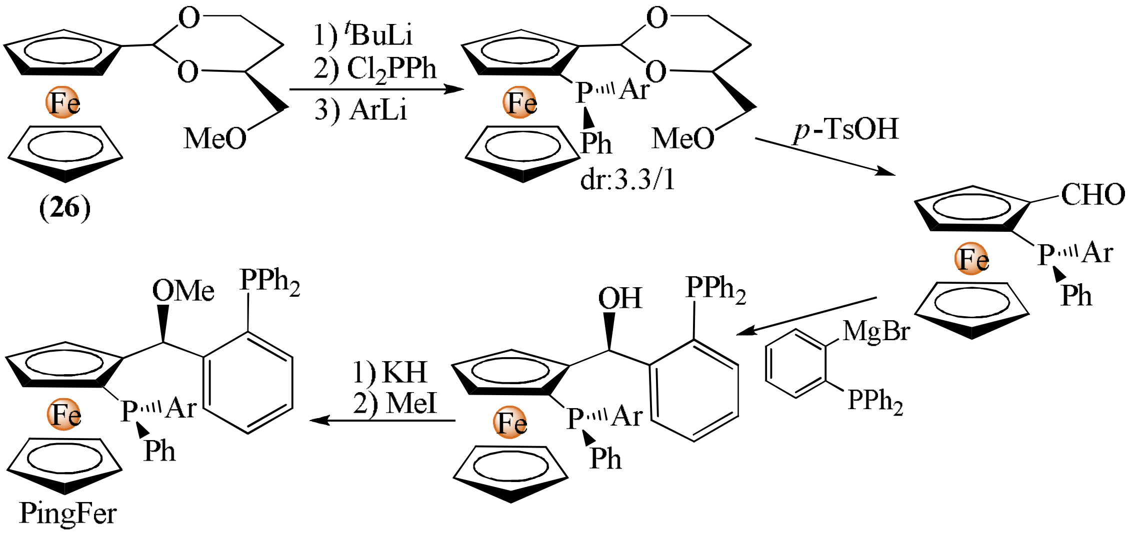
In spite of their work on the sulfoxide approach Kagan et al. felt the need for *"a more direct route to ferrocene with planar chirality"*.[73] Thus, also during the 1990's, a ferrocenyl chiral acetal was synthesized via protection of ferrocenecarboxaldehyde with (*S*)-1,2,4-butanetriol.[73,90] ^{t}BuLi mediated *ortho*-metalation and successive functionalization of the acetal, with a number of electrophiles, was accomplished with high diastereoselectivity, >99%. Following this step by acidic hydrolysis, with *p*-toluenesulphonic acid (*p*-TsOH), afforded optically active 1,2-disubstituted aldehydes with the chiral auxiliary being recovered,[73,90] as shown on **Scheme** 11.

Scheme 11 - Formation and use of chiral acetals in the synthesis of planar chiral 1,2-disubstituted ferrocenyl aldehydes.



These ferrocenyl aldehydes were shown to be useful starting materials for the synthesis of more complex planar chiral structures. Derivatization could undergo either by nucleophilic additions to the carbonyl group or by transformation of the substituent at the C2, for instance via palladium catalyzed cross-coupling reactions involving the iodo or tributylstannyl derivatives.[73] An example of chiral ligands formed in such a manner are Kagan's 1,3-bisphosphanes **19-23** which only possess planar chirality.[69] Moreover when combined to a 1'-directing aminal moiety[54,120,121] the 1,2-disubstituted aldehydes may undergo functionalization at the non-substituted Cp ring thus providing 1,2,1'-trisubstituted ferrocenyl aldehydes.[74] Finally Chen et al. have taken advantage of the acetal strategy[91] to synthesize Taniaphos type ligands. What's more the acetal group was demonstrated to induce some level of diastereoselectivity, 3.3:1, when forming P-stereogenic ligands PingFer.[122] The synthesis of such ligands is presented in the following **Scheme**.

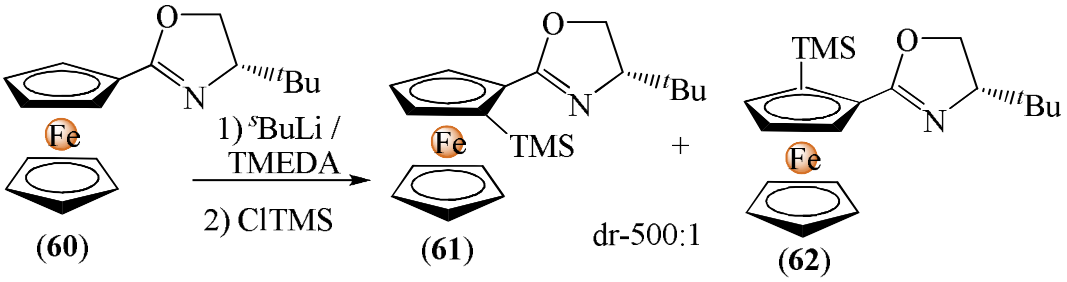
Scheme 12 - Acetal diastereoselectivity induction based synthesis of PingFer.



2.2.1.4 Oxazolines

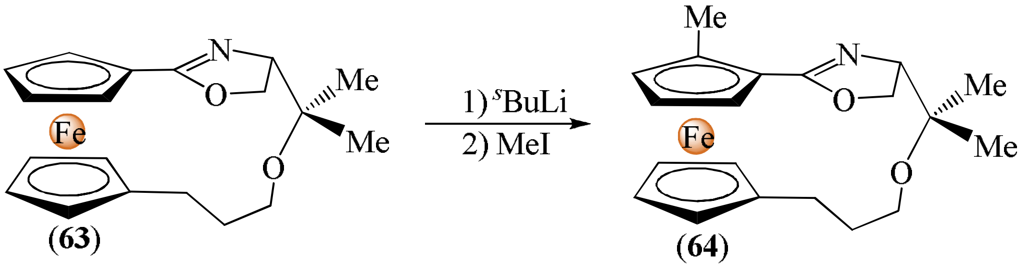
Planar chiral ferrocenes have since early times originated interest.[35] Also the application of chiral oxazolines in asymmetric catalysis has been successful.[123] Having in mind these affirmations one is not surprised by the fact that three independent groups[80-82] would simultaneously endeavour to make use of the chiral oxazoline moiety. Its *ortho*-directing aptitude was explored in order to manufacture optically active 1,2-disubstituted ferrocenyl ligands.[61] In 1995 Richards,[80] Sammakia[81] and Uemura[82] synthesized the new chiral ferrocene oxazolines from commercially available ferrocenecarboxylic acid and amino alcohols. They then investigated the diastereoselectivity outcome upon the oxazolines lithiation and consecutive quenching with an appropriate electrophile. They found the diastereomer ratio, sometimes being as low as 2:1, to be greatly dependent on reaction parameters, for example solvent, temperature and lithiating agent. Substituents at the oxazoline ring, such as ^{i}Pr, ^{t}Bu, ^{S}Bu, Me, Ph, $PhCH_2$ and others, were important as well.[61,74,80-82] Furthermore Sammakia noticed that additional ligands also had impact in the reaction, being able to optimize the diastereoselectivity by combining TMEDA with the lithium source in hexane.[74,124] The reaction is represented in **Scheme** 13.

Scheme 13 - Diastereoselective *ortho*-lithiation and functionalization of ferrocenyl oxazolines.



Sammakia was aware of the fact that both the nitrogen and the oxygen atoms could coordinate with lithium compounds,[125] and thus mediate the reaction. So he decided to verify whether the previous suggestion that all three authors had made in favour of a nitrogen directed reaction[80-82] was right. Seeking to get some mechanistic insight on the coordination and diastereoselectivity issue, he found some evidence signifying that the nitrogen atom in the oxazoline group is indeed the one directing the metalation step, instead of the oxygen one. In fact he prepared a macrocyclic ferrocenyl oxazoline in which rotation of the oxazoline moiety was restricted, therefore forcing both possible coordination modes, N vs. O, to generate distinct products. As shown on **Scheme** 14, after undergoing sequential *ortho*-lithiation and methylation this oxazoline resulted in a sole diastereomer presenting the methyl group vicinal to the nitrogen.[74,125]

Scheme 14 - Diastereoselective nitrogen directed *ortho*-lithiation of a macrocyclic ferrocenyl oxazoline.



In addition to the high diastereoselectivity related with their metalation step, ferrocenyl oxazolines allow a modular synthesis of important P,N chiral ligands.[35] Indeed different substituents can be incorporated either at the oxazoline ring or at the C2 in the ferrocenyl moiety. In fact a great deal of such ligands with different substitution patterns at both Cp rings have been synthesized.[61,74,75] Distinct planar chirality was achieved too by the use of a removable TMS blocking group.[80]

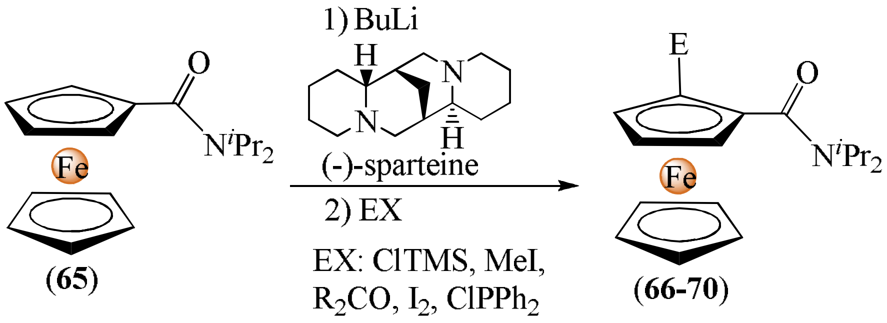
2.2.2 NON-DIASTEREOSELECTIVE METHODS

Despite its great efficiency and application in the field of ligand synthesis, the diastereoselective *ortho*-lithiation methodology may present a disadvantage associated with the preparation of chiral monosubstituted ferrocenes incorporating a CDG. Besides their synthesis there is frequently the need to substitute or convert that same CDG into a different functional group.[54,126] As a consequence alternative approaches have been considered to afford ferrocenyl planar chiral ligands as we will subsequently present.

2.2.2.1 Enantioselective *ortho*-Lithiation and Functionalization

A methodology for the synthesis of planar chiral ferrocenyl derivatives and ligands worthy of some attention is the enantioselective *ortho*-lithiation. Despite being a direct *ortho*-metalation strategy, this last is divergent to the diastereoselective one, in the sense that it involves achiral monosubstituted ferrocenes lithiated by external chiral inducing agents.[72,74,76] Among this agents those that afforded the best results are a combination of lithium bases and (-)-sparteine[126-130] or a (+)-sparteine surrogate.[130] However other combinations were used for instance involving (1*R*,2*R*)-*N,N,N’,N’*-tetramethylcyclohexanediamine,[131] or chiral lithium amide bases.[132] For instance, in 1996 Snieckus reported lithiation of *N,N*-diisopropyl ferrocenecarboxamide mediated by a mixture of BuLi and sparteine with subsequent functionalization of the corresponding carbanion. Thus employing several electrophiles to quench the lithiated ferrocene he obtained a variety of substituted ferrocenes with enantioselectivities ranging from 81 to 99% depending on the electrophile used,[126] as seen from **Scheme** 15.

Scheme 15 - Sparteine mediated enantioselective *ortho*-lithiation and functionalization of *N,N*-diisopropyl ferrocenecarboxamide.

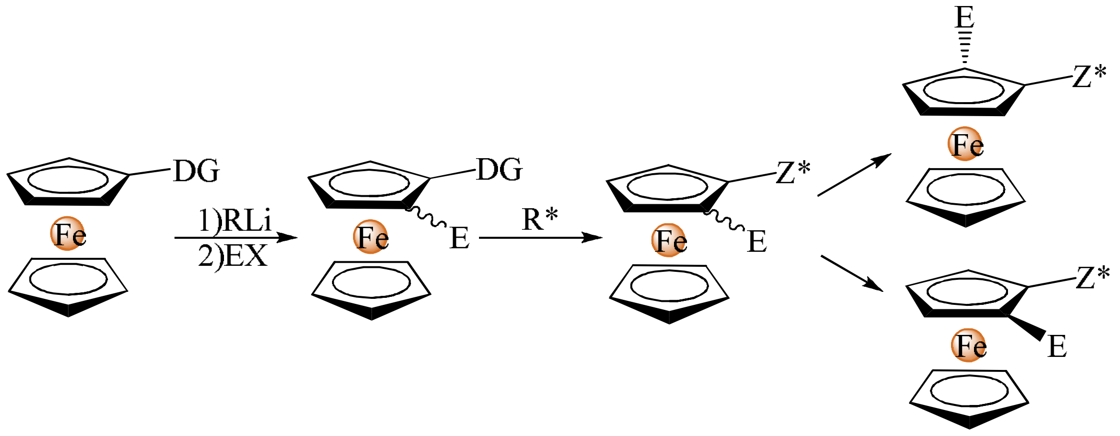


As mentioned some results revealed high enantioselectivities, including the means to obtain both possible enantiomers.[129,130] However, perhaps due to limitation in regards to the kind of monosubstituted ferrocenes successfully used as starting materials,[72] this strategy is yet to find significant application in the field of ligand synthesis.[35]

2.2.2.2 Sequential Non-Stereoselective *ortho*-Lithiation/Functionalization and Resolution

The want to obtain both possible enantiomers corresponding to a specific planar chiral ferrocene in a more practical way has prompted some chemists to make use of resolution techniques. Indeed stereoselective methods may imply troublesome separated synthesis of both opposite enantiomers.[86] Hence the desired 1,2-dissubstituted ferrocenes may be synthesized via sequential non-stereoselective *ortho*-lithiation and functionalization of monosubstituted ferrocenes containing achiral directing groups (DG). The racemic mixtures being afterwards resolved, via crystallization or chromatographic separation, with the aid of chiral auxiliaries (Z*) according with **Scheme** 16.

Scheme 16 - Sequential non-stereoselective *ortho*-lithiation/functionalization and resolution of ferrocenes containing achiral directing groups.



For instance resorting to this technique, and using dibenzoyl tartaric acid in the resolution step, Hayashi and Kumada have prepared both enantiomers of 1-dimethylaminomethyl-2-diphenylphosphino ferrocene, FcPN **10**.[105] Weissensteiner has used ephedrine and phenyl ethylamine to resolve compounds like 2-aminomethyl-1-iodoferrocenes.[133] Manoury and co-workers also using ephedrine and FcPN obtained both optical antipodes of sulphur protected 2-diphenylphosphino-ferrocenecarboxaldehyde. These were applied for the synthesis of new chiral ferrocenyl P,O ligands.[134] Finally Breit has separated racemic 2-diphenylphosphanylferrocene carboxylic acid, *o*-DPPFA, with the aid of glucose diacetonide.[86]

2.2.3 OTHER METHODS

Still with the aim of developing effective strategies for the synthesis of planar chiral ferrocenes, additional approaches have been tried. Among them are chemical methods such as diastereoselective formation of the ferrocene moiety,[85] insertion of carbenoids into Cp-H bonds of ferrocenes[135] and lithiation simultaneously directed by a sulfonate CDG and sparteine.[136] Also reported are an asymmetric version of P-S to P-C [1,3]-sigmatropic rearrangement in ferrocene[137] and kinetic resolution.[138,139] One can also mention biochemical methods like desymmetrization of meso 1,2-dissubstituted ferrocenes[85,140] and enzymatic kinetic resolution.[85]

2.3 CHIRAL FERROCENYL PHOSPHINE LIGANDS

2.3.1 WHY PHOSPHINES?

Phosphine ligands are among the most prominent efficient ligands that find application in homogeneous transition metal catalyzed reactions, their contribution to the field being well patent.[5] Among attractive characteristics that these ligands display one may notice their varied steric and inherent electronic properties. These can actually be modified as a means to better control the properties of the transition metal complex, especially bearing in mind the different steps of a catalytic cycle.[141,142]

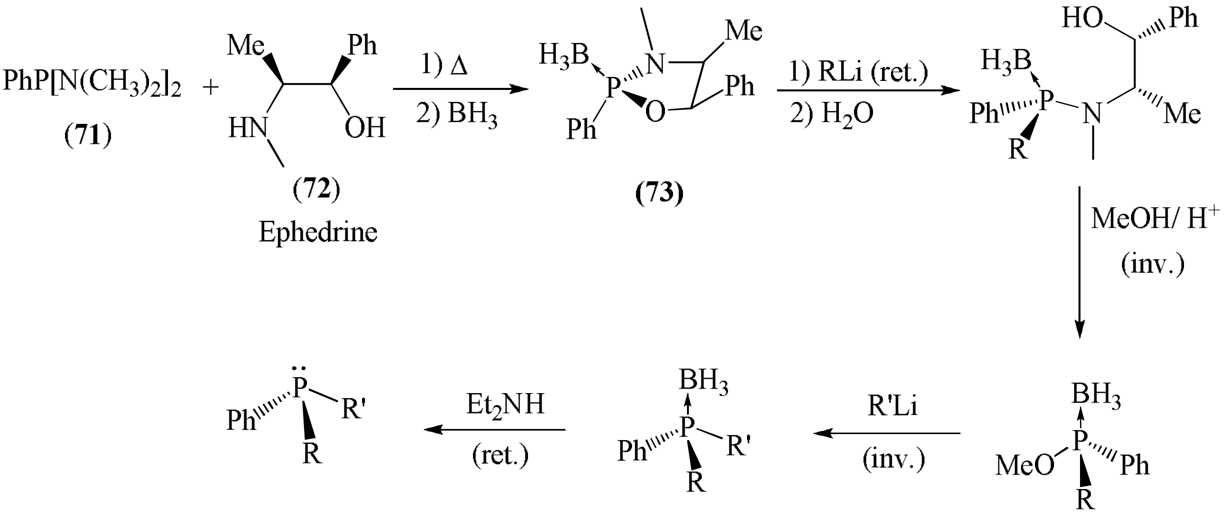
2.3.2 CARBON BASED STEREOGENICITY VERSUS P-CHIROGENICITY

Since in the catalytic reaction the chiral information is “transferred” from the catalyst to the organic product one is able to conclude the chiral agent design to be vital.[142] As a consequence the structure of the ligand itself is of great pertinence. In fact chiral phosphine ligands have been prepared in a variety of structures presenting one or more of the three elements of chirality.[5] However often the chiral center is located in the ligand backbone with chirality being transferred to the metal coordination sphere through a chiral array of aryl or alkyl groups on the phosphorus.[142] Examples are DIOP **1**, BINAP **3**, XYLIPHOS **5** in **Figure** 2, and PHOX in **Figure** 3, pages 6 and 13. In this type of phosphines with carbon based stereogenicity the way in which the substituents are orientated within the coordination sphere influences the reaction in terms of stereochemistry and chiral recognition ability. Nevertheless to some degree this secondary transfer of chirality from the ligand backbone may be inefficient.[142] On the other hand when the chiral center exists at the very same atom responsible of coordinating with the transition metal enantioselection benefits from a more efficient chiral environment.[142] For this reason P-chiral ligands are attractive ligands predicted to perform with high stereocontrol.

2.3.3 P-CHIROGENIC LIGANDS

Ligands like the aforementioned Monsanto catalyst DIPAMP **2** in **Figure** 2, have since early shown the potential that P-chirogenic ligands could reveal. Nevertheless its use has to some extent been restricted by the challenge implicated in their manufacture. Normally elaborate multistep synthesis frequently involving tedious resolution procedures are involved.[143-146] Yet in the last two decades this scenario has been changing in face of different strategies that have been developed.[143-146] One of these elegant strategies is based upon a resolved cyclic P-chiral precursor possessing two distinct leaving groups. Being submitted to stereoselective ring opening and sequential substitution reactions the precursor allows the formation of new P-C bonds also in a stereoselective fashion.[145]An important element for the diastereomerically pure formation of the key starting P-stereogenic precursor is a heterobifunctional chiral auxiliary.[145] On a route first delineated by Jugé,[146,147] ephedrine was the auxiliary applied for the synthesis of the starting cyclic oxazaphospholidine. This strategy which initially involved a Michaelis Arbuzov rearrangement in the ring opening step was further developed, by Jugé, and Brown groups. Accordingly with **Scheme** 17 the P atom was protected and stabilized in the form of a borane or an oxide thus substituting the first, rearrangement, step by a nucleophilic displacement one.[145-150]

Scheme 17 - Synthesis of P-chirogenic ligands via Jugé's methodology.[147,149,151]



As represented above Jugé's methodology first involves stereoselective formation of the borane protected phenyl-oxazaphospholidine. Following are two nucleophilic attacks and a methanolysis, culminating in deprotection with overall retention of configuration.[145,149] By varying the organolithium reagents different P-chiral compounds can be obtained. Plus this approach involves undemanding purification and deprotection altogether with chemical and configurational stability.[145,151]

2.3.4 BRINGING THE P-CHIRAL PHOSPHINE GROUP INTO THE FERROCENE UNIT

Amongst the several chiral ferrocenyl ligand families that have been synthesized and found application in the field of asymmetric catalysis the majority and usually the most important ones are phosphines.[5,35] As a matter of fact relevant features are associated with this type of ligands which make them so attractive and more amenable to asymmetric catalysis when in comparison with other ligands. For instance ferrocenyl phosphines are often synthesized in a modular fashion, being frequently stable, easy to handle and allowing separation of both optical antipodes. Combined with different transition metals these ligands originate an array of complexes with varied oxidation states and geometries, corresponding to effective catalyst precursors for several chemical reactions.[152]

Besides planar chirality, ferrocenyl phosphines may also present central chirality at the phosphorus atom thus representing important ligands. In truth not only chirality is brought closer to the catalytic centre but also and foremost both elements of chirality may act in a synergistic fashion, that is to say, with matched chirality. Many ferrocenyl phosphines bearing various chiral elements, in some cases altogether with central, planar and axial chirality, have been synthesized, studied and applied in the field of asymmetric catalysis. Regardless of this fact ferrocenyl ligands with a P-stereogenic atom are less common.[5,35,145] A comparative literature study points to the fact that the majority of ferrocenyl ligands containing P-chirality as the sole chiral element have been synthesized via a Jugé’s type stereocontrolled nucleophilic substitution sequence[145,151,153-158] as described above. Alternatively this type of ligands have been prepared by Imamoto[159-161] as a follow up on his previous work[162] based on Evans[163] and Livinghouse[164] approaches for the synthesis of P-chiral phosphines. Respectively (-)-sparteine mediated enantioselective deprotonation of phosphine boranes and (-)-sparteine mediated dynamic resolution of a racemic secondary phosphine borane were used.

Even more seldom are reports on the preparation of ligands bearing both P-chirality and a chiral plane. Perhaps the first reported case is from 1999 in which an enantiomeric planar chiral aminomethylferrocene palladium derivative was employed to produce a mixture containing compound **74** and its P-epimer. However the separation of both diastereomers was laborious implying loss of product.[165] Continuing his previous work[155-157] on ferrocenyl P-chiral ligands and starting from stereogenic ferrocenylphosphine oxides, Nettekoven exploited their ability as CDG's,[100] pages 27 and 28. Is aim was to generate a chiral plane via diastereoselective *ortho*-magnesiation, affording the desired C_2-symmetrical 2,2'-bisdiarylphosphino-1,1'-biferrocenyls after reduction of the oxides. Although obtaining good diastereoselectivity the results were limited in regards to the substrate used and to the use of diisopropylmagnesium bromide, since lithiation was not succsseful.[100,166] Through a multistep synthesis involving resolution and starting from a planar chiral Ugi's amine derivative, (R,S_p)-PPFA **8** in **Figure** 5, page 22, Barbaro, Giambastiani and Togni combined planar chirality with, phosphorus and carbon, central chirality in a tridentade phosphine **75**.[167] Finally Chen and Roberts have also worked with Ugi's amine to produce planar chiral P-chiral ligands. Besides the aforementioned ligands in pages 32/33 and 38/39 (PingFer) they have prepared a C_2-symmetric diphosphine, TriFer **76**.[168] **Figure** 8, presents some of the planar chiral Ferrocenyl mentioned above.

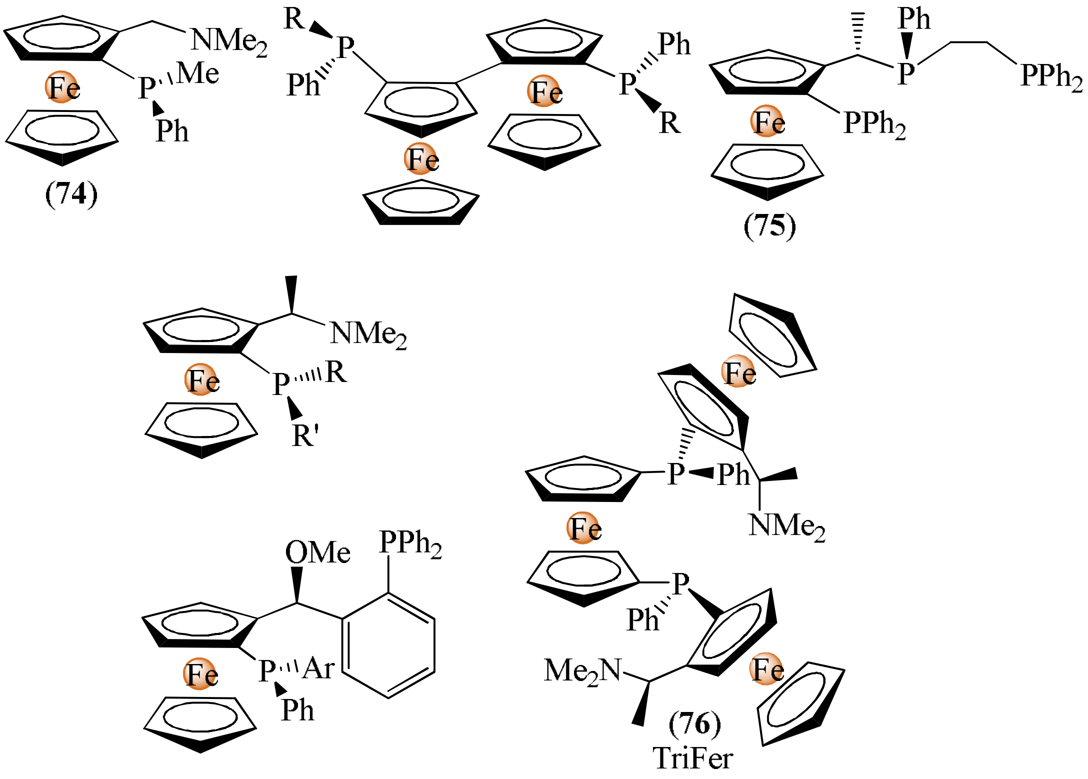


Figure 8 - Ferrocenyl ligands possessing both planar and P-chirality.

2.4 THE OXAZAPHOSPHOLIDINE OXIDE MOIETY: A VERSATYL CHIRAL *ORTHO*-DIRECTING GROUP

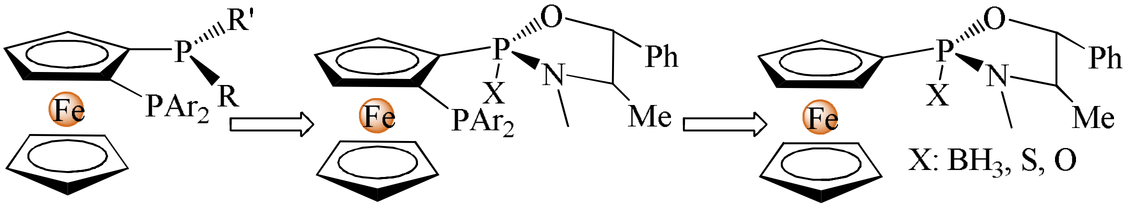
2.4.1 WHY ATTEMPTING TO USE THE OXAZAPHOSPHOLIDINE MOIETY AS A CHIRAL DIRECTING GROUP?

At this point one has to some extent noticed the array of planar chiral ferrocenyl ligands that have been synthesized and the variety of strategies that have been developed for that same purpose. This fact should per se transpire the remaining need for practical and reliable ways to achieve new efficient ligands. So far creation of new ligand families in a modular manner is preferred. It allows fine tuning of electronic, steric and stereo properties in order to obtain optimal results in the catalytic transformation. Bearing this in mind it becomes clearer why the diastereoselective *ortho*-lithiation and functionalization methodology continues to attract chemists into using and further developing it. Also we have highlighted the fact that the several strategies, several CDG's, involving this methodology work as a whole. They complement each other in the sense that each leads to a certain type or family of 1,2-disubstituted planar chiral ligand or derivative. Such reasoning, together with the significant results that planar chiral and P-chiral ligands may convey in catalysis, has previously led this group to endeavour into the development of a new CDG. Research was done aiming to contribute in a positive way for the synthesis of planar chiral ferrocenyl ligands, especially bearing P-chirogenic phosphines, and simultaneously for the establishment of a new ligand family to be applied in asymmetric catalysis.

2.4.1.1 Retrosynthetic Analysis

The targeted strategy for the preparation of planar chiral 1,2-disubstituted ferrocenyl ligands possessing a stereogenic phosphorus atom should therefore address the need to create both the chiral plane and the central chirality at the phosphorus atom.

Scheme 18 - Retrosynthetic analysis on the synthesis of P-chirogenic planar chiral ferrocenyl diphosphines from ferrocenyl oxazaphospholidines.



(77,78,31)

Accordingly with **Scheme** 18, in the envisioned approach the protected oxazaphospholidine moiety was elected with the expectation that it would efficiently perform as a CDG. Hence it should induce diastereoselective deprotonation/functionalization of ferrocene for the introduction of planar chirality. Also as a protected P-chirogenic precursor it should be able to be applied to a Jugé's ephedrine type methodology. Given that this last methodology requires the chiral precursor to be optically pure it becomes imperative for the previous sequential steps to convey high diastereoselectivity and ease of purification. In other words the formation of the starting protected ferrocenyl oxazaphospholidine ought to result in only one epimer or permit efficient separation of both optical antipodes. Also the lithiation must be highly regio- (*ortho*) and diastereomerically selective, after purification affording only one 1,2-disubstituted ferrocenyl diastereomer. These conditions being satisfied then the last step ought to lead to effective ring opening and stereocontrolled sequential substitution of the ephedrine fragment by alkyl or aryl groups. Following deprotection the desired planar and P-chiral ferrocenyl P-P* diphosphine would be produced.

Not having guaranties that the targeted strategy would be successful, the expectation could however find some ground in the following summarized evidences:

- Bisdimethylaminophosphinoxy,[169] diphenylphosphinoxy,[170] and, in particular, di-*tert*-butylphosphinoxy[171] groups have directed *ortho*-

lithiation reactions on substituted benzenes. What's more stereogenic phosphine oxides have diastereoselectively directed *ortho*-magnesiation at the ferrocene unit.[100]

- An *O*-methylephedrine derivative has proved to be an effective *ortho*-directing group for the diastereoselective deprotonation of ferrocene.[101, 172] Also, the easily accessible ephedrine was previously used as part of an oxazolidine ring to direct the *ortho*-lithiation on a Cp ring belonging to a chiral cymantrene derivative. On another instance diastereoselective ring opening of chiral ferrocenyl derived oxazolidines was performed, via reaction with Grignard reagents, to form chiral monosubstituted ferrocenyl amino alcohols.[85]
- Resolution of planar chiral 1,2-disubstituted ferrocene derivatives has been achieved via chromatographic separation employing ephedrine as a chiral auxiliary.[133,134]
- Jugé's type displacement methods involving oxazaphospholidine moiety, protected either by BH_3, S or O, have been successfully applied to the synthesis of several P-chiral phosphines, inclusively ferrocenyl ones.[143-150]

2.4.2 PREVIOUS RESULTS - A BRIEF SUMMARY

The early attempt to put the above strategy o **Scheme** 18 to the test succeeded in the execution of steps 1 and 2.[103,173,174] In detail, the starting material preparation led to the BH_3, S and O protected ferrocenyl oxazaphospholidines.[103,173,174] From these three substrates only the oxide proved to be an efficient *ortho*-directing group probably due to higher acidity at the Cp protons, caused by a more electrophilic phosphorus atom.[173] Deprotonation with an organolithium base was conducted with high diastereoselectivity, moreover revealing itself to be compatible with a spectrum of functionalities such as halogens, silanes, boronates, alcohols, alkyls and phosphites.[103,173,174] Unfortunately the last step, 3, was shown inefficient as the displacement method failed to be applied to a 1,2-disubstituted ferrocenyl oxazaphospholidine oxide.[173,174] In fact the technique could be applied to the starting materials, the monosubstituted ferrocenyl oxazaphospholidine oxide and sulfide, without any major impediment. Nonetheless the modified chemical environment due to the presence of an organic group such as diarylphosphino, *ortho* to the oxazaphospholidine oxide moiety, is expected to be the cause for the 1,2-disubstituted derivatives resistance to undergo ring opening.[174]

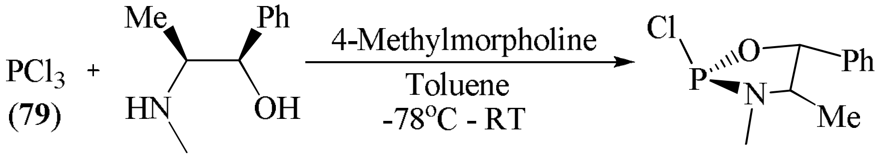
2.4.3 RESULTS AND DISCUSSION

In spite of the previously described setbacks that came about during the research to develop an effective methodology for the preparation of modular planar and P-chiral, ferrocenyl P-P* diphosphines the research was not brought to a halt. In truth some questions were still to be addressed. Plus the potential that the oxazaphospholidine oxide moiety revealed on the diastereoselective deprotonation of ferrocene was enough of a reason to carry the research and further explore the intrinsic worth of this CDG. Following we will describe the results from our research and discuss upon them.

2.4.3.1 Synthesis of the Ferrocenyl Oxazaphospholidine Oxide

Preparation of our starting material, the ferrocenyl oxazaphospholidine oxide, first requires diastereoselective formation of the corresponding phosphoramidite, or oxazaphospholidine, chloride **80**. In fact its synthesis was first reported in 1976 by Inch et al,[175] who also worked with the corresponding oxide[176]and sulfide.[177] However their method has since that time been improved with some relatively minor modifications.[103,150,178-181] Thus nucleophilic attack of (1*R*,2*S*)-(-)-ephedrine **72** to PCl_3 **79** was performed in the presence of *N*-methyl morpholine, first at -78 °C and then at room temperature overnight. (2*R*,4*S*,5*R*)-2-Chloro-3,4-dimethyl-5-phenyl-[1,3,2]-oxazaphospholidine **80**, *R*-ClPEph, was obtained in 93% yield as a single epimer. The reaction is presented in the **Scheme** below.

Scheme 19 - Synthesis of oxazaphospholidine chloride.



(79)

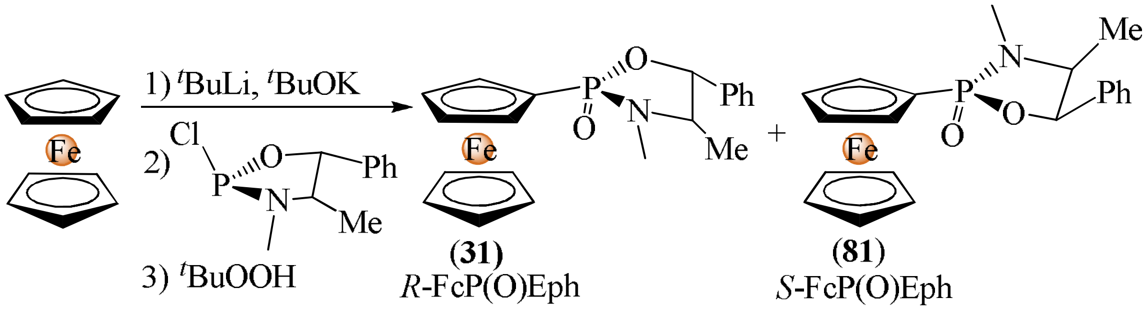
(72)
Ephedrine

(80)
R-ClPEph

Concerning to the relatively high yield obtained one wishes to notice that filtration of the morpholine hydrochloride salt was performed in a porous filter with a filter paper followed by washing with dry toluene. This allows less product loss in comparison to a filtration through celite and apparently without affecting the product's purity. This straightforward step which does not include any chromatographic procedure results in a yellowish waxy solid. Prior to use, the compound can be appropriately stored for several days without decomposition, as revealed by its ^{31}P NMR spectrum which shows only one peak at 172.4 ppm. Based on spectroscopic data and on the literature[180,181] the C-Ph and C-Me substituents in the oxazaphospholidine ring and the chlorine atom are in a trans disposition to one another. Consequently the configuration was assigned as *R*, accordingly with **Scheme** 19 above.

Without any further purification the oxazaphospholidine chloride **80** was used in the second step to prepare the ferrocenyl oxazaphospholidine oxide. This was achieved via nucleophile mediated chlorine displacement with lithium ferrocene. Hence, applying a slightly modified procedure by Mueller-Westerhoff,[182] ^{t}BuLi was added to a THF solution of ferrocene and ^{t}BuOK at -78 °C. The fine red-brick precipitate resulting after one hour of stirring at room temperature was transferred to a cooled solution (-78°C) of **80**, later the temperature being allowed to reach room temperature overnight. Finally, in order to protect and stabilize the formed ferrocenyl oxazaphospholidine, the mixture was previously cooled to 0 °C and ^{t}BuOOH was added. Following 4 hours reaction aqueous workup and purification by silica flash chromatography afforded the desired product (2*R*,4*S*,5*R*)-3,4-dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide **31**,[103] *R*-FcP(O)Eph, with 63% yield. Interestingly enough, while repeating the preparation of the former compound, another new product was isolated in an approximately 1:1 ratio relatively to the previous one, 40% of **31** and 35% of **81**. To our delight spectroscopic and analytical data revealed it to be the other P-epimer, (2*S*,4*S*,5*R*)-3,4-dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide **81**, *S*-FcP(O)Eph, as represented in the reaction **Scheme**.

Scheme 20 - Synthesis of ferrocenyl oxazaphospholidine oxide.



(31)
R-FcP(O)Eph

(81)
S-FcP(O)Eph

2.4.3.1.1 On the ferrocenyl oxazaphospholidine oxide structural data

The products from the above reaction were found to display distinct physical and chemical properties, such as polarity, melting point and optical rotation. On the other hand mass spectrometry and elemental analysis were identical which is in agreement with the presence of two isomers.

2.4.3.1.1.1 *NMR data*

^{31}P NMR spectrometry revealed the presence of a sole phosphorus atom for both epimers respectively at 40.8 ppm, for compound **31**, and 37.9 ppm, for compound **81**. More importantly ^{1}H NMR spectroscopy confirmed the presence of the ephedrine and substituted ferrocene moieties in both isomers, as well as the assigned configuration *R* and *S* respectively for epimers **31** and **81**. On the basis to this last conclusion is the information withdrawn by the proton attached to the ephedrine C-Ph carbon, in the oxazaphospholidine ring. Accordingly to the compound's configuration this proton may undergo strong coupling with the phosphorus atom or not. Effectively, in compound **31** the P=O double bond is orientated *anti* relatively to the CHMe and CHPh protons from the oxazaphospholidine ring. For this reason besides coupling with the CHMe proton the CHPh one is also submitted to coupling with the phosphorus, thus appearing as a triplet (dd), $^{3}J_{PH} = J_{HH} = 6.7$ Hz. On the other hand, in the new epimer **81** the P=O bond is orientated *syn* relatively to the CHMe and CHPh protons. Coupling between the proton and the phosphorus atom is therefore considerably weaker, hence a doublet is observed resulting only from proton-proton coupling between the CHMe and CHPh protons, $^{3}J_{PH} \approx 0$, $J_{HH} = 6.1$ Hz.

Also in the *syn* conformation the CHPh proton is more deshielded, δ - 5.88, when in comparison with the *anti* conformation, δ - 5.47. This is a characteristic of oxazaphospholidine compounds. The difference between $^{3}J_{PH}$ constant coupling values, normally <1 Hz in the *syn* conformation and ranging from 3 to 6.5 Hz in the *anti* conformation is typical also.[183,184] The ^{1}H NMR spectrum for each diastereomer is presented in the following **Figure** together with expansion on the peaks corresponding to the CHPh proton.

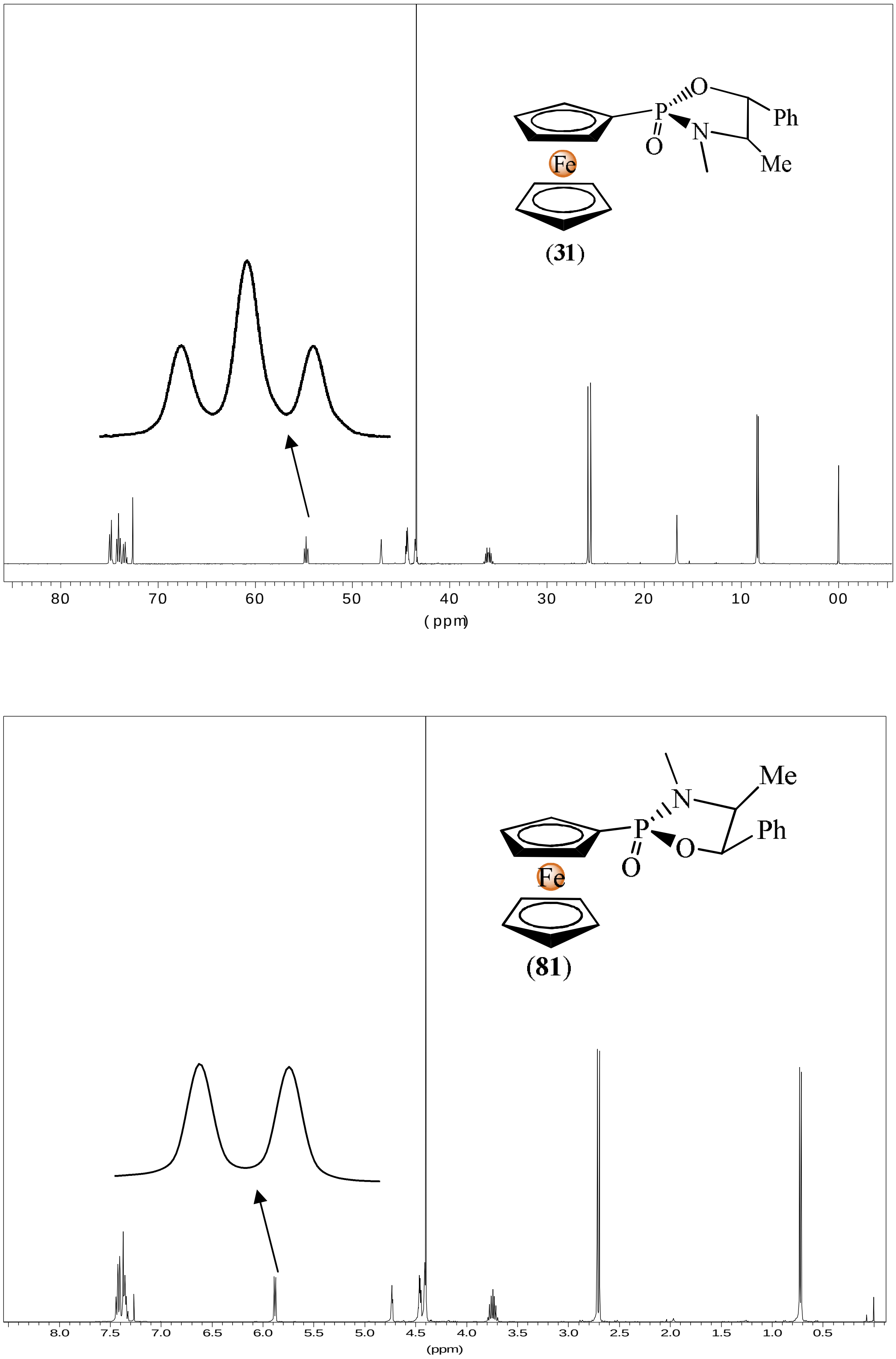


Figure 9 - ^{1}H NMR spectrum for each one of compounds **31** and **81** and respective expansion on the peaks corresponding to the CHPh proton.

2.4.3.1.1.2 *X-ray diffraction data*

Our conclusions regarding the structure of compound **81**, *S*-FcP(O)Eph, in comparison with the one from **31**, *R*-FcP(O)Eph, were confronted with more analytical data. Namely good quality crystals (R_{int}=0.0217) of the new diastereomer were grown in ethyl acetate and subsequently analysed by X-ray diffraction techniques. Both the already reported structure from **31**[174] and the one from **81** are shown on **Figures** 10 and 11.

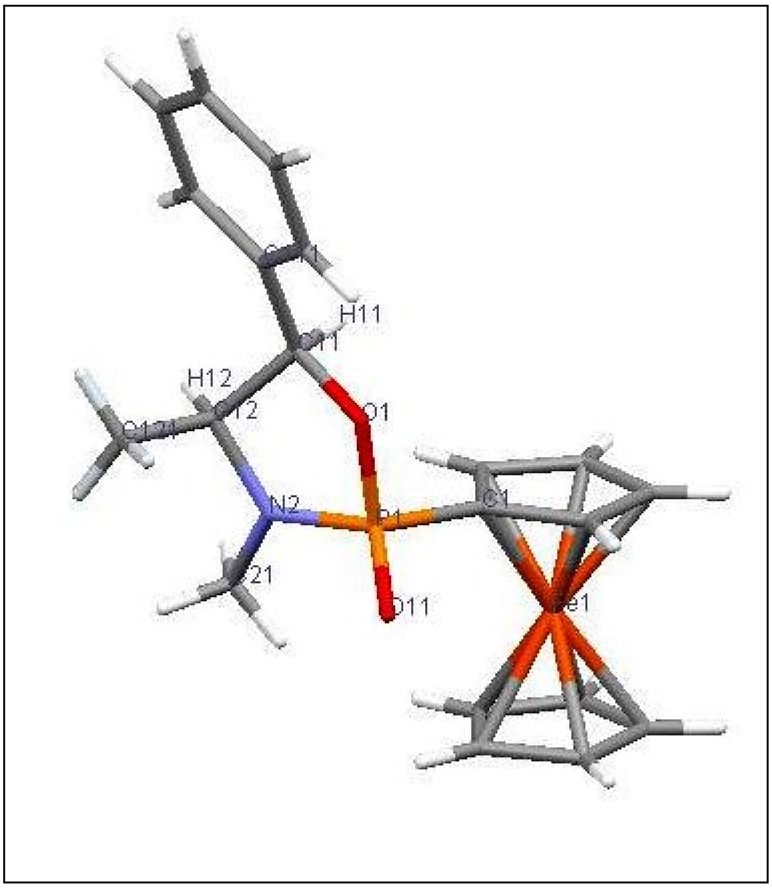


Figure 10 - Mercury view of compound **31** X-ray structure. Selected bond lengths (Å) and angles (deg): P1-O1 1.6054 (12), P1-N2 1.6375 (14), P1-O11 1.4675 (14), O1-P1-N2 94.82 (7), O11-P1-C1 112.61 (8), N2-P1-C1 109.39 (8).[174]

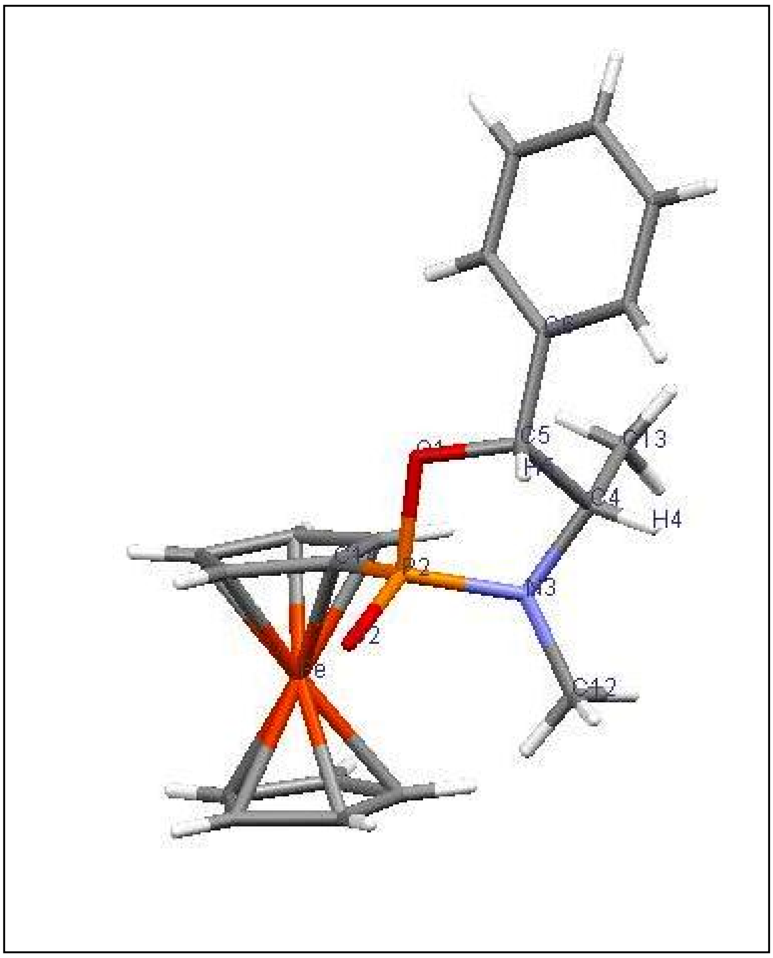


Figure 11 - Mercury view of compound **81** X-ray structure. Selected bond lengths (Å) and angles (deg): P2-O1 1.6085 (11), P2-O2 1.4753 (11), P2-N3 1.6509 (13), P2-C14 1.7663 (16), O1-P2-N3 95.16 (6), O2-P2-C14 111.86 (7), O2-P2-O1 116.01 (7), O2-P2-N3, 117.33 (7), N3-P2-C14 110.74 (7), O1-P2-N3-C4 1.35 (11).

The above X-ray structures are consistent with the early considerations based on ^{1}H NMR spectroscopy. The compounds are indeed diastereomers with inverted configuration at the phosphorus, P-epimers. To assign the absolute configuration at the phosphorus atom we need to take into account the Cahn-Ingold-Prelog rule that specifies the electrons lone pair as always being the one of lowest priority, and P=O of lower priority than P-O-C.[185] Consequently the *R and S* configurations are confirmed for structures **31** and **81** respectively.

A more detailed analysis of the X-ray structures shows that both epimers adopt an envelop conformation. The flap atom, C5 or CHPh carbon, is out of the plane formed by O1-P2-N3-C4, accordingly with the labels on **Figure** 11. The N3-methyl group from both epimers is pseudo-equatorial relatively to the oxazaphospholidine ring, and parallel to the ferrocene backbone. Flanked by these last two groups the P=O is pointing down being half distance between the substituted Cp ring and the iron atom. In order to minimize eclipsing and steric clashes with the ferrocene unit the ring C4 methyl, or CHMe, is pseudo-axial, while the C5 phenyl is pseudo-equatorial. In compound **31**, *R*-FcP(O)Eph, the flap is towards the ferrocene moiety which is *anti* relatively to the ring C4 methyl and C5 phenyl substituents. Also in this compound the phenyl plane is almost parallel to the oxazaphospholidine one. In contrast compound **81,** *S*-FcP(O)Eph, presents the flap away from the ferrocene moiety although in this case the ring C4 methyl and C5 phenyl substituents are *syn* in regards to it. In other words these three substituents are in the same side of the oxazaphospholidine ring. Finally in this epimer the phenyl plane is almost perpendicular to the oxazaphospholidine one. The descriptions given can be visualized in the structural representations of compounds **31** and **81**, in **Figures** 12 and 13.

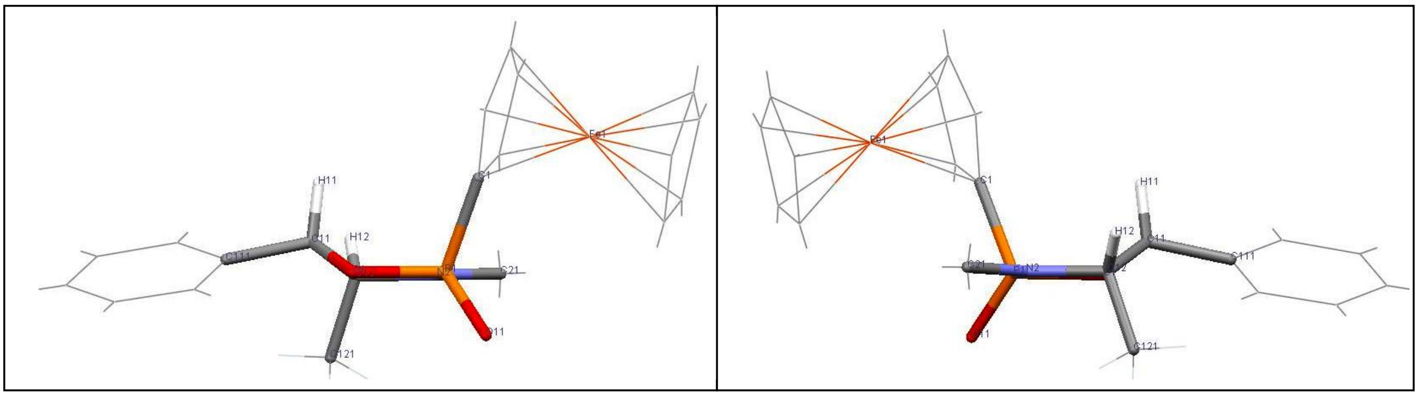


Figure 12 - Mercury X-ray structure side views of the oxazaphospholidine ring in compound **31**.

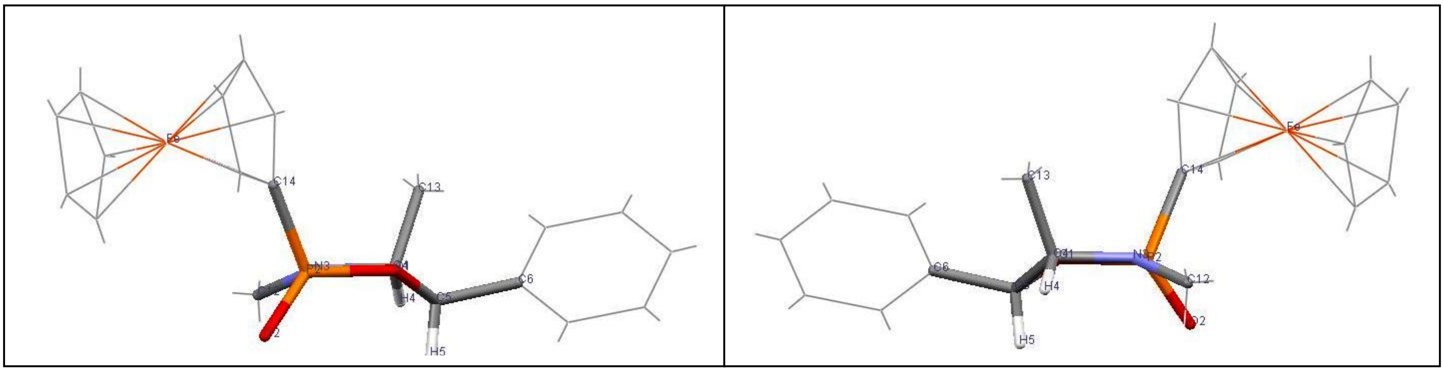


Figure 13 - Mercury X-ray structure side views of the oxazaphospholidine ring in compound **81**.

2.4.3.1.2 On the ratio between both ferrocenyl oxazaphospholidine oxide epimers

So far we have described a useful route involving two simple steps for the simultaneous synthesis of compounds **31** and **81** without requiring resolutions procedures. In addition it involves three relatively inexpensive and easily available reagents, namely (1*R*,2*S*)-(-)-ephedrine, phosphorus trichloride (PCl_3) and ferrocene. However the fact that two P-epimers were obtained instead of only one poses some questions.

2.4.3.1.2.1 *Exocyclic chlorine displacement versus P(III) oxidation*

Exocyclic chlorine displacement by carbon-based nucleophiles has been shown to undergo with predominantly overall retention of configuration at the phosphorus atom in compound **80**,[150,180] *R*-ClPEph. Such is also the case of the corresponding phosphoryl chloride.[176,184,186] In addition P(III) oxidations have been accepted as proceeding in a highly stereoselective manner also leading to overall retention of configuration.[181,187-189]

Based on the previous observations, only diastereomer **31** should be formed since its configuration is identical to the starting oxazaphospholidine chloride **80**. At least it should be the major product by far. Yet this was not always so in our case, neither when the borane and sulfide equivalents to our pair of epimers were synthesized.[173,174] Indeed a similar procedure to the one we described above only using S_8 instead of ^{t}BuOOH led to the formation of both epimers of ferrocenyl oxazaphospholidine sulfide in a 1:1 ratio.[173,174] Using $BH_3.S(CH_3)_2$ led to only one isolated diastereomer of ferrocenyl oxazaphospholidine borane in 64%. However changing the order of addition between the chloride **80** and the ferrocenyl lithium slurry would lead to the formation of a new minor borane P-epimer in a 3:1 ratio.[173]

In reality a closer look at some of the literature available regarding the synthesis of such oxazaphospholidines[150,180,183,184] suggests that the formation of two P-epimers is probably frequent. Though, probably due to diminutive incidence, many times the minor product is disregarded during the process of purification. In agreement to this last statement are some observations made by Carey and Brown. By ^{31}P NMR monitoring, during the formation of oxazaphospholidine chloride **80** they detected the initial presence of two diastereomers one of them in lower-field disappearing after 4 hours. Using that chloride and reacting it with a nucleophile, *o*-methoxyphenyl magnesium bromide, again two diastereomers were detected. After equilibrating at room temperature, oxidation with ^{t}BuOOH and purification by flash chromatography a major product was isolated in 61% yield. Also traces of the other diastereomer were observed in the last eluted fractions.[150]

Rationalizing on the prior observations we are prone to consider that the formation of both diastereomers occurs during the chloride displacement step and not in the oxidation one. Indeed agreeing with it is the fact that no matter the protection on the ferrocene oxazaphospholidine, BH_3, S or O, both epimers have been isolated. In addition protection with octatomic sulphur[190] and with boranes[191] is also considered to occur with retention of configuration. The early mentioned borane case corroborates this conclusion as well.

It is not clear whether the changes in the product ratio are caused by the variation on the reagents concentration, on the reaction temperature during the addition of nucleophile to the chloride, or even on the reaction time length. However it seems rather possible that these factors may play an important role in the reaction. Indeed on several reactions that we performed for the formation of our ferrocenyl oxazaphospholidine oxide products, we observed an inadvertently variation on the **31** to **81** ratio**,** *R*-FcP(O)Eph/*S*-FcP(O)Eph. This ratio ranging from 4:1 to 1:3, with overall yields varying from 40% to 75% normally close to 60%, supposedly limited by the formation of ferrocene lithium as the consistent recovery of ferrocene suggests.

2.4.3.1.2.2 *Testing the effect of temperature on the 31 to 81 ratio*

In order to clarify whether the temperature would have any influence in the epimers ratio a simple experiment was conducted. Accordingly with the aforementioned procedure the ferrocene lithium slurry and the oxazaphospholidine chloride solution were prepared. Each was equally divided into two different Schlenk tubes so as to make sure the concentrations would be identical. The reaction time length was also controlled to be identical. Although in both experiments the FcLi slurry was cooled to -78ºC only one of the chloride solutions (I) was cooled, first in an ice bath for 30 minutes and after that in a dry ice/acetone bath for 2h30. The FcLi slurry was transferred to the chloride solution, the bath being kept during and after the addition and the resulting mixture allowed reaching R.T. overnight. The other chloride solution (II) was allowed to stir at room temperature for 3 h before the FcLi would be transferred to it and kept without any bath overnight. Both mixtures were simultaneously cooled with ice baths and the products submitted to oxidation with BuOOH.

TLC and ^{31}P NMR analysis of the reaction mixtures before oxidation revealed the presence of three predominant compounds at (A) 156.8, (B) 144.6 and (C) 137.2 ppm. The two first compounds allegedly are the precursors to compounds **81** and **31** respectively, i.e., the free oxazaphosphilidines.[188,193] The third one probably is derived from the chloride which being added in excess, 1.5 folds relatively to the ferrocene, could not be detected at this stage of the reaction. In experiment I the B:A ratio was 5:3 and in experiment II 3:4. After oxidation again three predominant compounds were present this time at 41.2, 38.2 and 17.0 ppm. In this case the two first compounds correspond to products **31** and **81** respectively while the one at 17.0 is probably related with the compound at 137.2 ppm in the non-oxidized mixture. In experiment I the **31**:**81** ratio was 5:3 and in experiment II 2:3. After work-up and purification the overall yields to both experiments were 65 and 62% and the correspondent **31**:**81** ratios were 5:2 and 2:3.

It would have been also interesting to have a third reaction without cooling the FcLi slurry neither the oxazaphospholidine chloride solution. However the conducted experiment agrees with the formation of the P-epimers pair prior to oxidation. In truth both are present at that first stage with their ratio not changing significantly after oxidation. The suggestion that temperature influences the diastereomers ratio is also corroborated. Higher temperature seems to favour the formation of compound **81** while compound **31** is the major product at lower temperature. Considering how the previous results may be reasoned through, three possibilities come to our mind:

a) The first crucial exocyclic nucleophilic chloride displacement step occurs in a non-diastereoselective fashion with the epimers ratio depending on the temperature. Possibly more of the kinetic product is produced at lower temperatures and more of the thermodynamic one at higher temperatures, when more energy is available to overcome the higher energy barrier demanded in the formation of this last epimer;

b) The chloride displacement is diastereoselective however the product undergoes epimerization via reaction equilibrating prior to the oxidation step or even the starting chloride undergoes epimerization;

c) The displacement reaction is non-diastereoselective and the starting material and/or products undergo epimerization.

In the three hypothetical cases temperature is expected to play a role.

2.4.3.1.2.3 *Mechanistic considerations*

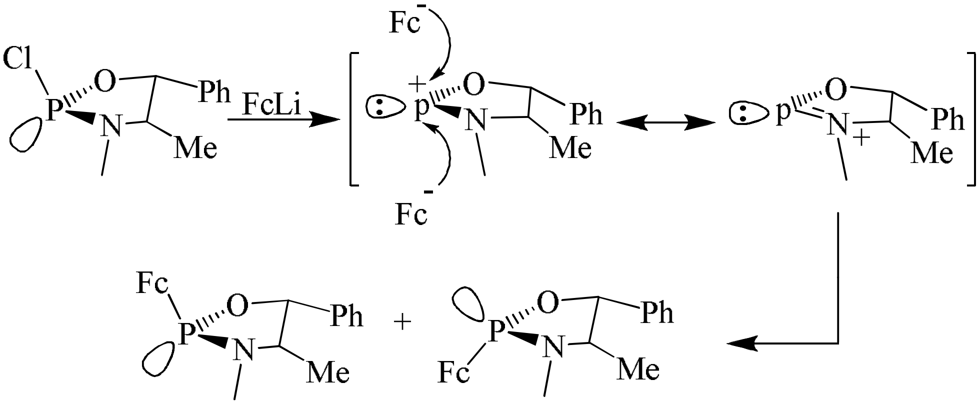
As aforementioned, chloride displacement in oxazaphospholidines has been reported to undergo with overall retention of configuration. Nevertheless per se this statement does not reveals if the actual displacement step occurs or not diastereoselectively with retention or inversion of configuration. Also not clear is the question whether if epimerization via reaction equilibrating is involved or not. In one hand high energy barriers are required for the inversion of tertiary phosphines.[192,194] On another hand under specific reaction conditions epimerization can be accelerated. Namely involving the presence of nucleophilic impurities, such as water, alcohols, amines, and others, or the presence of acids.[192,193] This has in fact been the case with several oxazaphospholidine compounds that have proved to undergo epimerization by reaction equilibrating.[150,183,187,192,193] An example is the previously stated oxazaphospholidine chloride **80** and its *o*-methoxyphenyl derivative.[150] Another instance is the phenyl analogous compound which during its formation both cis and trans isomers, at 152.9 ppm and 139.3 ppm, are present in a 1:1 ratio. Prior to oxidation and after equilibrating for about one day, again almost only the trans isomer remained.[183,187] The same type of behaviour occurs with the oxazaphospholidine phosphoryl chloride analogous compound to **80**. What's more, interestingly when formed in the presence of pyridine the trans isomer is the major one whereas if the base is triethylamine the cis isomer becomes the major one, 10:1.[193]

Mechanistically speaking inversion of configuration must be involved at some stage. Either the loss of diastereoselectivity is due to reagents or products nucleophile catalyzed epimerization, or by a non-diastereoselective nucleophilic displacement step. A possible explanation for inversion of configuration to occur is through a ring opening pathway. For instance acid catalysed inversion of configuration, involving ring opening in the oxazaphospholidine series, has been observed.[195] Also nucleophile catalysed inversion of configuration has been suggested to undergo via ring opening.[193]

Interestingly enough, ring opening has been reported during the process of chloride exocyclic nucleophilic displacement at compound **80**. In a case involving $LiN(SiMe_3)_2$, the nucleophile attack produced around 20% of a by-product in which the ring was opened and the chloride still remained in the structure.[180] In a somewhat similar way during the formation of **31** the ring was opened and the diferrocenyl derivative would be formed in 23% yield. This occurred when the amount of **80** was in a lower proportion, 1:1 in regards to FcLi.[103] However in both this cases the major product revealed retention of configuration.[103,180]

Another possible mechanism that could explain how inversion of configuration occurs to some extent is the dissociation of chloride at compound **80**, *R*-ClPEph, with the formation of a phosphenium ion.[103] The presence of lithium, a Lewis acid, could facilitate chloride dissociation. The phosphenium ion formed could then be stabilized by the presence of the ring nitrogen atom able to disperse the positive charge by resonance.[103,196] It has been suggested that the nucleophilic attack at this ion would preferentially occur trans to the methyl and phenyl ring substituents, leading to retention of configuration.[103] In spite of this one asks itself if rising the reaction temperature would be sufficient to significantly increase the proportion of the cis isomer which apparently would implicate higher energy barrier to be formed. The above possibility is depicted in the **Scheme** below.

Scheme 21 - Synthesis of ferrocenyl oxazaphospholidine oxide via the formation of a phosphenium ion and its subsequent nucleophilic attack trans and cis to the ring methyl and phenyl groups.



Finally with regards to a retention of configuration scenario, the lowest energy pathway for such a direct exocyclic displacement at the phosphorus would be the adjacent mechanism involving a pseudorotation step.[193,195,197]

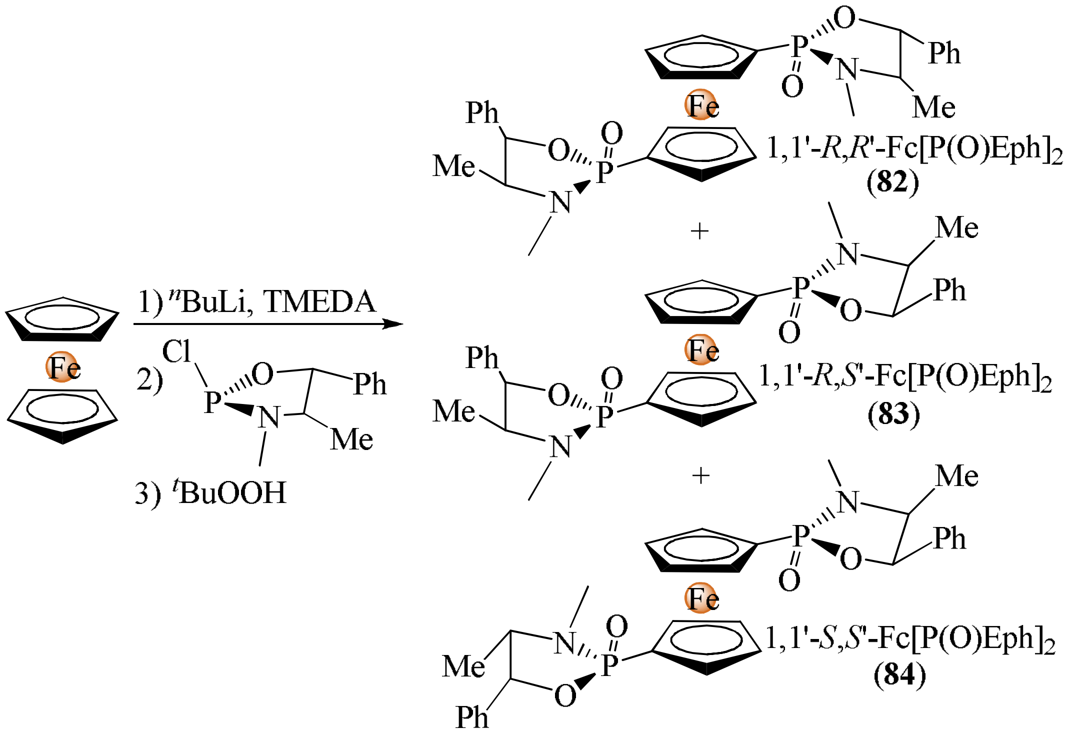
In reality, in a fivemembered ring, such as the oxazaphospholidine one, the factors that determine whether exocyclic displacement will occur with retention or inversion of configuration at phosphorus are complex.[195] In our case one was only able to conclude in which step the loss of diastereoselectivity was occurring, and to notice the effect of temperature in the reaction. A more detailed study needs to be done in order to bring more insight to the matter and to seek a way to control diastereoselectivity. The configurational stability of reagents and products should be verified having into account that during the displacement reaction, bases like ^{t}BuOK and ^{t}BuLi are present, leading to the formation of LiCl and KCl salts. Possibly even some residual morpholine or the corresponding hydrochloride salt from the chloride **80** solution could influence the reaction. Thus extended ^{31}P NMR monitoring of reagents and products in the presence of such salts, bases and acids could be done. The displacement reaction should also be investigated via ^{31}P NMR monitoring. The effect of the reaction time length and the reagents concentrations could also be considered.

2.4.3.1.3 1,1’-Disubstituted ferrocenes

The best known ferrocene ligand, dppf or 1,1’-bisdiphenylphosphino ferrocene, was first synthesized in 1965 via dilithiation of ferrocene with ^{n}BuLi followed by reaction with $ClPPh_2$.[35] Since then many ferrocenyl ligands bearing substituents at both Cp rings have been synthesized both chiral and achiral, the former ones providing interesting motifs for asymmetric catalysis. Effectively Hayashi, Ito, Ahn, Ikeda and more recently Knochel have reported relevant work on such ligands, especially C_2-symmetric ones.[35,61]

Accordingly, we investigated on whether our methodology for the synthesis of compounds **31** and **81,** *R*-FcP(O)Eph and *S*-FcP(O)Eph, could be adapted for the synthesis of the correspondent 1,1’-disubstituted compounds. For this we endeavoured into the application of chloride displacement on compound **80** by 1,1’-dilithium ferrocene. Hence dilithiation of ferrocene was achieved with ^{n}BuLi in the presence of TMEDA in dry hexane at room temperature. After 6 hours the resulting orange mixture was added to a solution of oxazaphospholidine chloride in dry THF at 0ºC, slowly warming to R.T. and stirring overnight. The mixture was cooled again to 0ºC and the products oxidized with ^{t}BuOOH in a similar manner as in the monosubstituted compounds’ synthesis. Work up and flash chromatography purification afforded the products as a mixture of three different diastereomers in 63% overall yield. Some ferrocene and the monolithiated products were obtained as well. A ^{31}P NMR of the mixture prior to oxidation revealed the presence of two major peaks at 144.6 and 144.5 ppm and two minor ones at 158.0 and 156.8 ppm. After oxidation there were two major peaks at 39.9 and 36.6 ppm and two minor ones at 40.1 and 38.0 ppm. As one could expect to be possible, from the synthesis of compounds **31** and **81**, three compounds appeared to be formed, namely, 1,1'-bis((2R,2R',4R,4R',5S,5S')-3,4-dimethyl-5-phenyl-[1,3,2]-oxazaphospholidin-2-oxide-2-yl)ferrocene **82**, 1,1'-bis((2S,2R',4R,4R',5S,5S')-3,4-dimethyl-5-phenyl-[1,3,2]-oxazaphospholidin-2-yl-2-oxide)ferrocene **83** and 1,1'-bis((2S,2S',4R,4R',5S,5S')-3,4-dimethyl-5-phenyl-[1,3,2]-oxazaphospholidin-2-yl-2-oxide)ferrocene **84**, accordingly with **Scheme** 22.

Scheme 22 - Dilithiation of ferrocene and quenching with oxazaphospholidine chloride to afford 1,1'-bissubstituted ferrocenyl oxazaphospholidine oxides.



Being the less polar amongst the three, isolation and characterization of compound **82,** 1,1'-*R*,*R*'-Fc[P(O)Eph]$_2$, was facilitated.

2.4.3.1.3.1 *NMR data*

^{1}H NMR confirmed that both Cp rings were substituted by the same group, the oxazaphospholidine ring with *R* configuration at the phosphorus. In detail this was concluded by the presence of four peaks between 4.8 to 4.5 ppm, roughly with the same intensity and corresponding to two peaks for each substituted Cp ring. Also in agreement is the presence of only one CHPh peak, a triplet at 5.3 ppm, together with a single peak at 38.6 ppm in the ^{31}P NMR. This is consistent with the equally 1,1'-disubstituted ferrocenyl compound in which the phosphorus lone electrons pair is *syn* relatively to the ring CHPh proton, facilitating P-H coupling. As well the P=O is *anti* to the same proton reason why it is at higher field. The majority of the following fractions revealed the presence of two compounds, **82** and **83**, 1,1'-*R*,*R*'-Fc[P(O)Eph]$_2$ and 1,1'-*R*,*S*'-Fc[P(O)Eph]$_2$. The last compound augmented in proportion at each new fraction and vice-versa. ^{1}H NMR from these mixtures revealed three peaks corresponding to the ring CHPh, namely, a doublet at 5.9 ppm, and two triplets at 5.6 and 5.3 ppm. Based on the chemical shift and on the multiplicity the first peak is believed to belong to an oxazaphospholidine ring presenting *S* configuration at the phosphorus atom, while the others are typical of *R* configuration. The first two oxazaphospholidine rings supposedly belong to one same compound, **83**. In this the CHPh proton from the peak at 5.6 ppm is deshielded relatively to the one in compound **82**, 5.3 ppm. This is probably due to non-bonding interactions with the other oxazaphospholidine group present in the same molecule. The other peak at 5.3 ppm indicates the presence of **82** in the mixture. All the other ^{1}H NMR peaks, related with the Cp ring protons, the CHMe and NMe groups, matched with our conclusion. ^{31}P NMR displayed two peaks at 38.8 and 35.2 ppm, the first corresponding to the oxazaphospholidine ring with *R* configuration present in both compounds and the last one, being present in compound **83** only. Finally ^{1}H and ^{31}P NMR data from two last fractions was also in accordance with the formation of **84**. Elemental and mass analysis corroborated our conclusions regarding compounds **82**, **83** and **84**.

2.4.3.2 *Ortho*-Lithiation

As aforementioned the diastereoselective deprotonation and functionalization of ferrocenyl oxazaphospholidine oxide **31**, *R*-FcP(O)Eph, has been considered, studied and shown successful. It allows high diastereoselectivity, >99%, with good to high yields and application to a series of substituents. Nevertheless for each substituent only one product with one planar chiral configuration could be prepared, normally R_p configuration depending on the substituent priority regarding the oxazaphospholidine moiety.[103]

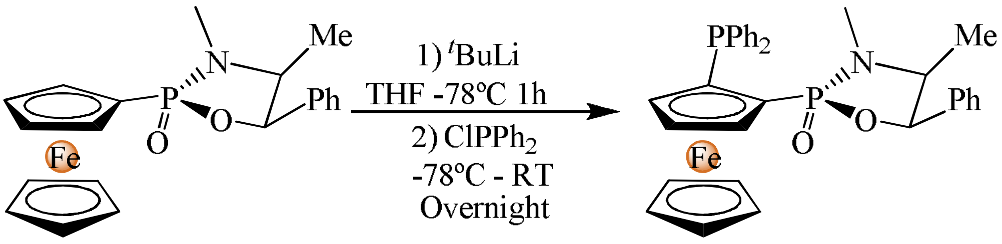
2.4.3.2.1 Performing a first test

Supposedly one of the advantages of obtaining two P-epimers, **31** and **81**, as the outcome of our methodology for the synthesis of ferrocenyl oxazaphospholidine oxide is that the new epimer, **81**, *S*-FcP(O)Eph, should solve the problem. Specifically it should lead to the formation of derivatives similar to those obtained from **31**, however with opposite planar chirality. Hence, we explored the behaviour of our new epimer under the same set of conditions previously used.[103,173] This was done bearing in mind the somewhat different chemical environment that this compound encloses, for instance a more acidic CHPh ring proton. As a matter of fact the presence of acidic protons in a supposedly potential CDG has been reported as leading to unexpected reactions before.[199] Such was also the case with an imidazoline containing a CHPh carbon.[200]

To fulfil our purpose a THF solution of **81** was cooled to -78ºC for 30 minutes before 1.45 equivalents of ^{t}BuLi was added and, at that same temperature, the reaction stirred for another hour. 1.50 equivalents of electrophile, chlorodiphenylphosphine, were then added followed by overnight stirring at room temperature. TLC analysis of the reaction mixture revealed the presence of a new compound. Work-up and flash chromatography purification afforded the pure product **85**, 1,2-*S*,S_p-Fc[P(O)Eph](PPh$_2$), as an orange solid with 61% yield.

^{1}H and ^{31}P NMR analysis of the product was in accordance with the expected product showing high diastereoselectivity, >99%. All the peaks corresponding to the ephedrine were present although with some deviations regarding their original chemical shift in compound **81**, *S*-FcP(O)Eph, possibly due to non-bonding interactions caused by the new *ortho*-substituent. Also the peaks from the substituted Cp ring suggested that indeed the lithiation and functionalization had occurred at that Cp ring and not in the oxazaphospholidine ring. This attests to an effective stabilization of the lithium compound at that position. The proportion between the ring CHPh proton and the Ph protons was now approximately 1:15 instead of the previous 1:5 proportion. Finally two distinct phosphorus atoms were now present, the original one at 35.9 ppm and the new one at -19.8 ppm. This last chemical shift is typical of free tertiary phosphines as the one expected. Elemental and mass analyses were also in agreement with the product on the next reaction **Scheme**.

Scheme 23 - Diastereoselective *ortho*-lithiation of ferrocenyl oxazaphospholidine oxide **81**.

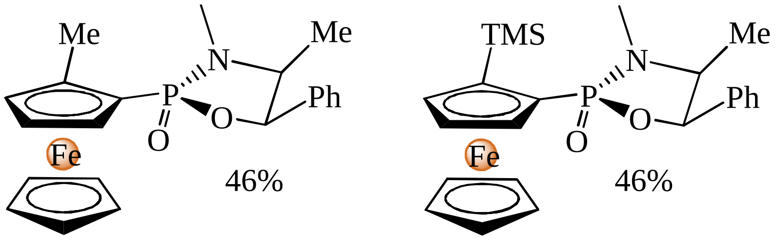


(81)

(85)
1,2-S,S_p-Fc[P(O)Eph](PPh$_2$)

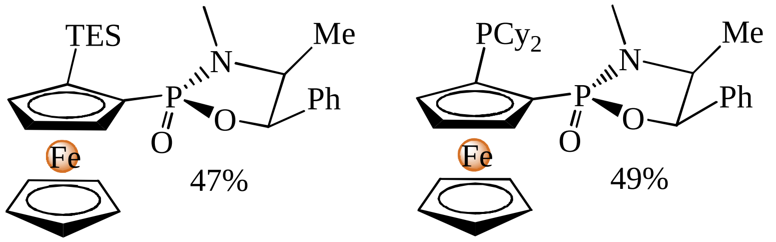
2.4.3.2.2 Checking on the reaction range

Motivated by this good result we decided to try the reaction with a few more electrophiles. Namely methyl iodide (MeI), trimethylsilane chloride (ClTMS), triethylsilane chloride (ClTES) and chlorodicyclohexylphosphine (ClPCy$_2$) were used according with **Figure** 14.



(86)
1,2-S,S_p-Fc[P(O)Eph](Me)

(87)
1,2-S,S_p-Fc[P(O)Eph](TMS)



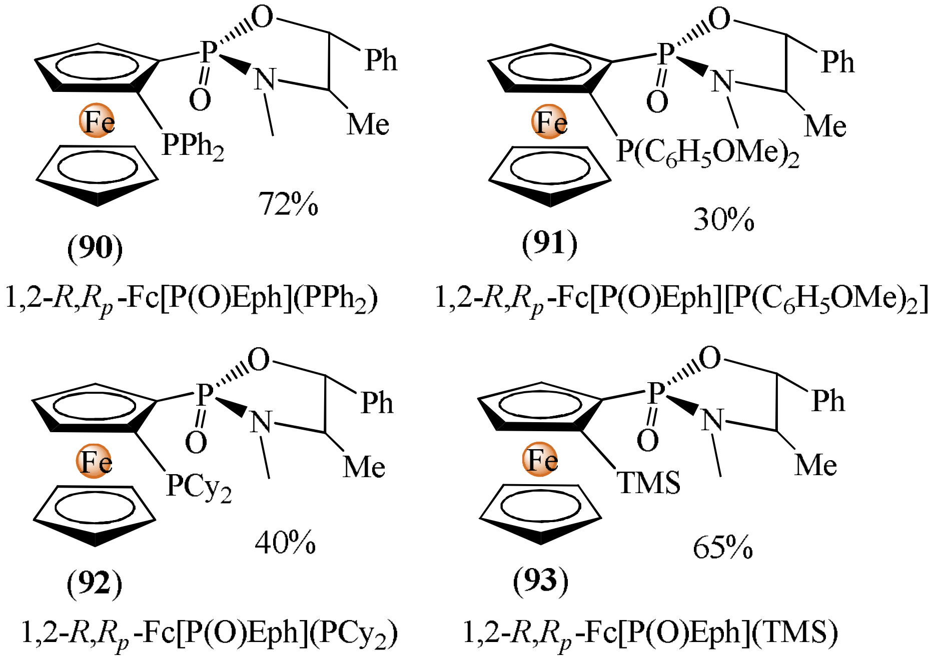
(88)
1,2-S,S_p-Fc[P(O)Eph](TES)

(89)
1,2-S,S_p-Fc[P(O)Eph](PCy$_2$)

Figure 14 - New planar chiral ferrocenes prepared via *ortho*-lithiation and functionalization of **81**.

In the same manner as with compound **85** all the analyses data, NMR, elemental and mass, were in agreement with successful diastereoselective *ortho*-lithiation and functionalization, by quenching with the respective electrophile. Indeed the technique's wide tolerance and applicability is confirmed.

In parallel to the new compounds mentioned above, derivatives from compound **31**, *R*-FcP(O)Eph, were also synthesized. Their analyses were in agreement with the literature[103,173] revealing that the methodology is reproducible. Chloro-bis(4-methoxyphenyl)phosphine ($ClP(C_6H_4OMe\text{-}o)_2$), necessary for the synthesis of compound **91**, was also prepared. The derivatives mentioned above are presented in **Figure** 15.



(90) 1,2-R,R_p-Fc[P(O)Eph](PPh_2)

(91) 1,2-R,R_p-Fc[P(O)Eph][$P(C_6H_5OMe)_2$]

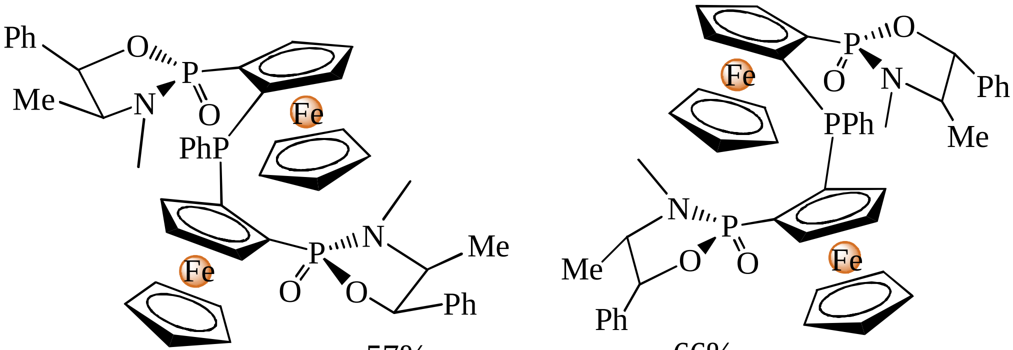
(92) 1,2-R,R_p-Fc[P(O)Eph](PCy_2)

(93) 1,2-R,R_p-Fc[P(O)Eph](TMS)

Figure 15 - Planar chiral ferrocenes prepared via *ortho*-lithiation/functionalization of compound **31**.

2.4.3.2.3 Synthesizing diferrocenyl derivatives

In addition to the previous examples we tested the possibility of using a phosphine dichloride as the electrophile, in order to form the corresponding diferrocenyl compounds. Besides compound **81** this reaction had not been tried with **31** as well. Thus we separately reacted both compounds with ^{t}BuLi and quenched the resultant lithiated species with dichlorophenylphosphine. As presented in the next **Figure**, compounds **94** and **95** were respectively afforded, 1,2-*S*,S_p-$[FcP(O)Eph]_2(PPh)$ and 1,2-*R*,R_p-$[FcP(O)Eph]_2(PPh)$.



57%

(94)

1,2-*S*,S_p-$[FcP(O)Eph]_2(PPh)$

66%

(95)

1,2-*R*,R_p-$[FcP(O)Eph]_2(PPh)$

Figure 16 - New planar chiral ferrocenes prepared via *ortho*-lithiation of **81** and **31** followed by functionalization with Cl_2PPh.

As one would expect it to be possible steric hindrance partially affected the outcome during formation of **94**, as a monoferrocenyl by-product was formed. Although we could not separate it from **94**, based on NMR and mass analysis we are prone to believe that it was formed by substitution of only one chloride at the free phosphine. During work-up the other chloride atom would subsequently undergo hydrolysis. On the other hand ^{1}H NMR of pure **94** does shows the presence of two ferrocenyl oxazaphospholidine substituents. In virtue of the molecule's spatial arrangement these two groups show to be in a dissimilar chemical environment. For instance two characteristic CHPh doublets were present at 5.89 and 5.75 ppm. Two sets of the substituted and non-substituted Cp protons were also present. Finally two CHMe groups and, with the biggest difference in chemical shift, two NMe groups at 3.07 and 1.89 ppm were present. In addition the ^{31}P NMR spectrum revealed the presence of two distinct oxazaphospholidine ring phosphorus atoms at 38.8 and 35.9 ppm. The spectrum showed also the high field free phosphine peak at -37.2 ppm. The same observations could be done regarding compound **95**. In this compound, besides experiencing coupling within the oxazaphospholidine ring the CHPh proton also seems to couple with the free phosphine. When compared with compound **90**, 1,2-*R*,R_p-Fc[P(O)Eph](PPh_2), instead of having two triplets (dd) in **95** we have two well separated multiplets at 6.30 and 4.92 ppm. On the other hand contrary to compound **94,** in this case the shift difference between the two NMe groups is inferior, 3.07 and 2.23 ppm. Again three phosphorus peaks were present at 39.8, 38.3, and -38.4 ppm. Proton decoupled $^{[H]}$ ^{31}P NMR analysis was done to confirm whether the two close peaks belong to two different oxazaphospholidines instead of only one phosphorus attached to a proton. Mass and elemental analyses of compounds **94** and **95** corroborated the presented structures.

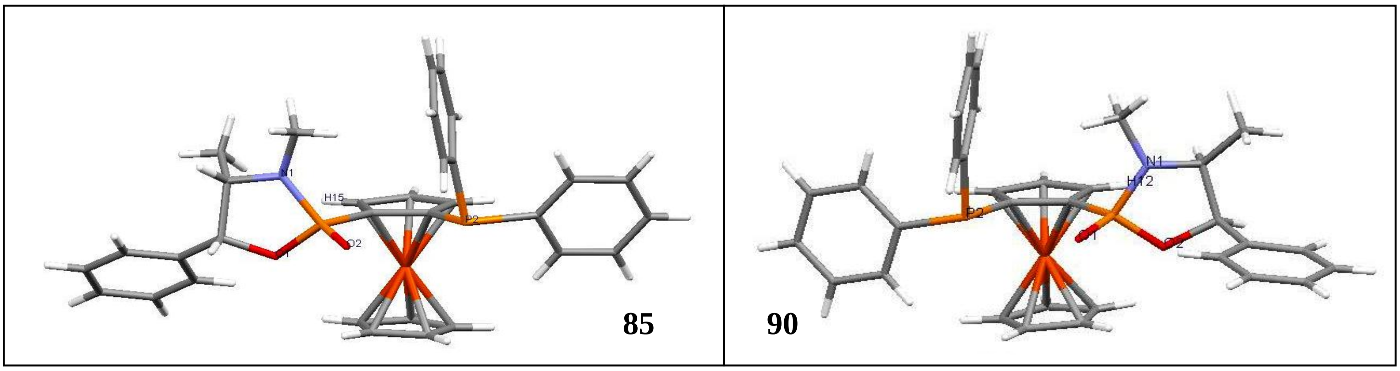
Cyclohexyldichlorophosphine (Cl_2PCy) was prepared and used for the synthesis of cyclohexyl analogues to **94** and **95**. Products separation and purification from the crude mixture revealed itself to be troublesome. However the same NMR patterns as for compounds **94** and **95** were noticed. For instance the analogue compound to **92**, 1,2-*R*,R_p-Fc[P(O)Eph](PCy_2), presented a very similar ^{1}H NMR, apart from the cyclohexyl protons. Three major peaks were also detected in the ^{31}P NMR spectrum at 41.0, 36.4 and -33.2 ppm.

2.4.3.2.4 On the *ortho*-lithiation diastereoselectivity

At this point it was established that compound **81,** *S*-FcP(O)Eph, could successfully undergo diastereoselective deprotonation/functionalization.

2.4.3.2.4.1 *Checking the configuration at the chiral center*

Since compounds **81** and **31** have opposite configuration, at the phosphorus, then we expected them to also direct lithiation in a manner that would bring forth derivatives with opposite planar configuration. To confirm this assumption, crystals of some of the synthesized compounds were grown and analysed by X-ray diffraction techniques. In the following **Figure** we may compare the X-ray structures of two diastereomers, respectively compound **85** and its analogue **90**, 1,2-S,S_p-Fc[P(O)Eph](PPh_2) and 1,2-R,R_p-Fc[P(O)Eph](PPh_2).



85 **90**

Figure 17 - X-ray structures Mercury views of compounds **85** and its analogue compound **90**.

As it becomes clear both the phosphorus chiral center and the chiral plane have opposite configurations, namely (S,S_p) in compound **85** and (R,R_p) in compound **90**. This shows that lithiation at compound **81** was indeed *ortho*-directed and diastereoselective thus complementing the previously achieved work with compound **31**. The synthesis of 1,2-disubstituted ferrocenyl oxazaphospholidine oxide derivatives, was now able to be separately prepared with both planar chiral configurations.

2.4.3.2.4.2 *Lithium stabilization*

High diastereoselective lithiation/functionalization implies diastereoselective lithiation. In its turn this involves formation of only one main lithiated species, which more likely is the most stable one. The stability of such species is thought as being related to lithium coordination with effective binding sites, present in the newly lithiated intermediate.

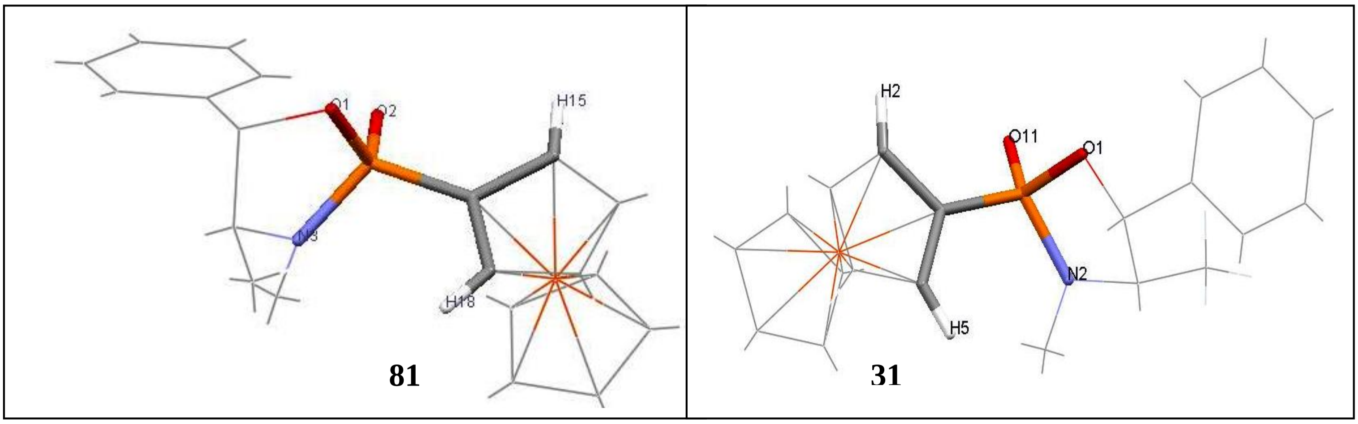
Considering structures **85** and **90**, during the metalation step at least one of three atoms is expected to coordinate and stabilize the incoming lithium atom. The three atoms are one oxygen and one nitrogen in the heterocyclic ring, and another oxygen on the phosphorus oxide (P=O). This last atom is the nearest one to the new substituent group; therefore we would expect it to take the major role in directing the metalation *ortho* to the oxazaphospholidine moiety. The other atoms, if at all participating in stabilizing the lithiated compound, would most likely do it to a minor extent. In fact, as will be discussed in the next chapter, the P=O oxygen atom has been shown able to coordinate to palladium.[198]

Then again, we have mentioned before that chiral *ortho*-directing groups containing nitrogen such as Ugi's amine,[77] oxazolines[80-82] and others[102] are known to induce high diastereoselectivity. Also phosphine oxides are not as effective, especially when lithium compounds are used.[100,166] Plus in the oxazoline ring the nitrogen is believed to be the one to coordinate with the lithium atom, in detriment to the oxygen atom also present in the ring.[74,125] Compared to the systems above ours is a different and somewhat rigid system. Nevertheless one is taken to ponder if the P=O coordination mode considered above could indeed be responsible for the high diastereoselectivity observed with the oxazaphospholidine moiety. Instead another coordination mode may be taking place during the reaction.

2.4.3.2.4.3 *Considerations on X-ray diffraction data*

X-ray structures of compounds **31** and **81**, on **Figures** 10 and 11, compared with the ones from compounds **90** and **85** respectively, show that the oxazaphospholidine moiety position has changed. In the starting materials **31** and **81**, *R*-FcP(O)Eph and *S*-FcP(O)Eph, the oxazaphospholidine ring is positioned in such a way that the nitrogen atom is clearly nearer to one *ortho*-proton on the substituted Cp ring.

In contrast the P=O oxygen atom is nearer to the other *ortho*-proton, as can be better understood from **Figure** 18.



81

31

Figure 18 - Mercury X-ray structures top view of compounds **81** and, its analogue compound, **31** respectively.

Interestingly the position of the mentioned atoms is such that it leads us into thinking that either the nitrogen or the P=O atom is the one ruling the diastereoselectivity outcome of the reaction. The ring oxygen atom is perhaps able to extra-stabilize the lithiated compound but apparently not able to greatly influence in the diastereoselectivity per se. Indeed it lies almost at the same distance from both *ortho*-protons, slightly closer to the one on the nitrogen side.

A careful comparison between each *ortho*-lithiation/functionalization product, **85** and **90**, and its starting material **81** and **31** respectively, shows that in fact the proton undergoing *ipso*-substitution is the one initially closer to the ring nitrogen atom. For instance the H15 proton present in compound **81** remains present in product **85,** while the H18 one has been substituted first by lithium and then by the biphenylphosphine group.

2.4.3.2.4.4 *Nitrogen- versus oxygen-lithium coordination*

The above observations lead us to consider the possibility that the nitrogen atom is indeed directing the *ortho*-metalation step as depicted in **Figure** 19.

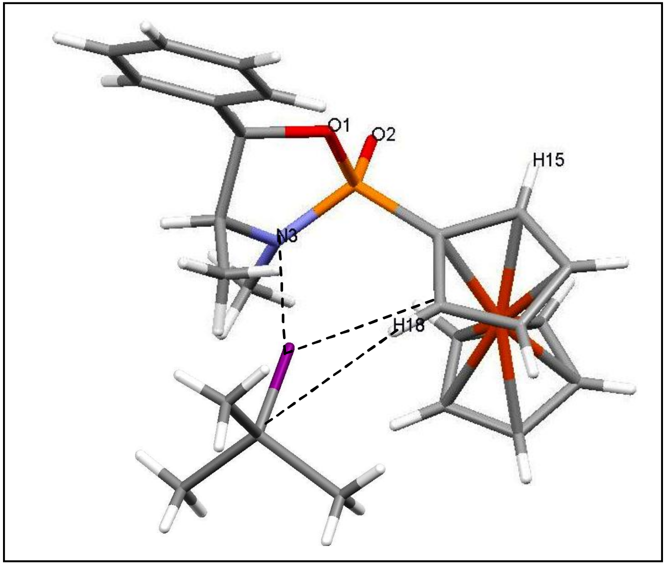


Figure 19 - *Ortho*-lithiation reaction of compound **81** mediated by the oxazaphospholidine nitrogen atom.

Accordingly, in the lithiated species the incoming electrophile would be approached opposite from the oxazaphospholidine ring, which at this stage would rotate approximately 180º. Specifically rotation would occur around the P-C bond between the oxazaphospholidine oxide moiety and the Cp ring, being counter wise to the incoming group. This would result in a more stable less hindered position in the new 1,2-disubstituted derivative, only now bringing the P=O oxygen atom closer to the new substituent.

Nevertheless what seems to be a major factor against this suggestion is the presence of two methyl groups which may cause some steric hindrance and aggravate the lithiating agent approach. In compound **81** one methyl group directly attached to the nitrogen atom may not cause significant steric hindrance since it is pointing away from the ferrocene unit. Nonetheless the other methyl group is pointing up towards to the ferrocene unit, leaving us to question if the remaining space is sufficient to allow the approach of the lithium reagent with the lithium atom closer to the nitrogen one. Alternatively in compound **31** only the nitrogen methyl group is present, pointing slightly towards the ferrocene unit. Interestingly these structural dissimilarities do not seem to affect the diastereoselectivity either suggesting that the lithiation is mediated by the P=O oxygen or that the possible steric constrictions are not significant. In regards to this it is noticeably that the lithiating agent steric bulk does not affect the diastereoselectivity outcome on the lithiation of compound **31**. In reality only the yield is affected due to competitive ring opening.[103,173]

Obviously more information is necessary to define which coordinating mode is indeed occurring. For instance synthesizing and using a derivative for compound **31** and/or **81** in which rotation of the oxazaphospholidine ring is restricted could clarify the matter. Reaction of such a compound with ^{t}BuLi, followed by quenching with a small dimension electrofile like MeI should originate a product in which the Me group would be on the same side as the lithium stabilizing atom. An example of this has previously been presented on page 40 regarding the lithiation/methylation of a macrocyclic ferrocenyl oxazoline.[74,125]

The crystal structure of **87**, 1,2-*S,Sp*-Fc[P(O)Eph](TMS), was also resolved by X-ray diffraction techniques leading to the same types of conclusions as redrawn from its family member **85,** 1,2-*S,Sp*-Fc[P(O)Eph](PPh$_2$). The fact that lithiation occurred in a similar manner as to **85**, with the same regio and diastereoselectivity, suggests that the reaction is wide-ranging. Whichever the coordination mode occurring during the reaction it does not depends so much on the electrophile used. **Figure** 20 presents the mentioned X-ray structure.

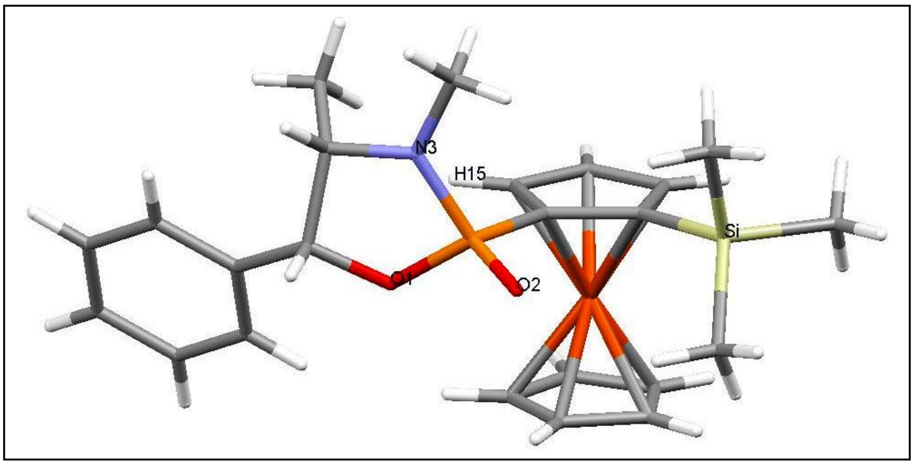


Figure 20 - Mercury X-ray structure view of compound **87**. Selected bond lengths (Å) and angles (deg): P2-O1 1.6054(18), P2-O2 1.465(2), P2-N3 1.649(2), P2-C14 1.778(2), O1-P2-N3 94.61(10), O2-P2-C14 111.96(11), O2-P2-O1 118.39(11), O2-P2-N3, 114.79(12), N3-P2-C14 112.97(12).

2.4.3.2.4.5 *Rotation of the oxazaphospholidine oxide moiety*

One thing that seems to be clear is the fact that at some stage of the reaction rotation of the oxazaphospholidine moiety occurs, around the bond axis between itself and the Cp ring. However one needs to consider that although free rotation is possible it surely implies certain energy barriers to be overcomed. During rotation the molecule inevitably adopts less stable, more energetic configurations, due to steric clashes between the oxazaphospholidine ring substituents and the ferrocene unit. In the solid state the starting materials, assuming the conformations depicted by their resolved X-ray structures, are most likely at a low energy level. However in solution the situation may change, reason why we can not state whether the favoured conformation is closer to the low energy level one or if it assumes a higher energy conformation, closer to the one depicted in the 1,2-dissubstituted derivatives. The first case could favour nitrogen-lithium coordination, whilst the second scenario should favour P=O oxygen coordination with the lithium compound. Molecular mechanic calculations on the energy barriers implicated in this rotation could facilitate the understanding of the reaction, as high energy barriers would apparently favour the nitrogen coordination mode. Also molecular mechanic simulations could bring about some insight as to which lithiated species would be more stable, the one stabilized by oxygen or the one by nitrogen.

2.4.3.2.5 Performing a second lithiation

2.4.3.2.5.1 *Why trying to accomplish a second ortho-lithiation?*

Though such a stereoselectivity level, as ours, surely represents a desirable goal it leaves us with the need to find an alternative for the preparation of the other two possible products. As discussed previously a normally followed approach is based on the protection of the most reactive *ortho* proton, to the CDG. Its substitution with a removable TMS blocking group allows the lithiation/functionalization to proceed at the other *ortho* proton. Then a final deprotection step affords the desired product. Would this method be efficient in our case and instead of only obtaining two diastereomers one would be able to obtain four diastereomers. For instance besides compounds **90** and **85**, 1,2-*R*,*Rp*-Fc[P(O)Eph](PPh_2) and 1,2-*S*,*Sp*-Fc[P(O)Eph](PPh_2) respectively, compounds with (R,S_p) and (S,R_p) configurations would thus be prepared as presented in **Figure** 21.

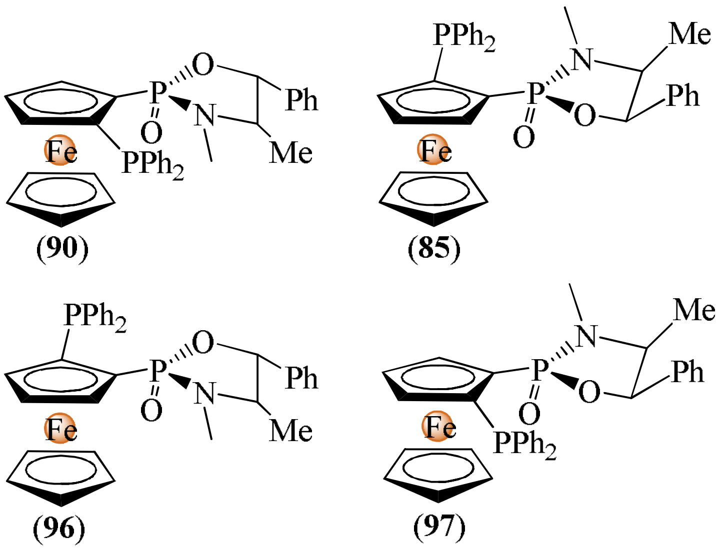


Figure 21 - Four possible diastereomers for (4*S*,5*R*)-3,4-dimethyl-2-diphenyl-phosphanyl-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide.

In reality a synthetic methodology that leads to the formation of such an array of diastereomer ligands, all belonging to the same family but displaying different chirality combinations is of interest. Indeed it raises the possibility of finding an appropriate ligand for a specific reaction, as well as understanding the role of each chiral element in the ligand. By appropriate ligand one means, among other necessary qualities, that all the chiral elements act in a synergistic fashion. In other words all present chiral elements are matched resulting in high stereoselective induction.

2.4.3.2.5.2 *Attempting a second ortho-lithiation*

The aforementioned prospect was tested by separately reacting compounds **87** and **93**, 1,2-*S*,S_p-Fc[P(O)Eph](TMS) and 1,2-*R*,R_p-Fc[P(O)Eph](TMS). First ^{t}BuLi was used followed by $ClPPh_2$ under fairly similar conditions as during the first *ortho*-lithiation/functionalization step. The reaction involving compound **93** led mainly to the starting material recovery, one fraction affording 47% of the pure compound. Other fractions revealed also the formation of different products with several phosphorus peaks appearing in the NMR spectrums. For instance one second major fraction indicated the presence of what could be the desired product with two main phosphorus peaks, at 39.3 and -22.4 ppm. Mass analysis was in agreement with the corresponding oxide, probably due to posterior oxidation of the product. Reaction repetition resulted again mostly in the starting material recovery and in the formation of a mixture of other products.

In stark contrast the reaction outcome with **87** was the formation of a new compound in 90% yield, as the major product. Nonetheless examination of the corresponding ^{1}H and ^{31}P NMR data showed that a different product from the desired one was obtained. Lithiation did not occur at the ferrocene unit, as will be discussed further ahead. In order to find more insight regarding this reaction, we decided to repeat it with two other substrates, namely compound **86**, 1,2-*S*,S_p-Fc[P(O)Eph](Me), and compound **85**, 1,2-*S*,S_p-Fc[P(O)Eph](PPh$_2$). The reaction outcome was similar to the previous one with a major compound being formed and deprotonation again not occurring at the desired proton.

2.4.3.2.5.3 *On the NMR data*

For all the above three compounds the number of phenyl aromatic protons rose, however there were no changes regarding the Cp protons. The CHMe ring proton appeared as no longer being present suggesting that the lithiation occurred at that proton. However a closer analysis to the ^{1}H NMR spectrum revealed that the methyl group next to that proton, CHMe, was still present as a doublet. This led us to realize that, as would be more natural, the lithiation occurred at the more acidic CHPh proton as presented in the **Figure** below.

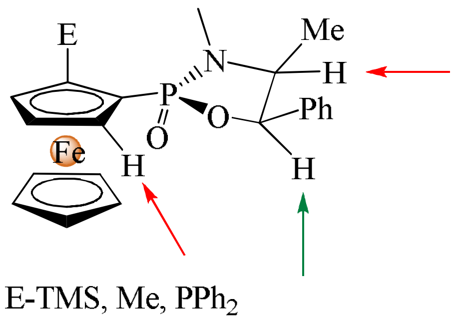
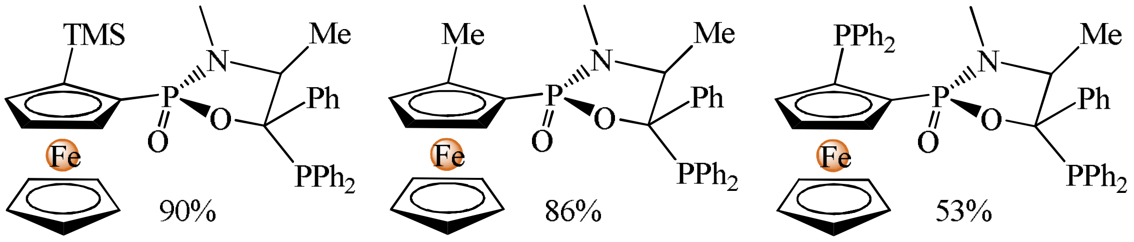


Figure 22 - CHPh proton abstraction/lithiation of 1,2-disubstituted ferrocenyl oxazaphospholidine oxides.

In reality, CHPh proton substitution by a new electrowithdrawing phosphine group caused the neighbour CHMe proton, present as a quadruplet, to become more acidic. Indeed its chemical shift was now almost characteristic of the one observed for the CHPh proton in the starting 1,2-disubstituted materials. Also the CHMe methyl group presented now a higher chemical shift. Coupling between the CHMe proton and the ones from the neighbour Me group was confirmed by their similar coupling constants, J_{HH}=7.2 Hz. A COSY NMR on **85**'s derivative, compound **100**, 1,2-*S*,S_p-Fc[P(O)(Eph'PPh_2)](PPh_2) corroborated the above considerations. The proposed structures for all three products are presented in **Figure** 23.



(98) **(99)** **(100)**

1,2-*S*,S_p-Fc[P(O)(Eph'PPh_2)](E) E-TMS, Me, PPh_2

Figure 23 - Planar chiral ferrocenes prepared via a second lithiation/functionalization step at the oxazaphospholidine CHPh ring proton on compounds **87**, **86** and **85** respectively.

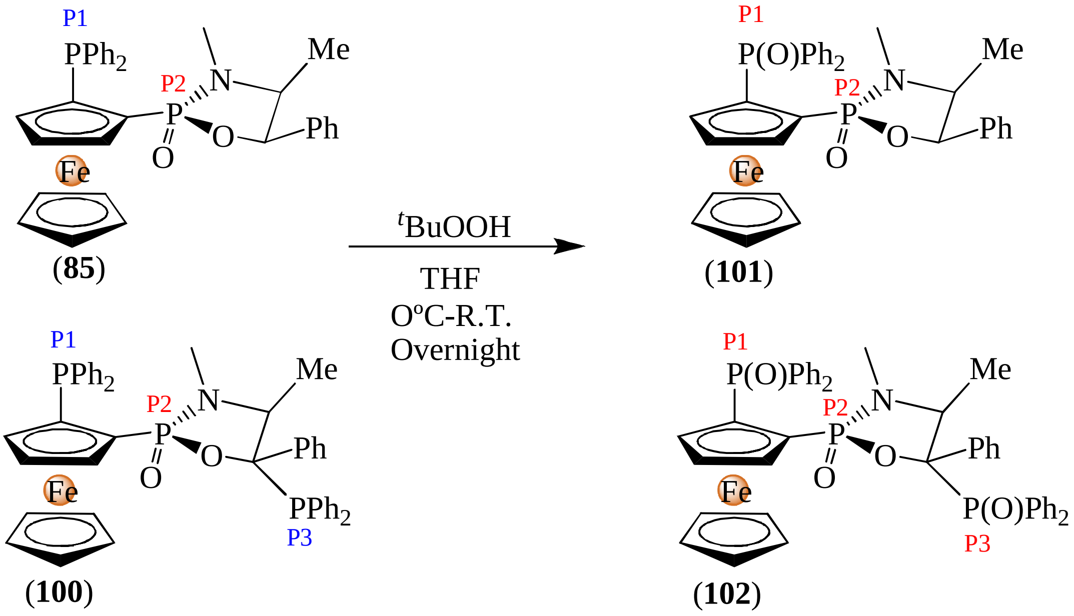
Regarding the ^{31}P NMR data, products **98** and **99**, 1,2-*S*,S_p-Fc[P(O)(Eph'PPh_2)](TMS) and 1,2-*S*,S_p-Fc[P(O)(Eph'PPh_2)](Me), possess two phosphorus atoms displayed as two doublets at 46.4 and 29.3 ppm, and at 48.4 and 30.0 ppm, respectively. This observation suggests coupling between the phosphorus on the oxazaphospholidine oxide and the new phosphorus atom on the PPh_2 group. Compound **100** presents three phosphorus atoms at 47.3, 27.6 and -19.0 ppm. The two first atoms appear also as doublets with very close $^{3}J_{PP}$ coupling constants around 75 Hz once again confirming phosphorus - phosphorus coupling.

2.4.3.2.5.4 *Assigning the chemical shift to each phosphorus*

Just by comparing the chemical shifts from each phosphorus atom we could not clearly indicate which one belonged to the oxazaphospholidine oxide, originally around 40 to 35 ppm. However based on coupling between the oxazaphospholidine oxide phosphorus and the N-Me protons we could assign the chemical shifts for each phosphorus atom. In reality not only the N-Me protons appear as a doublet but also each peak on the P-P doublet, at around 30 to 28 ppm, slightly undergoes splitting in two, due to H-P coupling, $^{3}J_{HP}\approx 10$ Hz. Hence the new phosphorus atom is the one close to 47 ppm while the chemical shift from the oxazaphospholidine oxide phosphorus was changed from around 36 ppm to approximately 29 ppm. In spite of the unusual high chemical shift displayed by the new phosphorus atom, mass and elemental analyses were compliant with the free diphenylphosphine substituted compounds.

Two of these three products were reddish oils, also we were not able to crystallize the solid one and hence to resolve its structure by X-ray diffraction. Therefore we decided to perform a simple experiment in order to double check our conclusions on the products structures. More specifically we oxidized compounds **85** and **100**, 1,2-S,S_p-Fc[P(O)Eph](PPh$_2$) and 1,2-S,S_p-Fc[P(O)(Eph'PPh$_2$)](PPh$_2$), with ^{t}BuOOH in THF first at 0ºC and then at R.T. overnight, as presented in **Scheme** 24.

Scheme 24 - Oxidation of compounds 85 and 100.



According with the **Scheme** above compound **85** with P1 at -19.8 ppm and P2 at 35.9 ppm originated compound **101** presenting P1 at 27.7 ppm and P2 at 34.5 ppm.

Compound **100** displaying three phosphorus, P1, P2 and P3 at -19.0, 27.6, and 47.3 ppm originated product **102** revealing P1, P2 and P3 now at 30.3, 28.9, and 21.1 ppm respectively. These results confirm the previous conclusions on the products chemical shifts. In compound **100** the chemical shift from P3 is relatively high when compared with P1, 47 vs. -19 ppm. However the experiment confirmed both phosphine groups to be free. Actually the chemical shift on P3 decreased upon oxidation, **102**.

2.4.3.2.5.5 *Reasoning on the new phosphorus chemical shift*

At this point we are still faced with the question as to why this new free tertiary phosphine would present such a high chemical shift. Whether this is mostly connected with relatively elevated electronegativity at the $C(PPh_2)Ph$ oxazaphospholidine ring carbon, or if somewhat diamagnetic anisotropy might also be associated is not clear. Regarding the first assumption it is worthwhile to notice that an HMQC NMR on compound **81**, the starting material ferrocenyl oxazaphospholidine oxide, *S*-FcP(O)Eph, shows the CHMe carbon to be at 61 ppm and the CHPh one at 80 ppm. On the other hand in compound **100** the first one is now at 109 ppm and the second, now $C(PPh_2)Ph$, is amongst the aromatic carbons ranging from 126 to 134 ppm. Pertaining to the second possibility we do not discard the likelihood that the oxazaphospholidine ring conformation and the PPh_2 relative position to it may be involved in its particular chemical shift. For instance the phenyl ring, right next to the PPh_2, may influence its chemical shift due to ring-current effect.

2.4.3.2.5.6 *Structure and reactivity*

Comparing the reaction yields for the second lithiation at each one of the 1,2-disubstituted ferrocenyl derivatives, **86**, **87** and **85**, 1,2-*S*,S_p-Fc[P(O)Eph](Me), 1,2-*S*,S_p-Fc[P(O)Eph](TMS) and 1,2-*S*,S_p-Fc[P(O)Eph](PPh_2), we do not observe significant variation between the outcome obtained with a Me and a TMS group. However when the PPh_2 derivative was used the reaction yield decreased. In truth, this reaction led not only to the formation of compound **100**, 1,2-*S*,*S*$_p$-Fc[P(O)(Eph'PPh_2)](PPh_2), but also to the formation of other products. Based on mass and NMR spectrometry these products are believed to be isomers to compound **100**, possibly including the previously desired product. We are not able to ascertain whether lower selectivity was due to higher steric hindrance caused by the bulkier PPh_2 substituent.

At this stage one of the conclusions that we are prone to take is that a second lithiation at 1,2-disubstituted planar chiral derivatives of compounds **31** and **81,** *R*-FcP(O)Eph and *S*-FcP(O)Eph, may proceed through more than one competitive pathway. How to control the reaction outcome and selectivity is a question that requires more investigation. For instance the reaction needs to be investigated regarding different parameters that may impact it. More specifically, solvent, substrate, lithiating agents such as ^{n}BuLi and ^{sec}BuLi or even Grignard reagents, and additives like TMEDA, could be tested. The idea is to better understand the role of steric and electronic factors upon the reactivity and selectivity.

One aspect that is to some extent understandable about the above results is the different reactivity displayed by the planar chiral derivatives of compounds **31** and **81**. Again this is explained on the basis of each one of their structures. As a matter of fact even during the first *ortho*-metalation/functionalization step we have noticed a tendency for the reaction on compound **81** to produce relatively lower yields. The reason behind it is the higher propensity that its 1,2-disubstituted derivatives have to undergo lithiation at the CHPh proton. This does not seems to be only based on higher electronegativity. In fact in these compounds the side of the ring where the CHPh proton is located is the less hindered and the same one of the P=O. This oxygen atom, and even the nitrogen and oxygen on the ring, could play a role on the lithiation at the CHPh proton. A **Figure** of compound **85** clarifies these observations.

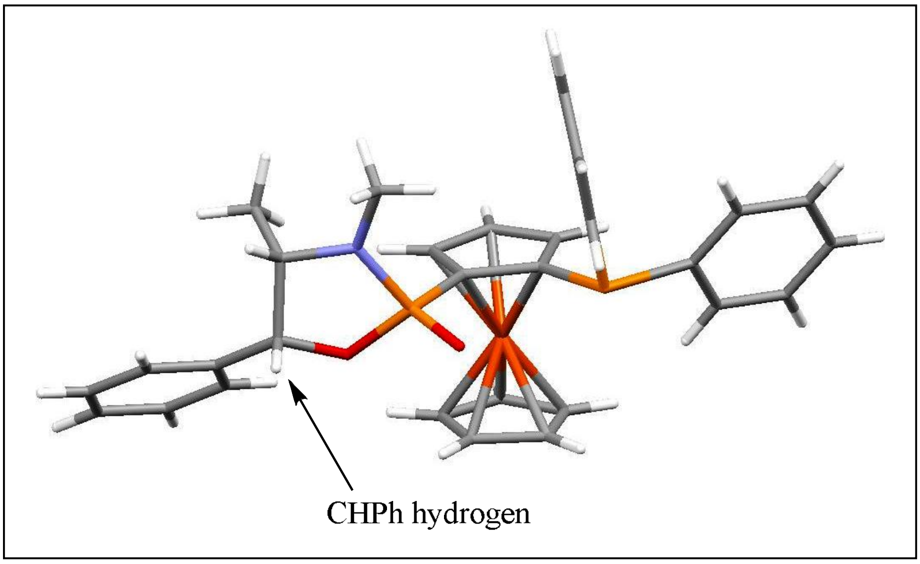


Figure 24 - X-ray structure of compound **85**.

Indeed on every lithiation that we performed on compound **81**, to afford planar chiral ferrocenes, one of the first fractions contained the bislithiated compound. This resulted from lithiation at the substituted Cp ring and at the CHPh proton. For instance the synthesis of product **89**, 1,2-*S*,S_p-Fc[P(O)Eph](PCy_2), also led to formation of the bislithiated by-product as shown by NMR data. Namely ^{1}H NMR shows loss of the CHPh proton and ^{31}P NMR shows three peaks at 59.3, 27.7 and -8.9 ppm. In another case when preparing compound **85**, 1,2-*S*,S_p-Fc[P(O)Eph](PPh_2), we obtained 54% of the desired product together with 25% of compound **100**, 1,2-*S*,S_p-Fc[P(O)(Eph'PPh_2)](PPh_2), 79% overall yield. Clearly the exceeding ^{t}BuLi, 1.45 equivalents, reacts with some of the monolithiated compound. This claims for the need to decrease the amount of ^{t}BuLi used with substrate **81**, *S*-FcP(O)Eph, unveiling the likelihood to increase the yields at the first lithiation/functionalization step.

Regarding compound **31**, *R*-FcP(O)Eph, it can also be affected by CHPh proton abstraction.[103] In fact when compounds **90** and **92**, 1,2-*R*,R_p-Fc[P(O)Eph](PPh_2) and 1,2-*R*,R_p-Fc[P(O)Eph](PCy_2), were reacted with MeLi, in order to cause ring opening, CHPh proton abstraction was probably occurring.[174] However the propensity of CHPh proton abstraction, to occur is lower on **31** derivatives versus **81** ones. Indeed **Figure** 25 unveils that the chemical environment around the CHPh proton on compound **90** does not favour its abstraction so much.

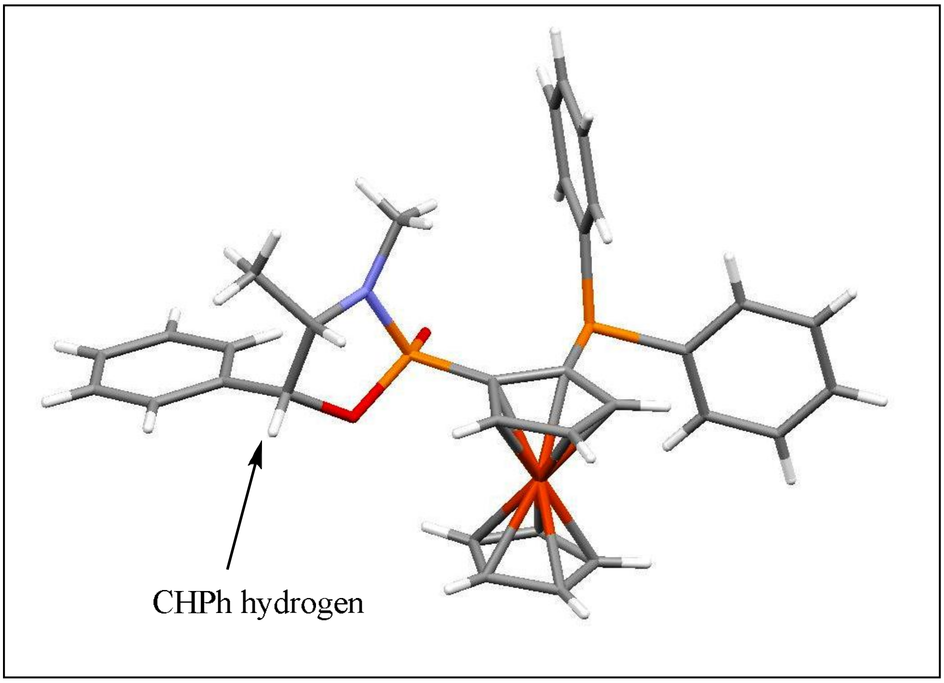


Figure 25 - X-ray structure of compound **90**.

During lithiation of **31** normally higher yields are obtained even with higher quantities of lithiating agent.

Finally lithiation performed at a mixture of compounds **82** and **83**, 1,1'-*R*,*R'*-Fc$[P(O)Eph]_2$ and 1,1'-*R*,*S'*-Fc$[P(O)Eph]_2$ seems to corroborate the above observations. Specifically the CHPh ring proton on the oxazaphospholidine ring with *S* configuration is more prone to be lithiated than the one on the *R* isomer.

2.4.3.2.5.7 *Possible solution to achieve a selective second ortho-lithiation*

The above results on the second lithiation of ferrocenyl oxazaphospholidines allowed the synthesis of different unexpected but interesting compounds such as bisphosphine **100**, 1,2-*S*,S_p-Fc[P(O)(Eph'PPh_2)](PPh_2). Even so it is probably possible to further explore the potential of this chiral directing group by performing some structural modifications. For instance the substitution, protection, of the CHMe and CHPh protons by other groups, such as methyl or ethyl, may avoid undesired secondary reactions. Lithiation and functionalization at both *ortho* positions, to the CDG on the ferrocene should then result in the formation of 1,2, and 1,2,3 poly-substituted ferrocenes with diverse planar chirality and central chirality at the phosphoryl atom.

Expectedly the choice of substituent used in the protection of these protons would further change steric, electronic and even stereo properties at the CDG allowing ligand fine tuning according with desired needs. The derivatives proposed above are presented in **Figure** 26.

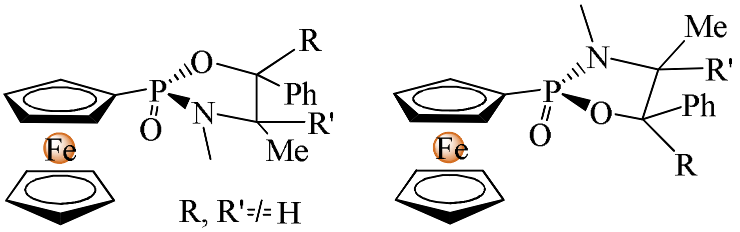
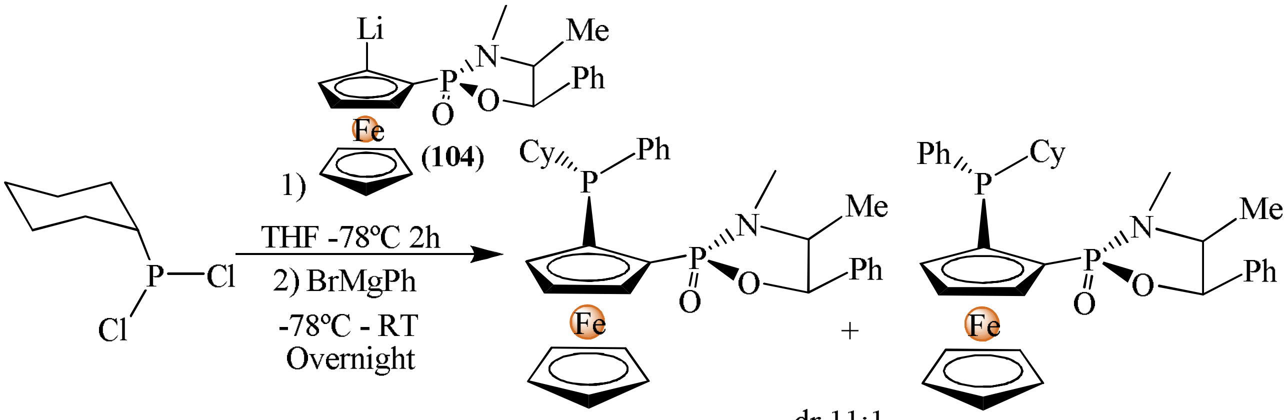


Figure 26 - Representation of ferrocenes presenting a modified oxazaphospholidine oxide CDG relatively to the one in compounds **82** and **83**.

2.4.3.3 P-Chiral Ligands

The potential that P stereogenic ligands may represent has been mentioned. With the purpose to apply our CDG in the synthesis of P-chiral ligands we decided to shortly investigate on its aptitude to induce chirality for the synthesis of such ligands. Hence our *ortho*-lithiation/functionalization technique was adapted with the purpose of building the stereogenic phosphine group in *situ*. Thus compound **81,** *S*-FcP(O)Eph, was lithiated with ^{t}BuLi and added to a dichlorocyclohexylphosphine **103** solution in THF at -78ºC and stirred for about 2h slowly warming to R.T. Parallel to this reaction a solution of phenylmagnesiumbromide in THF was prepared from bromobenzene and magnesium, at 0ºC during addition and then at room temperature during approximately 4h. This was then added to our previous mixture which was again cooled to -78ºC. The mixture was warmed to room temperature overnight before work-up and flash chromatography was performed. The reaction **Scheme** is presented below.

Scheme 25 - Formation of P-chirogenic disubstituted ferrocenyl oxazaphospholidine oxide phosphines via oxazaphospholidine oxide mediated diastereoselective induction – using compound **81**.



(103)

(105)
1,2-S,S_p-Fc[P(O)Eph](PCyPh)

(106)
1,2-S,S_p-Fc[P(O)Eph](PPhCy)

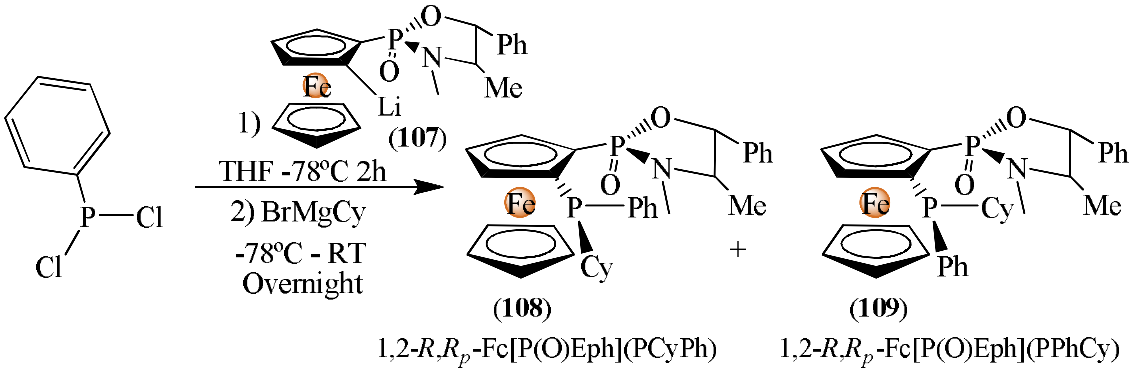
Accordingly to **Scheme** 25, the lithiated ferrocenyl compound was added to the electrophile, and not the inverse. Indeed this last case would imply higher concentration of lithium compound, when compared with the phosphine, leading instead to substitution of both chloride atoms and consequently to the formation of the diferrocenyl product.

A crude ^{31}P NMR unveiled the occurrence of two products, a major and a minor one in an 11 to 1 ratio, represented by four peaks at 36.8, 34.9, -17.5 and -20.6 ppm. Also the ^{1}H NMR presented two distinct CHPh ring protons. Purification of the crude mixture proved to be troublesome, both products having close polarity. However a fraction containing the pure major product **105**, 1,2-*S*,S_p-Fc[P(O)Eph](PCyPh), in 31% yield was isolated, displaying two phosphorus atoms at 36.2 and -16.2 ppm. Other fractions contained more of the major and minor product together. Mass spectrometry and elemental analysis also agreed with the suggested compound.

At this point we still intended to have more data in which to take conclusions regarding the reaction and verify if indeed the previously formed compounds were indeed P-epimers or not. Thus, starting from compound **81** once more we repeated the same procedure only this time using dichlorophenylphosphine and cyclohexylmagnesium bromide (CyMgBr). Both previously mentioned compounds were present yet now with inverted relative abundance. More specifically the major product contained two phosphorus atoms with chemical shifts at 36.1 and -19.9 ppm and the minor one at 36.5 and -16.2 ppm. A fraction of the pure major product **106**, 1,2-*S*,S_p-Fc[P(O)Eph](PPhCy), was isolated in 37.1% yield, mass analysis also agreeing with it being the P-epimer of **105**. In fact compound **105** presents an optical rotation of 60° compared with -220° for diastereomer **106**. This suggests that they have diferent chiral configurations at the free phosphorus atom, however we are not able to assign the respective absolut configuration to each P-epimer, **105** and **106**.

This last reaction was repeated with substrate **31**, *R*-FcP(O)Eph which also led to the formation of two compounds, **108** and **109** in about 78 % overall yield. The major one with phosphorus peaks at 39.0 and -20.5 ppm and the minor at 40.8 and -14.2 ppm. A fraction of the pure main product was isolated in a 18.9 % yield, with all analytical data confirming formation of the expected product **108**, 1,2-*R*,R_p-Fc[P(O)Eph](PCyPh). We believe that also in this case both P-epimers were formed, again with the formation of one being especially favoured. Also in this case we are not able to assign the absolut configuration at the free phosphorus.

Scheme 26 - Formation of P-chirogenic disubstituted ferrocenyl oxazaphospholidine oxide phosphines via oxazaphospholidine oxide mediated diastereoselective induction – using compound **31**.



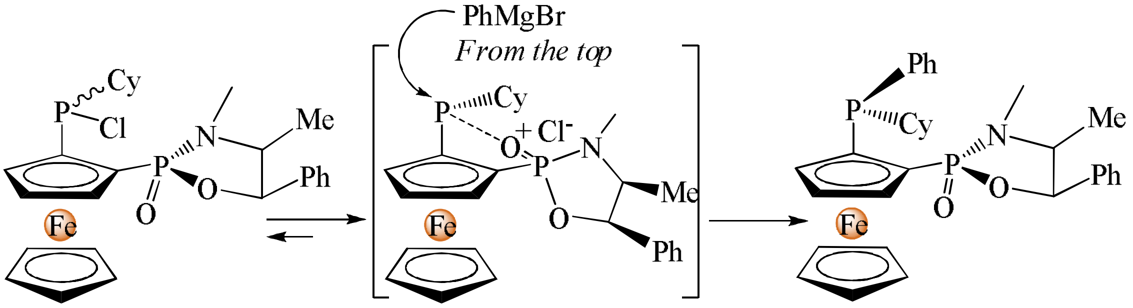
To double check on this, compound **31**, dichlorocyclohexylphosphine and phenylmagnesiumbromide were used in an attempt to synthesize more of the P-epimer to **108**. Sadly the reaction was not sufficiently clean reason why we were not able to isolate the product, only confirm what seems to be the formation of its oxide.

Based on the above observations we are inclined to conclude that in fact the oxazaphospholidine oxide moiety is able to induce diastereoselectivity upon *in situ* formation of a phosphorus chirogenic atom.

2.4.3.3.1 Reasoning on the stereoselectivity induction

Formerly in this chapter we mentioned how Ugi's amine has proved to induce diastereoselectivity in the formation of P-chiral ferrocenyl compounds,[112] the same happening with acetals and taniaphos type compounds.[122] It is therefore not so unscientific to expect a similar behaviour from our CDG, possibly accordingly with the following **Scheme**.

Scheme 27 - Stereocontrolled, oxazaphospholidine oxide induced nucleophilic attack to the phosphine chloride.



(110) **(105)**

As it is suggested, after the first chloride substitution and prior to the second one, the reaction may involve an intermediate formed by Cl$^-$ dissociation in which the phosphenium ion may coordinate to the nearby P=O oxygen. The positive charge can be dispersed by resonance in the oxazaphospholidine ring, especially by the nitrogen atom.

The formation of such a five-membered ring complex would imply restrictive approach orientations for the incoming nucleophilic organometallic therefore favouring the formation of one particular P-epimer. It is also probable that the incoming Grignard reagent would coordinate with the phosphoryl oxygen, thus resulting in an even more restrictive approach. It is possible that in the suggested intermediate the new incoming nucleophilic Grignard reagent would attack the electrophilic phosphorus from the top. This would cause the first substituent at the phosphorus atom, in this case the Cy group, to move further away adopting a somewhat parallel position to the oxazaphospholidine ring pointing away from it. These assumptions are perhaps better perceived on the X-ray structure from compound **85**, 1,2-S,S_p-Fc[P(O)Eph](PPh$_2$), **Figure** 24, page 89.

Even though crystals from compound **105** were grown unfortunately crystal twinning was observed hampering us from confronting our results with crystallographic data. Indeed an X-ray structure was obtained however with poor resolution, reason why we chose not to present it.

2.4.3.4 Reduction of the Oxazaphospholidine Oxide Moiety

Following we will present and discuss on work related with the reduction of the oxazaphospholidine oxide moiety.

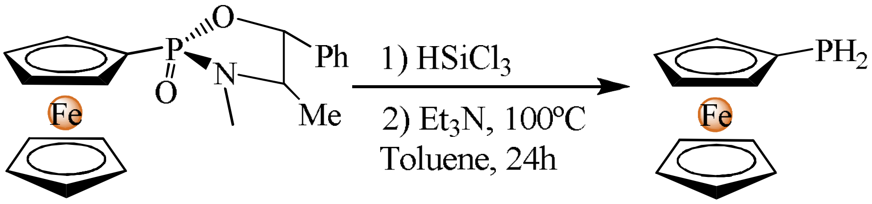
2.4.3.4.1 Reduction of the oxazaphospholidine oxide moiety - what for?

It has been previously stated how the 1,2-disubstituted ferrocenyl oxazaphospholidine oxides failed to produce P-chiral ligands via application of the displacement method.[173,174] The strong P=O bond on the oxazaphospholidine oxide moiety may be responsible for such behaviour, either increasing the steric hindrance around the phosphorus atom and/or causing the P-N and P-O bonds on the ring to be stronger.[174] Therefore it is reasonable to assume that reducing the phosphine oxide into a free phosphine would favour ring opening via nucleophilic attack. Nevertheless an earlier attempt to do so was inconsistent with the envisaged product and more symptomatic of reduction and total removal of the ephedrine fragment giving place to a primary phosphine.[174] Such a result presented itself as a new opportunity in our goal, given that primary phosphines may be used as resourceful starting materials. For instance they have intelligently been explored for the formation of important ligands, namely pseudo P-chiral cyclic electron rich phosphanes,[201-208] phospholanes and phosphetanes, some of which possessing a ferrocene backbone.[209-212]

2.4.3.4.2 Confirming Total Removal of the Ephedrine Fragment

With this background in mind we first started to explore the oxazaphospholidine oxide reduction reaction on compound **31**, *S*-FcP(O)Eph. For that purpose, using Schlenk techniques, trichlorosilane ($HSiCl_3$) was added to a toluene solution of **31** and the mixture allowed stirring for a few minutes before NEt_3 was added. The temperature was raised to 100ºC and the reaction left stirring overnight. The mixture was cooled to R.T., the solvent being evaporated under reduced pressure. Purification was performed by flash chromatography with degassed Et_2O under N_2, however we were not able to isolate the compound in a pure form reason why the yield was not quantified. Nevertheless ^1H NMR analysis of a first fraction did reveal both the presence of the ferrocenyl unit and the absence of the ephedrine moiety with a major high field triplet at -144.2 ppm, J_{PH}=203 Hz. In a proton decoupled NMR this triplet was converted into a singlet, characteristic of a primary phosphine, in this case ferrocenyl phosphine, as depicted in **Scheme** 28.

Scheme 28 - Total reduction of the oxazaphospholidine oxide moiety to afford ferrocenyl phosphine.



(31)

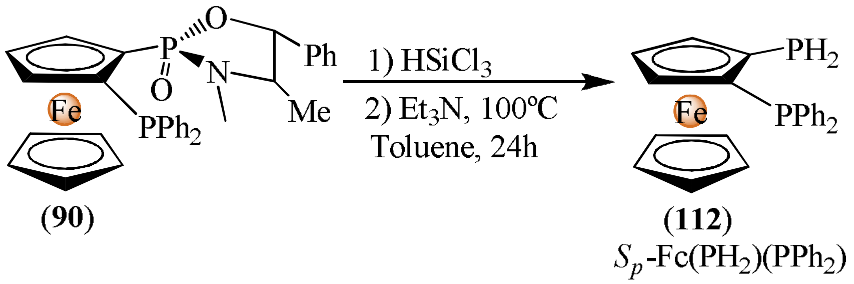
(111)
$FcPH_2$

The ^{31}P NMR data agreed with the literature,[213,214] δ -145.1/-143.3 (t), J_{PH}=203, for compound **111**, $FcPH_2$. Mass spectrometry analysis was also in accordance with formation of ferrocenyl phosphine, although ferrocene was also detected either formed during reaction or probably due to decomposition of the sensitive product during analysis. Two fairly small ^{31}P NMR peaks at ca. -86 and -90 ppm were also present in the mixture.

A second more polar fraction contained a different compound in which the ephedrine fragment could be noticed, at 214.9 ppm. The reaction was repeated with compound **81**, *S*-FcP(O)Eph, under the same set of conditions imparting a similar result.

We then decided to apply the methodology to compound **90**, 1,2-R,R_p-Fc[P(O)Eph](PPh$_2$) which resulted in the formation of **112**, S_p-Fc(PH$_2$)(PPh$_2$), as the major product. The reaction **Scheme** is represented below displaying this important and rather unique planar chiral ferrocenyl primary phosphine **112**.

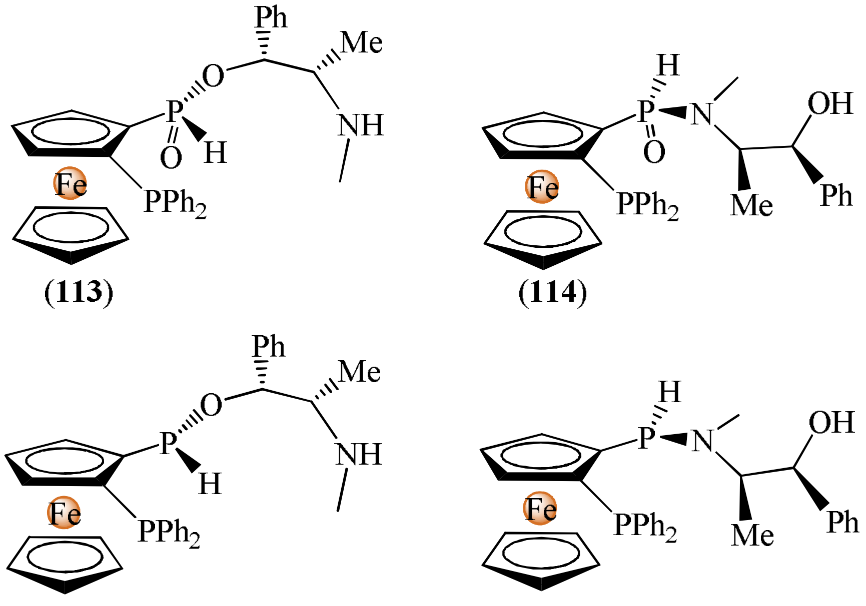
Scheme 29 - Total reduction of the oxazaphospholidine oxide moiety on a planar chiral 1,2-dissubstituted ferrocenyl phosphine to afford a ferrocenyl planar chiral ferrocenyl primary phosphine.



Indeed the main product displayed two phosphorus atoms, one at -19.9 ppm corresponding to the diphenylphosphine group and the other at -150.2 ppm corresponding to the primary phosphine. The two phosphine groups couple with one another, $^{3}J_{PP}$=31 Hz. Besides this coupling, and more importantly, the free phosphine displays coupling with two hydrogen atoms, J_{PH}=204 Hz. We believe such compound has only been previously identified and reported in our group.[174] However our results are also in agreement with the corresponding 1,1' disubstituted ferrocenyl compound, ^{31}P NMR (CDCl3): δ −17.1 ppm (s), −144.6 ppm (t), J_{PH}=204 Hz.[215] Mass spectrometry analysis data of our compound also corroborated the observations made above.

2.4.3.4.3 Drawbacks on the reduction reaction

Besides compound **112** other by-products were formed, the reaction apparently being hindered by the presence of the *ortho*-substituent. The ephedrine fragment occurrence on the ^{1}H NMR spectrum suggests that the other products are intermediates in which its removal was not complete. Probably ring opening may occur either at the P-N or P-O bond resulting in different possible intermediate secondary phosphines which should appear as doublets in the ^{31}P NMR. As a matter of fact four doublets at ca. -38, -91, -102 and -108 ppm were present in the NMR which could correspond to free or oxidized secondary phosphines, as presented in the following **Figure**.



(113) **(114)** **(115)** **(116)**

Figure 28 - Secondary phosphines suspected to occur during reduction of compound **90**, 1,2-*R*,R_p-Fc[P(O)Eph](PPh$_2$).

Repetition of the previous reaction imparted a similar result with isolation of an orange solid in 59.3 % yield.

The observations above mentioned confirmed what had previously been suggested in the group. Namely the oxazaphospholidine oxide moiety can be abstracted from the phosphorus atom attached to the ferrocene unit forming a ferrocenyl primary phosphine. However the methodology was not satisfactory since the reaction was not complete when the disubstituted substrates were used, and in addition low yields were obtained. Indeed the primary phosphines obtained are sensitive to air, leading to formation of the corresponding oxides and phosphinic acids,[214] thus requiring careful handling especially during work-up and purification. These two steps were in fact a hitch for us since it seems rather important to perform them in an adequate form. Product loss and decomposition ought to be minimized at the same time that the product should be pure from by-products, for instance from those containing the ephedrine fragment. As a matter of fact little work, if any, has been done on the reduction of the oxazaphospholidine oxide moiety. Hence we had to turn to and try to explore some of the methodologies and reducing agents that have been used on other phosphine oxides, mostly on acyclic phosphines, and phosphonates.

2.4.3.4.4 Attempting to further explore and improve oxazaphospholidine oxide reduction

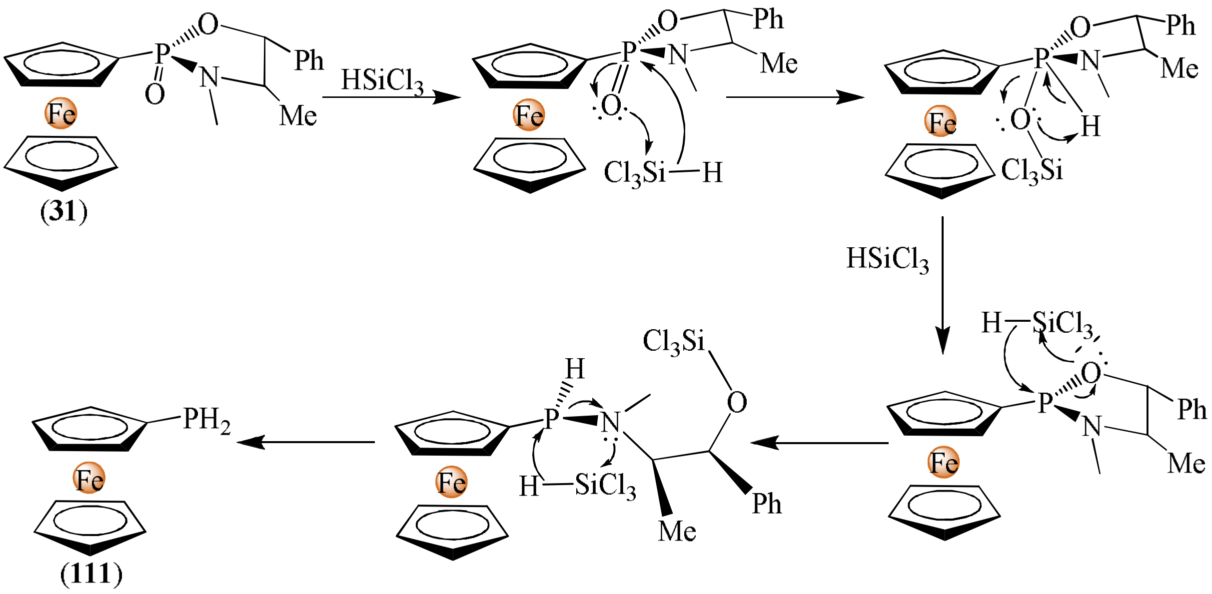
A literature survey on the reduction of phosphine oxides unveils work that has especially been done since the second half of last century. Two major groups of reducing agents are highlighted, namely aluminium hydride based systems, mostly with $LiAlH_4$ or LAH, and silanes. Really besides being used by itself $LiAlH_4$[216,217] has been also combined in several different systems. Examples are $LiAlH_4$-$NaBH_4$-$CeCl_3$,[218] $LiAlH_4$-$CeCl_3$,[219] $LiAlH_4$ and cobalt salts,[220] $LiAlH_4$ and TMSCl,[221] $LiAlH_4$ and silica chloride,[222] $LiAlH_4$ and methylation reagents,[223] or as its related compounds diisobutylaluminium hydride (DIBAL-H)[224,225] and alane (AlH_3).[226] Among the several silane based systems one may mention $HSiCl_3$ used by itself, combined with an amine base, $HSiCl_3$-NR_3,[227,228] or with an oxygen acceptor, $HSiCl_3$-PPh_3.[229] Phenyl silane

$PhSiH_3$,[230,231] other phenyl silanes mixtures, Ph_2SiH_2, Ph_3SiH, $PhSiH_3$-$PhSiCl_3$ and $PhSiHCl_2$,[232,233] polymethylhydrosilane (PMHS),[232] hexachlorodisilane ($Cl_3SiSiCl_3$)[234] and silane-titanium systems have also been used.[235,236] In addition to the aforementioned examples phosphine oxide reduction has shown to undergo with boron derivatives,[237,238] transition metal systems (Mg-Cp_2TiCl_2),[239] and even a combination of triflic anhydride, *N*,*N*-diisopropylethylamine and pentanethiol,[240] to mention just a few.

The majority of these systems is based on an oxophilic atom, Z, present in the reducing agent or in an additional activating agent. At some stage of the reaction this atom coordinates with the P=O oxygen atom thus weakening the P=O bond, normally resulting in the formation of a new Z-O bond. Depending on the system used, the oxophilic atom may be Li,[216,217,225] Ce,[218,219] Si,[228,230,234] C on a methylation reagent[223] or other reagent,[238] Ti,[235] B,[237] S on triflic anhydride,[240] etc.

Considering what has been stated we propose the mechanism on **Scheme** 30 as a possible explanation for the reduction and removal of the ephedrine fragment on our ferrocenyl oxazaphospholidine oxides by $HSiCl_3$.

Scheme 30 - Proposed mechanism for the oxazaphospholidine oxide moiety total reduction.



As depicted, coordination of oxygen to silicon and hydride transference to the phosphorus occur in a concerted step weakening the P=O bond. A new silicon-oxygen bond is formed, as well as phosphorus-hydrogen, resulting in a pentavalent intermediate. After P-OSi bond breaking, and proton abstraction at the phosphorus atom, the intermediate results in the trivalent free oxazaphospholidine with formation of trichlorosilanol (Cl_3SiOH). In a rather similar fashion, coordination of silicon to the ring oxygen, or to the nitrogen atom, and simultaneous hydride transfer to phosphorus result in ring opening. After two steps the process culminates in the formation of the primary ferrocenyl phosphine. As a matter of fact silanes have been appointed as not discriminating between P=O and P-O(C) bonds. Thus if a compound possesses both types of bonds reduction gives way to the formation of secondary or primary phosphines.[241,242] For instance the $HSiCl_3$-NEt_3 system was used to reduce a ferrocenyl phosphonate into a ferrocenyl primary phosphine.[243]

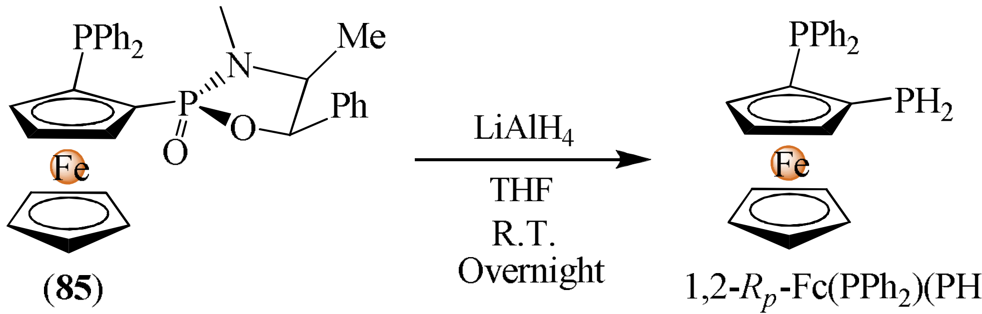
2.4.3.4.4.1 *Trying $LiAlH_4$*

Hoping to accomplish a complete reduction of our substrates we tried the reaction with the other main reducing agent, specifically with LAH. Hence, a THF solution of compound **81**, *S*-FcP(O)Eph, at 0ºC was added to a suspension of $LiAlH_4$ also at that temperature. After stirring for 30 min. the reaction was allowed to reach R.T. and stirring overnight. At 0ºC excess $LiAlH_4$ was destroyed with MeOH, followed by aqueous work-up with Et_2O, an aqueous solution of Na_2CO_3 and brine. The reddish oil product was obtained in 14.5% yield. Crude ^1H and ^{31}P-NMR revealed what was somehow expected, that is, the reduction to occur with no discrimination between P=O and P-O(C) bonds. Again the main product was the primary phosphine with the presence of by-products similar to the ones formerly yielded with the silane reducing agent. Interestingly this time a small triplet was present at 0.2 ppm (J_{HP}=483 Hz), which we believe is the more polar primary ferrocenyl phosphine oxide $FcP(O)H_2$.

In point of fact $LiAlH_4$ is known to first reduce the P-O(C) bond of phosphonates in detriment to the P=O one.[241,244] Such might be the case here as well. It is actually reasonable for the mechanism in this case to be different from the one with silanes since the initially negatively charged aluminium atom is not expected to coordinate immediately with the P=O oxygen. First hydride transfer must occur, facilitating ring opening. Later the neutral alane should be more prone to coordinate with the P=O oxygen.

Given that repetition of the last reaction would lead to the same results, 27.2%, we tried the reaction with compound **90**, 1,2-R,R_p-Fc[P(O)Eph](PPh_2). The planar chiral primary phosphine **112**, S_p-Fc(PH_2)(PPh_2), was also the main product, ca. 90% based on ^{31}P NMR data of the crude mixture. The expected PH_2 and PPh_2 phosphorus were present, at -150.2 ppm (t), J_{PH}=204 Hz, $^3J_{PP}$=31 Hz, and -21.3 ppm, $^3J_{PP}$=31 Hz. Another peak was present at -23.9 ppm also with a small doublet at -41.0 ppm possibly belonging to by-products from incomplete ephedrine removal. With very similar results reaction involving **85**, 1,2-S,S_p-Fc[P(O)Eph](PPh_2), afforded the primary phosphine with opposite planar chirality **117**, R_p-Fc(PPh_2)(PH_2).

Scheme 31 - Formation of R_p-Fc(PPh_2)(PH_2) via reduction of compound **85** with $LiAlH_4$.



(85)

1,2-R_p-Fc(PPh_2)(PH_2)
(117)

This time some primary phosphine oxide was detected as well, -0.1 ppm (t), J_{PH}=488 Hz. A proton decoupled phosphorus NMR was in accordance.

We noticed that compound **81**, *S*-FcP(O)Eph, and derivatives such as **85**, show higher resistance towards reduction than its P-epimer, **31**, and derivatives like **90**. It is not clear whether if this happens because of a somewhat relatively different steric and electronic environment around the two P-epimers P=O bonds. Also not impossible is that the presence of the oxide in one reaction and not on the other is just a fortuity event.

2.4.3.4.4.2 *Combining $LiAlH_4$ and TMSCl*

Given the last referred presence of primary phosphine oxide, in order to facilitate its complete reduction, we decided to use a system that combines LAH and a silane compound, TMSCl (Me_3SiCl).[221] On a first attempt, to a suspension of LAH in THF at -78ºC TMSCl was slowly added in a 1 to 1 proportion. The mixture was allowed to stir for one hour and a solution of **90,** 1,2-*R*,R_p-Fc[P(O)Eph](PPh_2), was slowly added. R.T. was reached and the reaction stirred overnight. Contrary to what has been described in the literature for phosphonites[209] and phosphonates,[214,215] even though four equivalents of reducing agent were used, after 15h the previous conditions did not lead to reduction. Even a second attempt at reflux temperature was found insufficient. However this time instead we decided not to do the work up but to cool the temperature to 0ºC and add four more equivalents of LAH. After refluxing for 3h, a TLC suggested the formation of a new compound and substrate absence. Excess reducing agent was destroyed with MeOH, followed by aqueous work up. Analysis of the resulting mixture revealed the reaction was not complete. Besides the expected product NMR signals another major compound possessing a doublet at around 26 ppm and a singlet at around -21 ppm was detected. The doublet was converted into a singlet on a proton decoupled NMR again suggesting the presence of a PH bond, P(O)H judging on the chemical shift.

A small triplet at -2.9 ppm, J_{PH}=489 Hz, also suggested the presence of a $P(O)H_2$ fragment. The reaction was repeated, this time using seven equivalents of reducing agent slurry and performing the reaction at reflux temperature. The planar chiral primary phosphine was the major product, -150.2 ppm (t), and -20.0 ppm (s), with the presence of some “usual” minor by-product around -80 ppm.

Besides these, another compound was produced with a triplet at -145.2 ppm, more typical of the monosubstituted primary phosphine, which does not appears to be coupling with another phosphorus atom. This raises the question whether C-P bond breaking with loss of the PPh_2 group and formation of ferrocenyl phosphine could be occurring. The presence of two other singlets at -14.9 ppm and 30.8 ppm was noticed. Despite flash chromatography purification of the crude mixture this last by-product could not be completely isolated from other by-products, hindering its identification.

2.4.3.4.4.3 *Combining $LiAlH_4$ and $HSiCl_3$*

At this point the LAH reducing agent seemed to be the most effective one although not totally satisfactory. Using TMSCl together with it, in a 1 to 1 ratio, reduced its activity although favouring reduction of the P=O bond. We thus determined to combine $LiAlH_4$ with $HSiCl_3$ in a different manner. First undergoing the reduction with $LiAlH_4$ and subsequently adding $HSiCl_3$ with the purpose to minimize the presence of oxides. Indeed the presence of chloride on the silane increases its oxophilicity.[245,246] Accordingly, to a slurry of LAH at 0ºC a solution of **90**, 1,2-*R*,*R*$_p$-Fc[P(O)Eph](PPh_2), was added and after 1h at R.T. $HSiCl_3$ was also added. Stirring was allowed overnight before methanol was added at 0ºC and the solvent removed after half an hour. The product was extracted with hexane and filtered through a small silica pad, 79.2%. The reaction proceeded almost to completion mostly affording the desired planar chiral primary phosphine. The product presents two aspects that better characterize it. One is coupling between both phosphorus at -20.0 ppm (d, J_{PP}=30.8 Hz) and -150.2 ppm (t (dt), J_{PH}=204.1 Hz, J_{PP}=30.6 Hz). The other is the presence of two doublets at 3.50 (1H, dd, showing further splitting, *J*=3.9 Hz, *J*=12.4 Hz, J_{HP}=208.1 Hz) and 3.87 (1H, dd, with further splitting, *J*=3.3 Hz, *J*=12.4 Hz, J_{HP}=212.2 Hz). Truly due to planar chirality the two PH_2 protons are not equivalent thus appearing as two doublets instead of one.

Some secondary phosphine by-product was also detected. This presented a ^{31}P NMR doublet at −39.0 ppm, J_{PH}=218.7 Hz, with its ^{1}H NMR doublet having a higher chemical shift than the ones from the primary phosphine product.

We tried the reaction with compound **81**, *S*-FcP(O)Eph, this time prolonging the reaction with LAH overnight only then adding the silane allowing it to react for 2h. Crude ^{1}H and ^{31}P NMR still displayed the primary phosphine without the corresponding oxide, thought also still with the presence of minor by-products. Flash chromatography purification however led to partial product oxidation with the PH_2 phosphorus going from −144.6 ppm (t), J_{PH}=203 Hz, to −0.01 ppm (t), J_{PH}=482 Hz. The PH_2 protons changing shift from 3.8 ppm (d), J_{HP}=203 Hz, to 7.6 ppm (d), J_{HP}=482 Hz.

In addition to these reducing systems we also attempted reduction with sodium borohydride in reflux methanol though with no reaction taking place.

2.4.3.4.4.4 *Challenges and possible solutions to attain better results*

Taking into account the previous results, the most promising strategy is the one that combines the actions of LAH and $HSiCl_3$ in a stepwise manner. Hypothetically, due to steric hindrance LAH can perform better than the silane. On the other hand once ring opening is achieved the silane facilitates oxide reduction. According to this suggestion one probably ought to prolong the reaction at the LAH initial step and at the second one, with the silane. Also increasing the temperature could lead to a complete reaction hopefully without resulting in the formation of other by-products. What's more other systems may be used for example $LiAlH_4$-$NaBH_4$-$CeCl_3$. This system could present a different reactivity besides having the advantage of forming BH_3 protected phosphines, thus facilitating its purification and manipulation.[218] The combination of LAH with a methylation agent could enhance the oxide reduction via P=O oxygen methylation.[223] In our case, most likely this combination could have a double effect. The presence of the nitrogen atom at the oxazaphospholidine ring is prone to undergo quaternization therefore improving ring opening.

It is important to notice that together with a system that leads to the formation of primary phosphines from oxazaphospholidine oxides, one that allows for a selective reduction of the oxide into a free oxazaphospholidine is also desirable. For that the investigation of other systems and conditions is once again important. An instance where a selective reduction has taken place was reported for phosphonate-phosphane oxides. Under reducing conditions with phenyl silane, the phosphane oxide was reduced and the phosphonate group was found to be stable.[231] The use of hexachlorodisilane could too afford the desired product on a selective fashion. This given that it possesses an oxophilic atom to help performing the reduction yet without the hydride hence reducing the propensity for ring opening to occur.

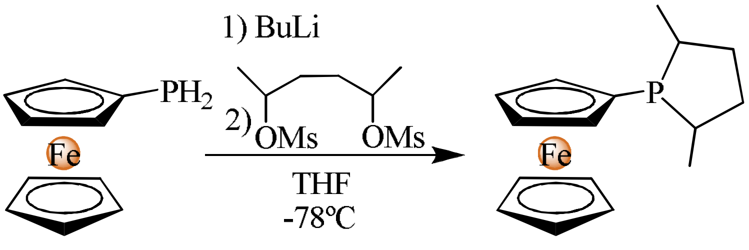
It then is rather clear that finding the appropriate reducing system and reaction conditions may be challenging. Also as previously mentioned a suitable work up and purification procedure is of great importance. For example an aqueous work up is normally associated with some product reoxidation,[226] reason why if possible it should be avoided. Using alane instead of $LiAlH_4$ has proven convenient for that matter.[226] During our study besides varying the reaction conditions, such as reagent type and amount, temperature and reaction time length, we attempted to be aware at which work up and purification procedure could be more suitable. Besides making use of aqueous work-up, in several occasions we have tried to destroy the excess reducing agent, evaporate the solvent and simply extract the product with an apolar solvent such as hexane.[209] Nonetheless many times removal of the ephedrine fragment during reduction was incomplete. So purification was still needed which per se is also susceptible of leading to some product loss and/or reoxidation. The need for a more effective reduction is reinforced.

Publications on the synthesis of ferrocenyl primary phosphines, via reduction of phosphonites and phosphonates,[243] present good results. When confronting such results with ours one needs to consider that though the desired product may be similar the substrate and the reaction mixture are different. Reduction of phosphonates and phosphonites results in the formation of relatively small alkoxy fragments whereas in our case in the ephedrine fragment. In our case the heterocyclic ring conveys rather dissimilar electronic and steric properties. This clearly hinders the reduction, when in comparison with the reduction of acyclic and less steric phosphonates and phosphonites.

2.4.3.4.5 An example on the application of ferrocenyl primary phosphines

Regarding possible ways in which primary ferrocenyl phosphines may be applied, several reactions were made involving some of the above primary phosphines and either mesylates, sulfones or bromides according with the example on **Scheme** 32.

Scheme 32 - Derivatization of ferrocenyl primary phosphines into cyclic phosphines.



(**118**)

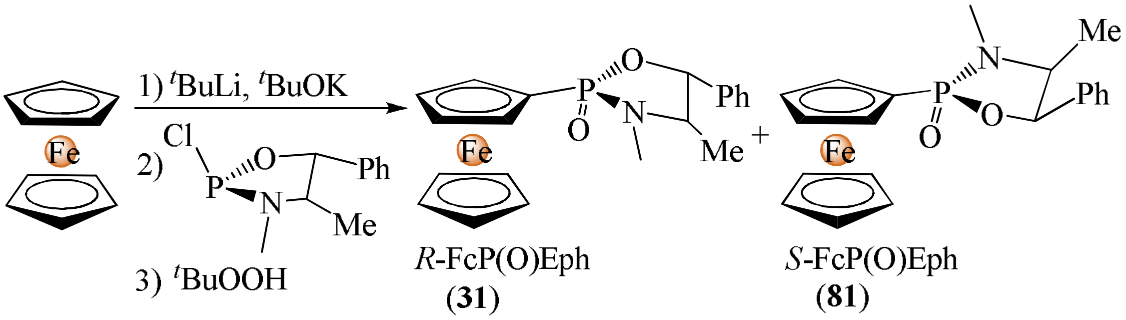
^{31}P-NMR δ: 1.4 ppm

Although due to the small amounts used we were not able to isolate the pure products, TLC monitoring and especially ^{1}H and ^{31}P NMR analysis suggested that the expected products were formed. For instance, the use of chiral diols allows the preparation of chiral mesylates and sulfones which undergoing reaction with the primary phosphine expectedly result in the formation of pseudo P-chiral phosphines.[201-212] The development of adequate reaction conditions for the formation and derivatization of ferrocenyl primary phosphines from ferrocenyl oxazaphospholidine oxides, especially those presenting planar chirality, is therefore attractive.

2.5 CONCLUDING REMARKS

The work presented in this chapter directs us to consider the oxazaphospholidine oxide moiety as a very interesting and promising chiral *ortho*-directing group. Stereoselective lithiation of ferrocenes containing this CDG leads to the formation of several structurally different derivatives. First, two ferrocenyl oxazaphospholidine oxide epimers are formed, **31** and **81**, *R*-FcP(O)Eph and *S*-FcP(O)Eph, and efficiently separated accordingly with **Scheme** 33.

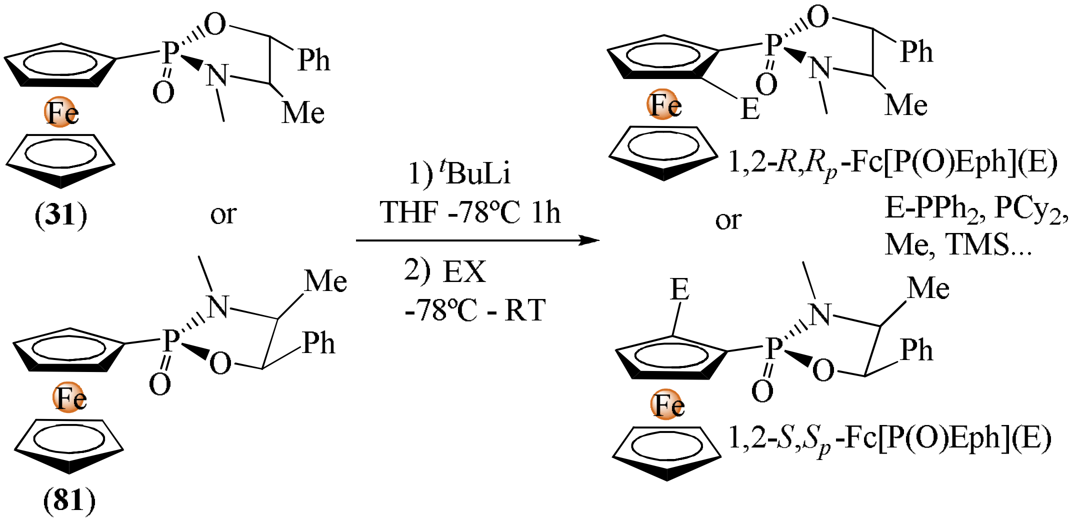
Scheme 33 - Synthesis of compounds **31** and **81**.



When using 1,1'-dilithium ferrocene three 1,1'-ferrocenyl oxazaphospholidine oxide compounds, **82** to **84**, are formed, 1,1'-*R*,*R*'-Fc[P(O)Eph]$_2$, 1,1'-*R*,*S*'-Fc[P(O)Eph]$_2$ and

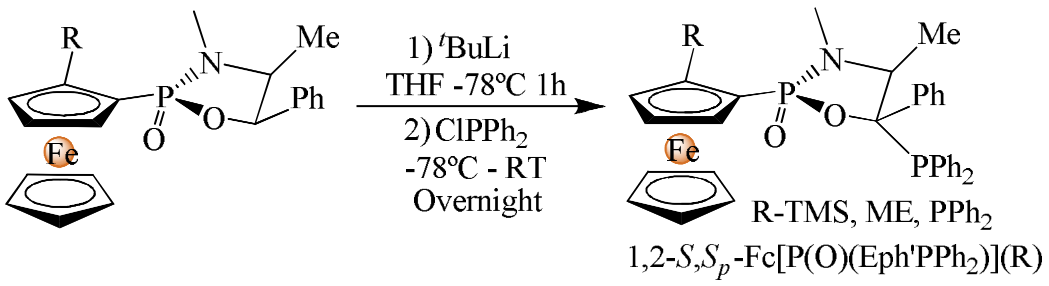
1,1'-*S*,*S*'-Fc[P(O)Eph]$_2$. These last three compounds may pose some selectivity challenges to be *ortho*-lithiated. In stark contrast both mono-substituted compounds, **31** and **81**, undergo successful sequential *ortho*-lithiation/functionalization. The reaction is compatible with varied electrophiles, thus resulting into 1,2-disubstituted diastereomers with distinct central and planar chirality. Compounds **85** to **93**, 1,2-*S*,S_p-Fc[P(O)Eph](E) and 1,2-*R*,R_p-Fc[P(O)Eph](E), are among the derivatives synthesized in this thesis, including the formation of diferrocenyl compounds, **94** and **95**, *S*,S_p-[FcP(O)Eph]$_2$(PPh) and 1,2-*R*,R_p-[FcP(O)Eph]$_2$(PPh). Lithiation reaction of **31** and **81** is next presented.

Scheme 34 - Lithiation/functionalization of **31** and **81** to form planar chiral disubstituted ferrocenes.



These 1,2-disubstituted derivatives could not undergo effective further *ortho*-lithiation at the other ferrocene vacant site, to afford 1,2,3-trisubstituted compounds. Supposedly due to their particular conformation (*S*,S_p)-derivatives suffer clean CHPh proton abstraction and functionalization. A door was thus opened to the formation of new derivatives with further modified steric, electronic and stereo properties, 1,2-*S*,S_p-Fc[P(O)(Eph'PPh$_2$)](E). **Scheme** 35 displays the aforementioned reaction.

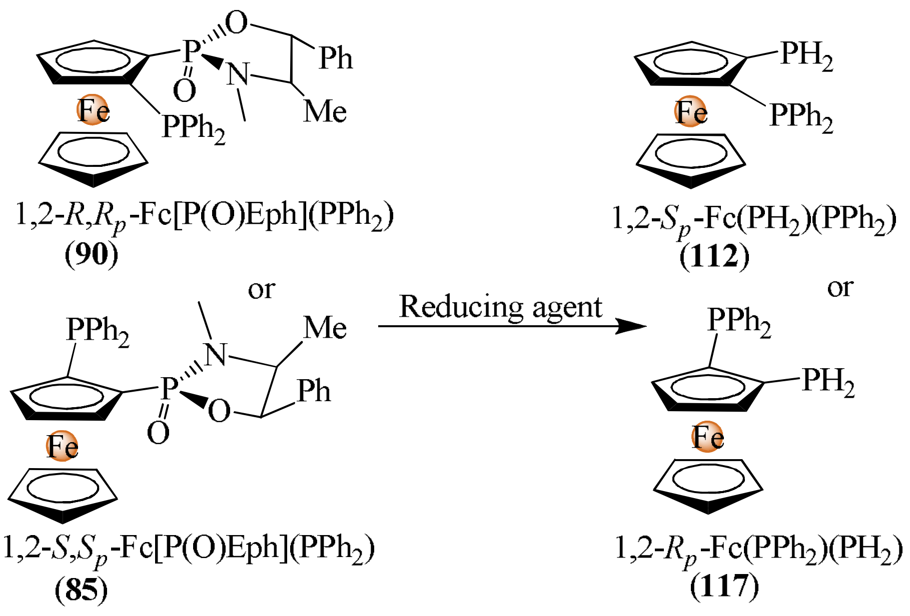
Scheme 35 - Litiation and derivatization of (S,S_p)-1,2-ferrocenyl oxazaphospholidine oxides.



In addition to this positive outcome it is possible that the regiocontrol challenges found when attempting to produce 1,2,3-trisubstituted derivatives may be avoided by protection of that proton. This would be of interest since it would allow the formation of 1,2-disubstituted derivatives with (S,R_p) and (R,S_p) configurations. The oxazaphospholidine oxide moiety has also shown to educe diastereoselectivity conducing to the formation of P-chiral ligands such as ligand **105**, 1,2-S,S_p-Fc[P(O)Eph](PCyPh).

Finally the possibility to convert this CDG into primary phosphines was also proved. A way for the synthesis of rare planar chiral 1,2-dissubstituted ferrocenyl primary phosphines **112** and **117** with different configurations, S_p-Fc(PH_2)(PPh_2) and R_p-Fc(PPh_2)(PH_2), was disclosed, as presented in the **Scheme** below.

Scheme 36 - Planar chiral primary phosphines via reduction of the oxazaphospholidine oxide.



3

Catalysis, Asymmetric Catalysis and Chiral Ferrocenyl Ligands - Testing the Ferrocenyl Oxazaphospholidine Oxide Ligands

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Herein a brief trial on **Chapter**’s ***2*** planar chiral ferrocenyl oxazaphospholidine oxides ability to act as ligands in catalytic reactions, inclusively in asymmetric ones, will be portrayed. Accordingly relevant notions on Suzuki-Miyaura cross-coupling and on asymmetric allylic alkylation will be approached.

Chapter 3

3.1 INTRODUCTION

The importance represented by catalysis, especially by asymmetric catalysis, its increasing development and some basic concepts have been mentioned in **Chapter *1***. Also we have referred ferrocenyl chiral ligands as being of great importance in the field of asymmetric catalysis. These ever increasing ligands have been involved in a vast array of reactions. Therefore, next we whish only to present some application examples, focusing on those that may be of greater interest, especially in the context of our work.

3.2 ASYMMETRIC HYDROGENATION

A great deal of chiral compounds present a hydrogen atom at the stereogenic center. Such chiral centers may be formed by asymmetric hydrogenation (AH) of unsaturated bonds in suitable prochiral precursors. As a result this catalytic transformation has earned huge importance and emerged as one of the chief strategies in the manufacture of highly enantiomerically pure products, such as alkanes, alcohols and amines.[142,247] Really asymmetric hydrogenation is economical and environmentally friendly, involving dihydrogen and minute quantities of transition-metal complexes. Normally it involves rhodium(I) and ruthenium(II) complexes with diphosphine-based chiral ligands, allowing in certain cases high reaction rates and excellent enantioselectivities.[142]

3.2.1 MECHANISTIC ASPECTS ON AH

Mechanistically speaking, hydrogenation of unsaturated substrates implies dihydrogen activation by a low-valent state complex before it can be transferred to the substrate. In other words during the *oxidative addition* step the metal complex activates hydrogen, via cleavage of the dihydrogen bond. It then undergoes *association* with the substrate via coordination to its double bond, to which hydride is transferred in the *insertion* step. Finally the product is eliminated bringing the catalyst to its initial state, in the *reductive elimination* step.[248,249]

3.2.2 AH and Ferrocenyl Ligands

Since the last three decades hydrogenation has undergone admirable development, with particular attention given to the design of efficient chiral agents.[142] The literature displays not a small number of chiral ferrocenyl ligands that have been applied for the highly stereoselective hydrogenation of several different types of unsaturated substrates.[35,61,152] Plus there seems to be a tendency for new ferrocenyl ligands to be tested in asymmetric hydrogenation, many leading to successful results suggesting that ferrocene based ligands are privileged in this type of reaction.[35] Among often employed substrates to test new ligands, olefins and selected arylenamides may be underlined. For C=O test, substrates are frequently acetoacetone and alkyl acetylacetates (AcAc, AcAcOR) and acetophenones. Finally a variety of acetophenone derivatives are used for the C=N test accordingly to **Figure** 29.[248]

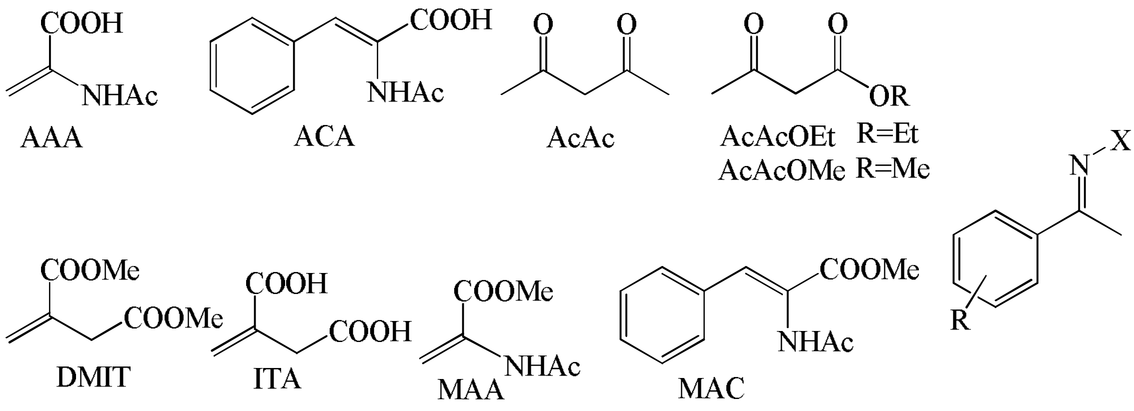


Figure 29 - Substrates typically used to test ligands on AH.

Several types and families of chiral ferrocenyl ligands, mainly involving the above substrates, have displayed very high enantioselectivities, in various cases higher than

99% ee.[35,61,248] For instance Bophoz,[117,250-252] Josiphos,[253,254] Mandiphos,[255] Taniaphos,[255,117] Trap,[256] Ferrotane,[257-259] Reetz's Binol based diphosphonite **119**,[260] Zang's sugar-substituted phosphine **120**,[261] and Chan and Zheng's hybrid phosphine-phosphoramidite-Binol ligand.[262,263] These ligands are depicted in **Figure** 30.

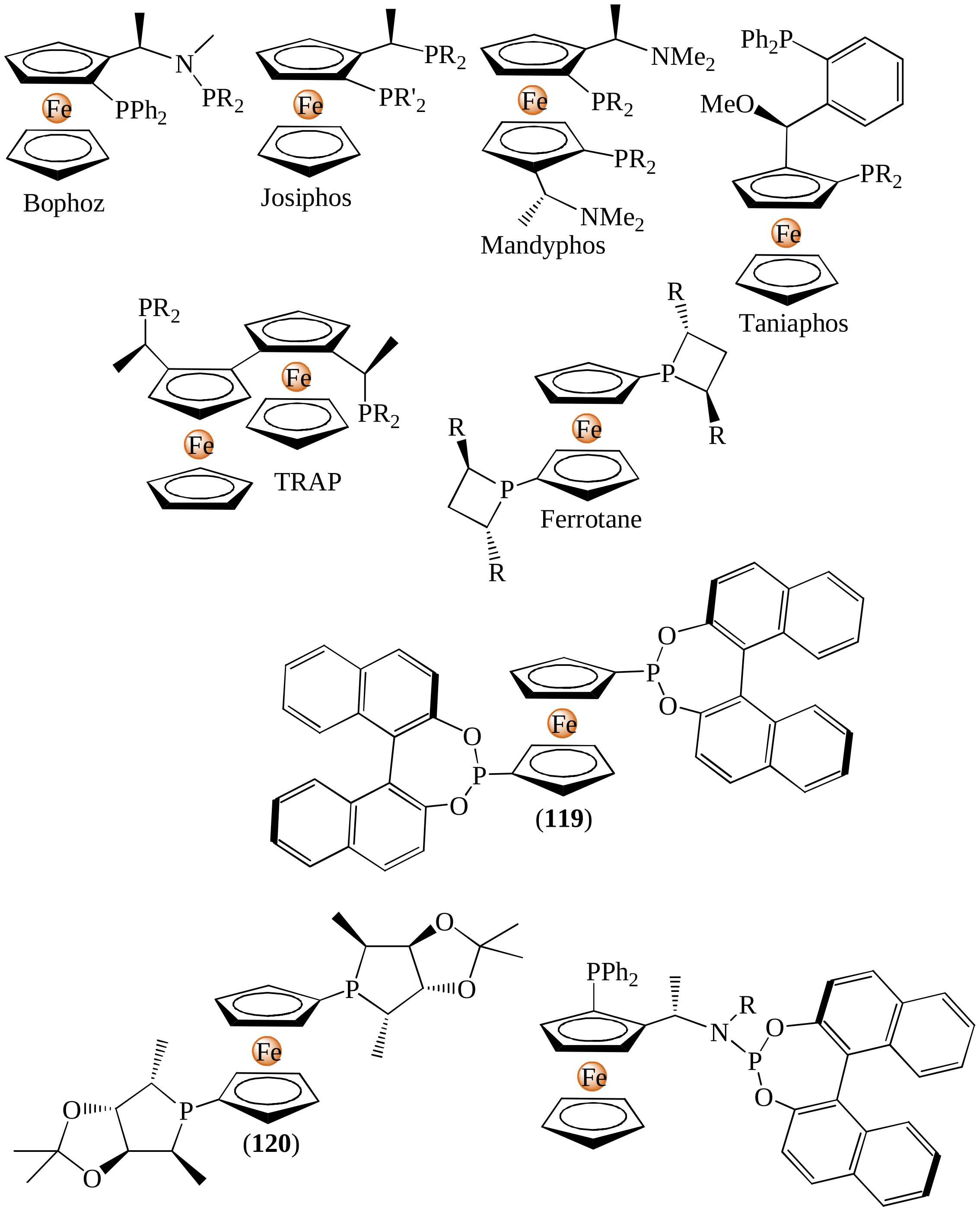
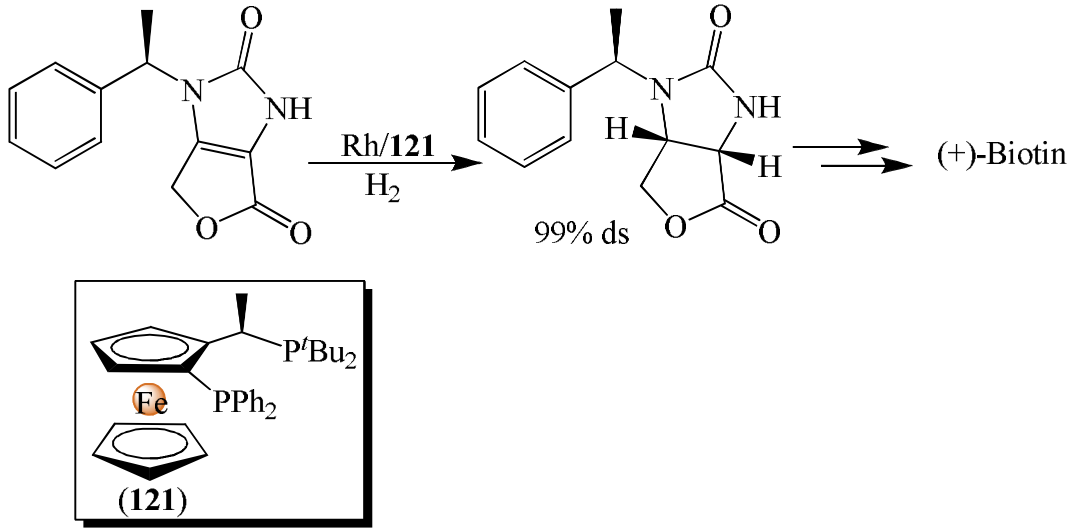


Figure 30 - Chiral ligands used on AH.

Amongst other factors the relevance of each result varies according with the ligand's activity and ability to induce enantioselectivity. However it is often at more demanding levels such as in the industry that the definite test is performed, revealing its substrate scope and tolerance to different functional groups.[248] Josiphos ligands have shown to be very effective often being highlighted for their application in production scale.[248] For example Lonza's Rh-catalyzed asymmetric synthesis of vitamin H, (+)-Biotin, is induced by a metal complex containing a bulky $^{t}Bu_2P$-based ligand **121**.[72] Accordingly to **Scheme** 37 the reaction leads to hydrogenation of a fully substituted olefin in high diastereoselectivity.

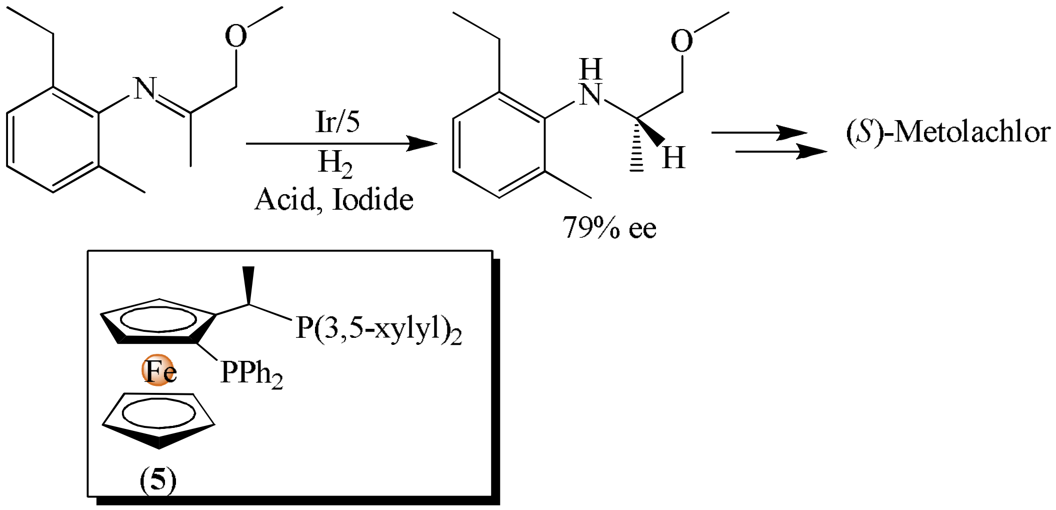
Scheme 37 - AH of a (+)-biotin precursor.



Even more significant is the production of (*S*)-Metolachlor, today's largest application of asymmetric catalysis (15000 tons/year)[247] which makes use of Xyliphos **5**. Contrary to the last example this reaction does not present such high enantioselectivity, 80%. Even so this imine Ir-catalysed asymmetric hydrogenation is performed with a s/c ratio of more than 1.000.000 being completed in ca. 4h with initial TOF of more than

1.800.000 h^{-1}.[264] The hydrogenation step involved in the synthesis of (*S*)-Metolachlor is presented in **Scheme** 38.

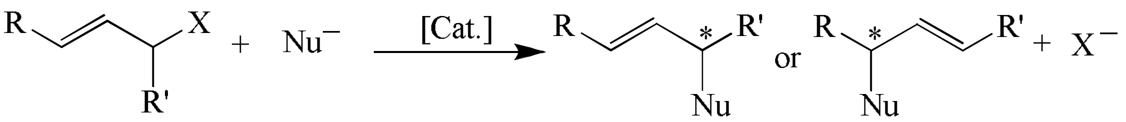
Scheme 38 - AH of a (*S*)-Metolachlor precursor.



3.3 ASYMMETRIC ALLYLIC ALKYLATION

The first example of an asymmetric allylic alkylation (AAA) reaction was reported by Trost and Strege over three decades ago, in 1977.[265] Since then this strategy has demonstrated great synthetic utility in asymmetric synthesis also being involved in the formation of biologically important molecules.[5,6,266,267] Behind this fact are important particular characteristics that distinguish the strategy from other important usual ones such as hydrogenation and oxidation. For example AAA is versatile in the sense that it may involve the formation of various types of bonds, i.e., C-H, C-C, C-N, C-O, C-S and C-P. Plus it usually displays tolerance to several functionalities proceeding under mild reaction conditions. Also the reaction involves a sp^3 center instead of an usual sp^2 one. The chiral elements can be set either at the electrophile, the nucleophile or both. In addition while other reactions imply one enantiodiscriminating event, for instance, molecular recognition of an enantiotopic face on a C=C or C=O bond, AAA may involve four different such possible mechanisms. Finally it is normal for the enantiodiscriminating bond changing events to occur outside the coordination sphere, distal to the chiral ligands. It is therefore noticeable how AAA presents itself as a challenging potential strategy in asymmetric catalysis.[266,267] A general equation for the AAA reaction is presented in the **Scheme** below.

Scheme 39 - General equation for the AAA reaction.



Accordingly with the above equation acetates and carbonates are frequent leaving groups (X$^-$) for the AAA in contrast to other reactions which make use of more reactive halides and sulfonates. Although several transition metal complexes have been used to catalyse the reaction, Pd is the most used among all. In this case stabilized carbanions or amines are typical nucleophiles, called “soft” nucleophiles.

3.3.1 MECHANISTIC ASPECTS ON AAA

The AAA catalytic cycle includes four consecutive steps. Initially olefin *complexation* with the Pd(0) catalyst occurs, generating a π-complex. Secondly *ionization*, or oxidative addition, via elimination of X$^-$ forms a (η^3-allyl)palladium (II) complex in which the allyl system is activated. Afterwards there is *nucleophilic addition* at the allyl termini, and finally *decomplexation* of the product from the resulting unstable Pd(0)-olefin complex. Among these steps the three first ones allow enantiodiscrimination to occur. Nevertheless the formation and posterior reaction of the (η^3-allyl)palladium (II) complex is of central importance since it implies the bond-breaking and bond-making events from which the chiral induction derives. Furthermore it is important to point to the fact that structural modifications, such as σ–π–σ isomerisation, may occur at this key intermediate (η^3-allyl)palladium (II) complex. The catalytic cycle is displayed in **Figure** 31.[5,6,266]

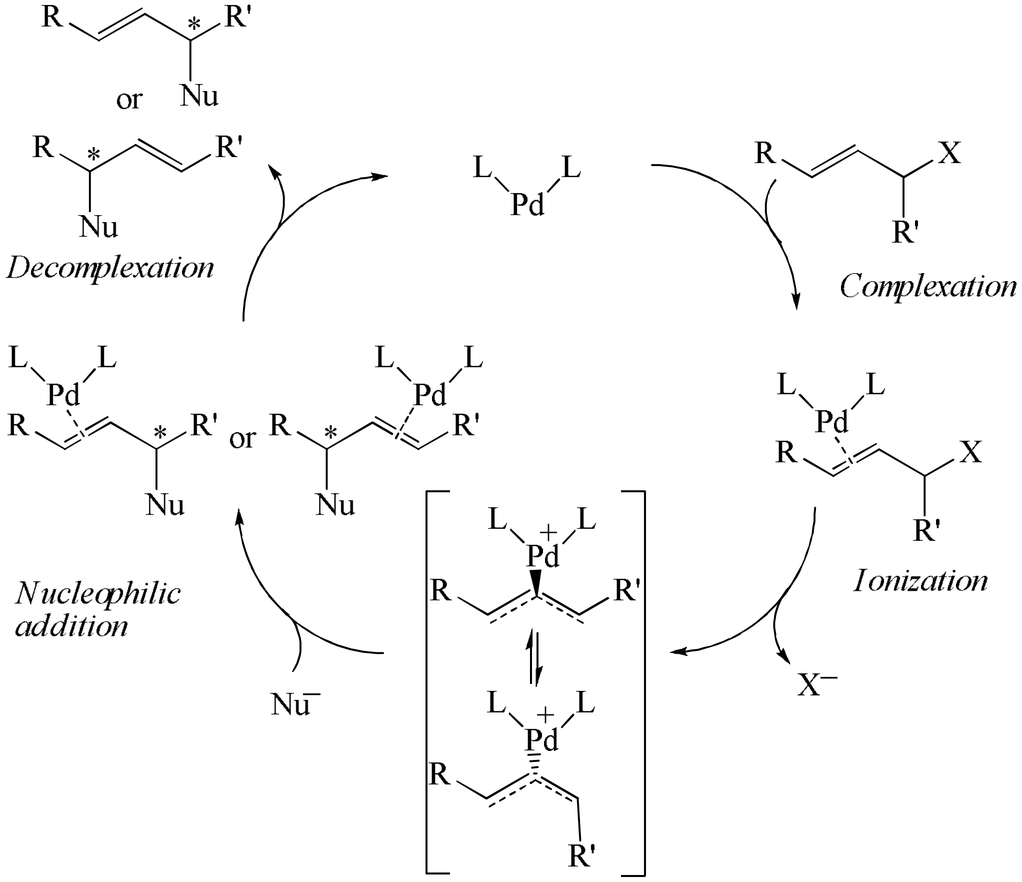
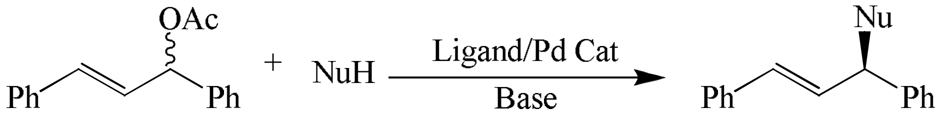


Figure 31 - AAA catalytic cycle.

3.3.2 AAA AND FERROCENYL LIGANDS

Just an overview at some literature reviews on asymmetric catalysis involving chiral ferrocenyl ligands reveals the number and variety of these that have been used, many times successfully, in AAA reactions.[35,59,61,75,76] In fact there is a trend in the academia to apply the Pd catalysed allylic alkylation of 1,3-diphenyl-2-propenyl acetate with soft nucleophiles to test new ligands.[35,59,61] This is so even in spite of its little interest from an industrial point of view. The reaction is presented in the following **Scheme**.

Scheme 40 - Palladium catalysed AAA of 1,3-diphenyl-2-propenyl acetate.



Within the many ligands that have been used with this system one may perceive different coordination modes, such as P,P, P,N, P,S, N,S, S,S, and P,P,N,N.[35,59,61,75,76] In the subsequent **Table** we present a selection of results in which ferrocenyl ligands were used in allylic alkylation reactions with the above system.

Table 1 - Examples of palladium catalysed AAA reactions in which ferrocenyl ligands were used.

Entry	NuH	Conditions	L*	Yield %	Ee %	Ref.
1	$CH_2(CO_2Me)_2$	DCM, RT	**122**	63	99.6	268
2	$CH_2(CO_2Me)_2$	C_6H_6, RT	**123**	99	99.6	269
3	$CH_2(CO_2Me)_2$	DCM,10ºC	**124**	93	99.0	270
4	$CH_2(CO_2Me)_2$	DCM, RT	**125**	99	98.5	271
5	$CH_2(CO_2Me)_2$	DCM, RT	**126**	99	98.6	271
6	$BnNH_2$	THF, RT	**127**	82	99.5	118
7	$BnNH_2$	THF, RT	**128**	93	99.5	118
8	$BnNH_2$	THF, 40ºC	**129**	90-95	99.5	45, 108

As seen on **Table** 1 these ligands were capable to induce high stereoselectivity around 99% ee. The ligands, mostly P,N ones, are presented in the following **Figure**.

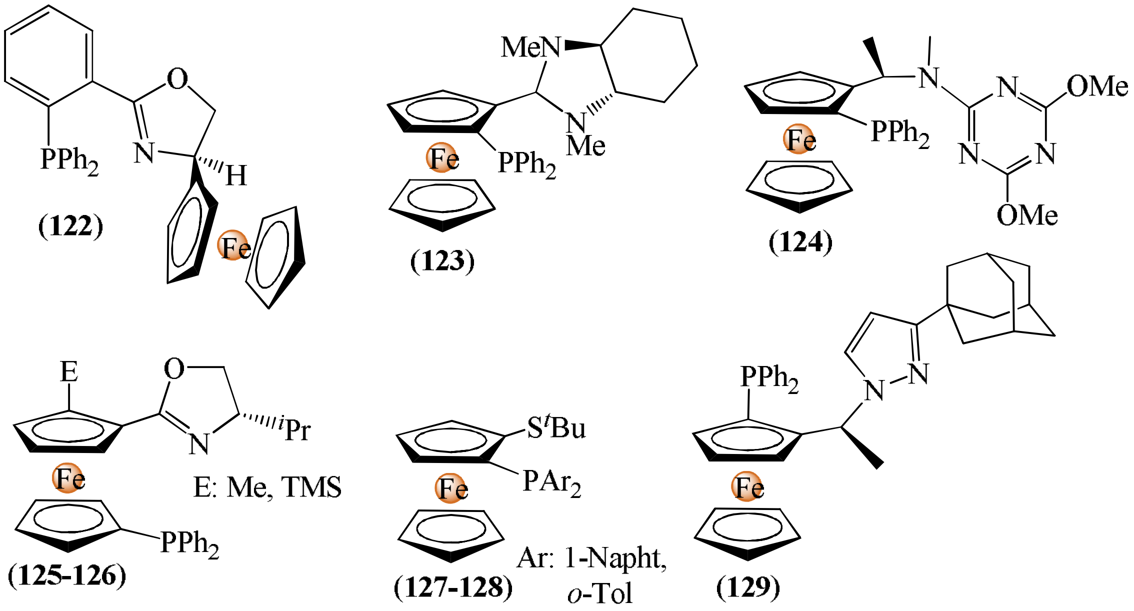
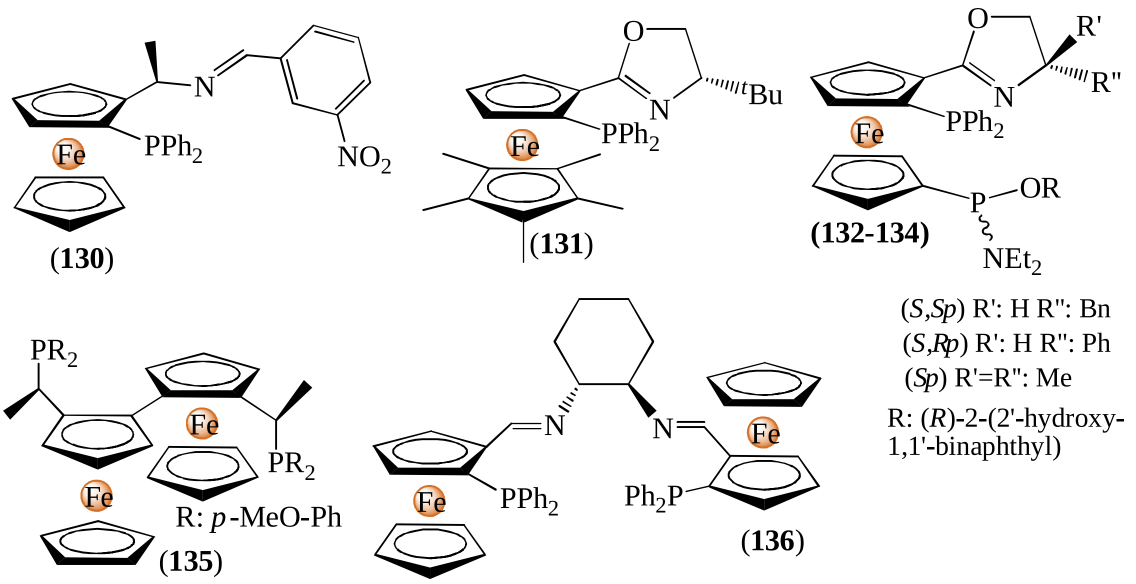


Figure 32 - Selection of ferrocenyl ligands used in AAA reactions.

It is frequent to have effective ferrocenyl ligands for the 1,3-diphenylallyl system which do not reveal to be as efficient with other substrates, for instance cycloalkenyl esters or unsymmetrical allylic substrates. However from a synthetic point of view these more demanding substrates are also more relevant, leading chemists to seek for ligands that will suit them. Amid such relatively scarce ligands, which have provided important results with enantioselectivities above 80% ee, are Zheng's ferrocenyl phosphine-meta-nitrophenyl imine **130**[272] and Helmchen's bulky planar-chiral Phox ligand **131**.[273] Also among them are Dai and Hou's chiral P,N-1,1'-disubstituted ferrocenes bearing a P-chiral phosphorus atom connected to a Binol unit **132-134**,[274,275] Ito's *p*-$MeOC_6H_4$-Trap **135**,[276] and Hou's ferrocenyl pocket ligand **136**.[277] **Figure** 33 shows these successful ligands.



(130) **(131)** **(132-134)** **(135)** **(136)**

(*S*,*Sp*) R': H R": Bn
(*S*,*Rp*) R': H R": Ph
(*Sp*) R'=R": Me
R: (*R*)-2-(2'-hydroxy-1,1'-binaphthyl)

R: *p*-MeO-Ph

Figure 33 - Selection of ferrocenyl ligands used in AAA reactions.

3.4 ASYMMETRIC SUZUKI-MIYAURA CROSS-COUPLING REACTION

Transition metal catalyzed cross-coupling reactions of aryl and vinyl halides, or pseudohalides, with organometallic reagents are considered as resourceful tools for the formation of new C-C bonds.[277,279]

Scheme 41 - General equation for the transition metal catalyzed cross-coupling reaction.

$$\mathrm{RX + R'M} \xrightarrow{\text{Catalist}} \mathrm{RR' + [MX]}$$

Accordingly with **Scheme** 41, a number of organometallic reagents, from Mg, Sn, Zn, Cu and other metals, may be used in cross-coupling reactions. However, since Suzuki and Miyaura work in the late 1970’s and early 1980’s,[280-282] boron derivatives have gained prominence.[278,279] Indeed, contrary to other organometallics boronic acids are known for their non-toxicity, stability to heat, air and moisture, as well as compatibility to a wide range of functional groups. Also attractive is the fact that boron by-products are non-toxic and easily separated from the Suzuki reaction product. Plus a large structural variety of boronic acids and boron derivatives are commercially available. The Suzuki-Miyaura coupling allows for a variety of reaction conditions, generally low temperature and mild conditions, including the use of aqueous solvents. Typically good yields and selectivity are involved; low amounts of catalyst suffice, in some cases even without ligands. The reaction is quite versatile and often used for the synthesis of valuable organic compounds, mostly biaryls. It is attractive even from a large-scale synthesis perspective, for instance in the synthesis of pharmaceuticals and fine chemicals.[278, 279,283-285]

3.4.1 MECHANISTIC ASPECTS ON THE SUZUKI-MIYAURA REACTION

Though the first examples on the Suzuki-Miyaura coupling involved alkenyl reactants[280,281] its scope has been extended. Alkyl, alkynyl, aryl and alkenyl organic boron nucleophiles may thus be cross-coupled with alkyl, alkynyl, aryl, benzyl and alkenyl electrophiles such as halides (Br, Cl, I) or pseudohalides ($OP(=O)(OR)_2$, OTf, OTs).[284,286,287] Palladium species have become the catalyst of choice for the reaction, nonetheless nickel catalysts are also employed. In part due to boron’s electronegativity, 2.0, Suzuki coupling normally requires the presence of a basic additive so as to form a higher valent more reactive “ate” boron complex prone to undergo transmetalation.[278,279] The reaction mechanism comprises a sequence of three main steps, namely *oxidative addition*, *transmetalation* and *reductive elimination*. The organic halide electrophile undertakes addition to the Pd(0) complex giving rise to a organopalladium(II) halide species. This is normally the rate determining step, reason why the relative reactivity among different halides and pseudohalides decreases in the order $I > OTf \geq Br >> Cl$. The reactivity depends as well on the substrate structure, namely on the presence of electron-withdrawing or electron-donating groups. Generally the first substituents favour reactivity whilst the last ones hinder it.[279,283,287]

Pertaining to the transmetalation step it has been suggested that the base pKa, and accordingly the reaction pH, have significant influence in the reactivity, more specifically in the formation of boron active species.[279,288] In addition the base plays a role at the coordination sphere of the organopalladium(II) halide complex. It causes the halide ion to be exchanged by an alkoxide or hydroxide group, depending on the base. Supposedly alcoholic solvents or the presence of a small amount of water may interfere in the reaction outcome also. Subsequent to halide substitution the newly formed more active complex accelerates the transmetalation step originating a diorganopalladium(II) complex. Via reductive elimination the new C-C bond is formed and the initial catalyst is regenerated. The mechanism is depicted in the **Figure** below.[283,287-289]

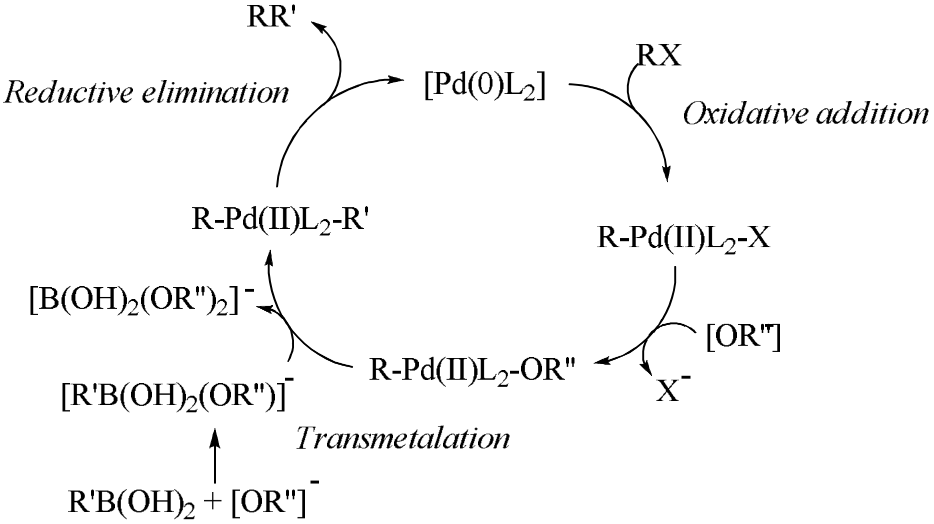


Figure 34 - Catalytic cycle for the Suzuki-Miyaura cross-coupling reaction.

3.4.2 SUZUKI-MIYAURA CROSS-COUPLING AND FERROCENYL LIGANDS

Phosphines are usual effective ligands used to stabilize Pd(0) species that take place in the Suzuki cross-coupling reaction.[283] Though triphenyl phosphine has often been employed, especially during the early stages of the reaction development, many new more effective ligands were created. In fact this was due to the need for ligands that would be amenable to the use of low catalyst loadings as well as demanding substrates such as chlorides especially those bulky and “deactivated” by the presence of electron rich groups.[279,283] Typically bulky electron rich ligands such as Buchwald’s dialkylbiaryl phosphines, Fu’s trialkylphosphines, bisdiphenylphosphino-alkyl, and palladacycles have led to successful cross-coupling.[279,285,290,291] Besides dppf,[279] other ferrocenyl phosphines have also revealed appealing features in the Suzuki reaction. For instance, they allow low catalyst loadings (**137**,**138**),[292] coupling bromides with boronic acids under R.T. conditions,[293] (**139**,[294] **140**[295]). Ferrocenyl ligands are effective with chlorides (**139**,**140**), even with non-activated ones (**140**, **141**,[119] **142-143**,[296] **144**[297]) and at R.T. (**144**). They are also remarkably tolerant to both electron-withdrawing and electron-donating substituents either on the chloride or boronic acid.[298] The ferrocenyl ligands mentioned are presented in **Figure** 35.

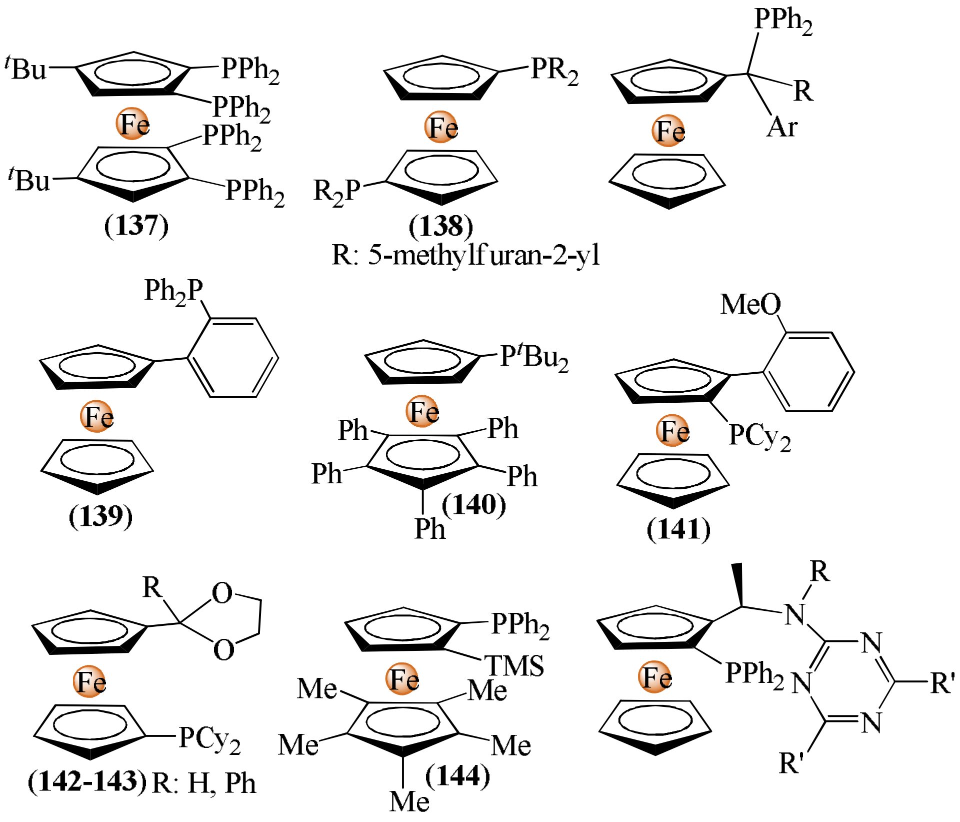
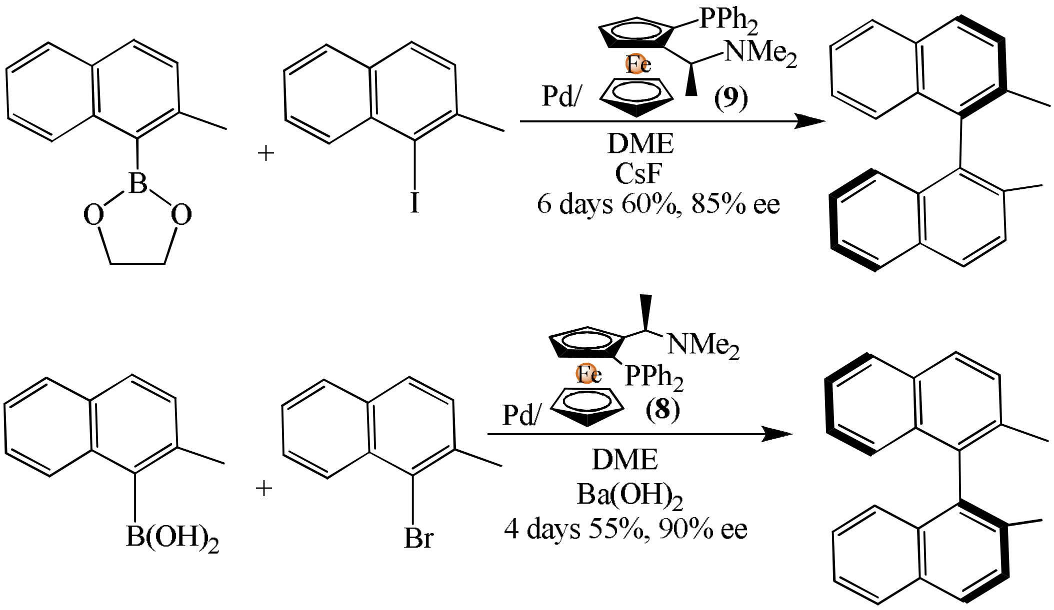


Figure 35 - Selection of ferrocenyl ligands used in the Suzuki-Miyaura cross-coupling reaction.

Notwithstanding the great interest and application of the Suzuki-Miyaura reaction for the synthesis of biaryls, even at industrial levels,[287] a general practical and efficient methodology that yields enantiomerically pure axially chiral biaryls remains unattained. In fact rendering the reaction asymmetric could provide a significant way to produce important compounds. For example those presenting chiral biaryl subunits which often occur on natural products, crown ethers, liquid crystals, useful ligands and other chiral auxiliaries for asymmetric syntheses.[35,61,299-303] Truly a limited number of examples on the asymmetric Suzuki coupling have been reported.[300,302] Perhaps this fact reflects more the inherent difficulty in coupling two sterically hindered arenes in a transition-metal-mediated process, than the interest in achieving it.[298-300] Indeed configurationally stable atropisomeric biaryls require the presence of at least three ortho substituents.[304] The stereoselective synthesis of such compounds usually involves stoichiometric chiral auxiliaries or chiral starting materials, as well as cumbersome procedures.[299,300,302] Due to its supra-mentioned advantages over other coupling reactions, the Suzuki-Miyaura one has attracted attention as a possible alternative to standard methods used for the synthesis of optically pure biaryls.[305] Few ligand types have been efficiently used for the asymmetric Suzuki reaction. Among those, chiral ferrocenyl,[302,306,307] binaphthyl,[299,309] and imidazoindole phosphine ligands[303] are worth mentioning, as well as C_2-symmetric bis-hydrazones.[308] As a matter of fact, on one of the early asymmetric Suzuki coupling investigations Cammidge used ferrocenyl ligands.[306] In reality he did it similarly to Hayashi’s pioneering work on asymmetric Kumada coupling. With ferrocenyl ligands Hayashi obtained axially chiral biaryls with high enantioselectivity, 95% ee.[310] Although with lower enantioselectivities, 85% ee, Cammidge et al. revealed that the reaction and particularly ferrocenyl ligands have potential to afford good results.[306,307] Building upon those results Espinet et al. achieved higher selectivities, 90% ee.[302] Both cases are presented in **Scheme** 42.

Scheme 42 - Examples of asymmetric Suzuki-Miyaura cross-coupling reactions.



Albeit good ee's were obtained the need for more efficient ligands and/or catalytic systems clearly remains.[303]

3.5 RESULTS AND DISCUSSION

3.5.1 FERROCENYL OXAZAPHOSPHOLIDINE OXIDE PHOSPHINES AND THEIR COORDINATION CHEMISTRY

The coordination behaviour of a ligand with a specific transition metal determines the structure of the catalyst, or pre-catalyst, thus formed and influences its performance in the catalytic reaction. Having this notion in mind we sought to investigate on our oxazaphospholidine oxide ligands' coordination chemistry.

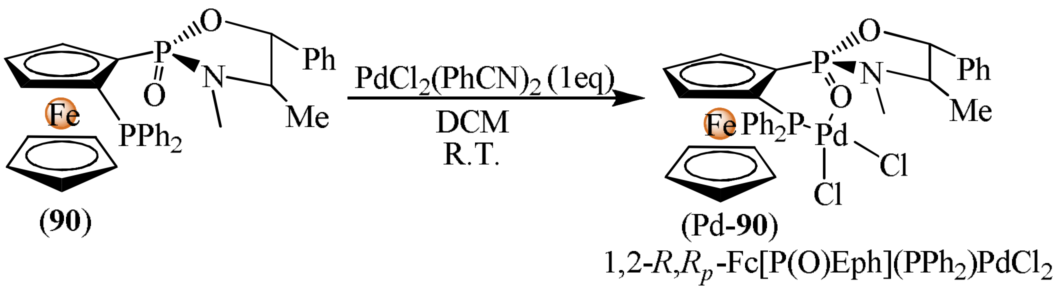
3.5.1.1 Reasoning on the Oxazaphospholidine Oxide Coordination Site

The oxazaphospholidine oxide group presents three atoms with possibility to coordinate with a metal atom. These are the oxygen and nitrogen atoms on the oxazaphospholidine ring, and the oxygen atom on the phosphorus oxide. Each of these coordination modes would lead to a metal complex with distinct steric and electronic properties from the others. As a matter of fact, besides the expected coordination with the free phosphine, the metal atom is probably more prone to establish a bond with the phosphoryl oxygen atom or alternatively with the nitrogen on the ring. This observation is based on the X-ray structures for the diphenylphosphine derivatives **85** and **90**, 1,2-*S*,S_p-Fc[P(O)Eph](PPh_2) and 1,2-*R*,R_p-Fc[P(O)Eph](PPh_2), in **Figure** 17, **Chapter *2***. Both these options would lead to a six-membered ring. However, in the first case the distance between the free phosphorus and the second binding site is shorter, implying shorter P-M-OP bonds. In addition metal coordination with the oxide is more likely to involve less steric hindrance. On the other hand, in the second case, if one does not consider distances, and steric factors, the nitrogen may be a stronger chelating atom. Considering both arguments the ring's oxygen atom is expected as less prone to chelate with an incoming metal atom.

3.5.1.2 Checking on the Oxazaphospholidine Oxide Coordination Site

To infer on the discussion above, because of the great importance of palladium in catalysis,[311] a 1:1 Pd/ligand complex was formed via reaction between ligand **90**, 1,2-*R*,R_p-Fc[P(O)Eph](PPh_2), and bis(benzonitrile)dichloropalladium(II) in fresh distilled DCM. According with the next **Scheme Pd-90,** 1,2-*R*,R_p-Fc[P(O)Eph](PPh_2)$PdCl_2$, was formed in 91% yield.

Scheme 43 - Formation of a palladium complex via coordination with ligand **90**.



^{31}P NMR analysis data indicated the disappearance of the peak correspondent to the diphenyl phosphine fragment, at -20 ppm in the free ligand, and the appearance of a new peak at around 15 ppm which could indicate Pd-P coordination. The peak from the phosphoryl in the oxazaphospholidine oxide group, at 37 ppm, disappeared also and a new one appeared at 45 ppm suggesting Pd-OP coordination. Opportunely crystallization and subsequent X-ray diffraction analysis confirmed Pd coordination with the free phosphine and the phosphorus oxide O atom, as depicted in the next **Figure**.

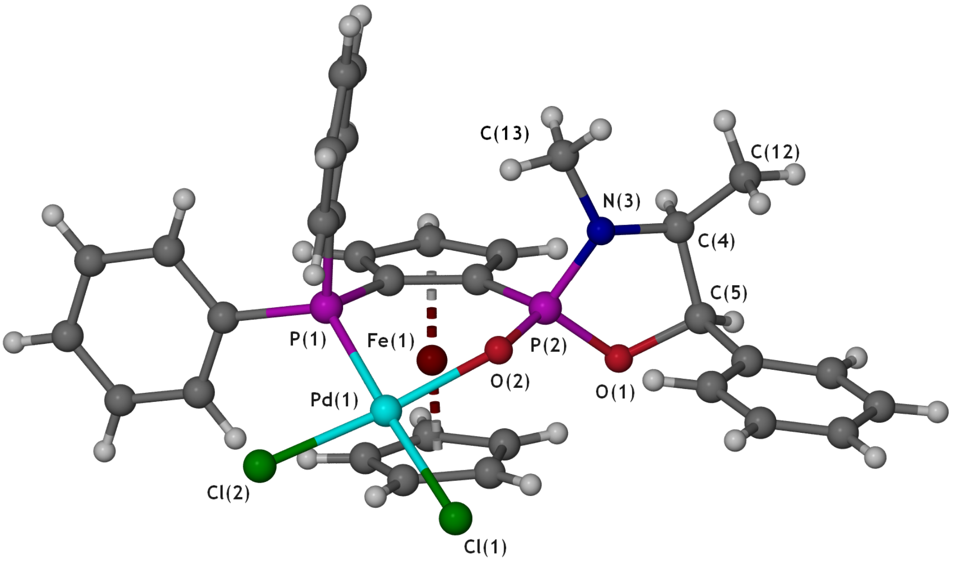


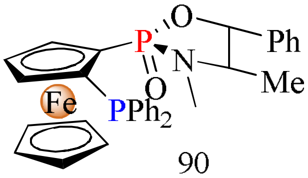
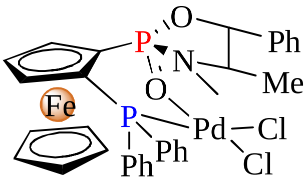
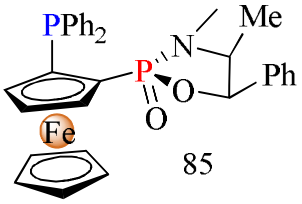
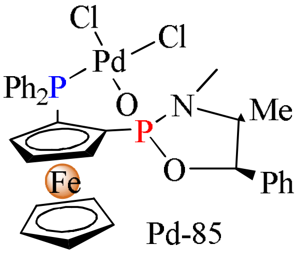
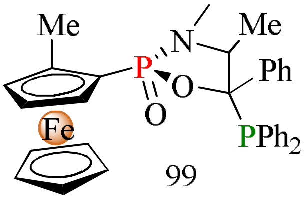
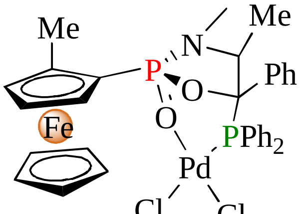
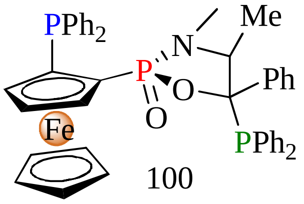
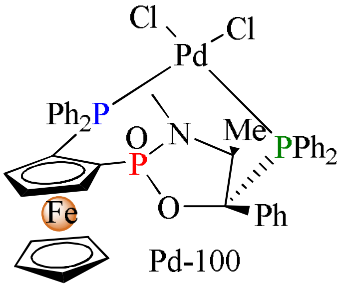
Figure 36 - X-ray structure of **Pd-90**. Selected bond distances (Å) and angles (°): Pd(1)-O(2) 2.071(4), Pd(1)-P(1) 2.229(2), Pd(1)-Cl(2) 2.262(2), Pd(1)-Cl(1) 2.364(2); O(2)-Pd(1)-P(1) 88.93(14), O(2)-Pd(1)-Cl(2) 172.8(1), P(1)-Pd(1)-Cl(2) 89.94(7), O(2)-Pd(1)-Cl(1) 88.4(1), Cl(2)-Pd(1)-Cl(1) 92.77(7).

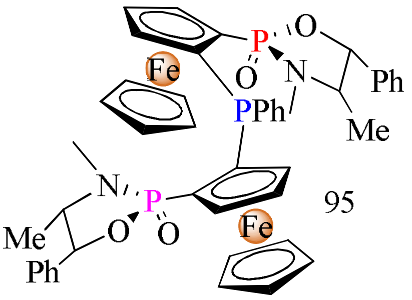
The compound crystallizes in the chiral space group $P2_1$ with two **Pd-90** molecules, a benzonitrile and a DCM molecule in the asymmetric unit, the two organometallic molecules being chemically and nearly structurally identical. Examination of the orientation of the two molecules and the crystal packing reveals no missing symmetry elements, and the refined absolute structure parameter [0.00(2)] is further evidence that the crystals are indeed chiral. **Figure** 31 shows the molecular structure of one of the two molecules. The coordination geometry about the Pd(II) atom is square planar, with P, O and the two Cl atoms *cis* to each other. The two Pd-Cl bonds are noticeably different [2.262(2) and 2.364(2) Å]. The longer Pd-Cl bond, which is *trans* to P(1), is likely to be due to the stronger *trans* effect of a P atom than an O atom. The three chiral centres P2, C4 and C5 have *R*, *S*, and *R* configurations, respectively, plus the complex is planar chiral with an *R* configuration.[198]

3.5.1.3 Further Considerations on Ferrocenyl Oxazaphospholidine Oxide Ligands Coordination Modes

In order to draw some conclusions about their coordination with Pd, other ligands were reacted in the same fashion as with **90**. Though we did not grow any more crystals or isolated these complexes we analyzed them by ^{31}P NMR. Having the example of **Pd-90** and comparing the free ligands' ^{31}P NMR chemical shifts with the ones from the respective complexes we established the following structures for each complex, as presented in **Table** 2.

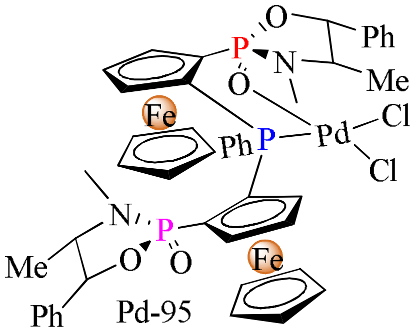
Table 2 - ^{31}P-NMR's of some of our ferrocenyl oxazaphospholidine oxide ligands and of their corresponding palladium complexes.

Free Phosphine	**Pd complex**
 90 ^{31}P-NMR δ: 37.0; -20.6	 Pd-90 ^{31}P-NMR δ: 45.4; 15.2
 85 35.9; -19.7	 Pd-85 42.8; 18.3
 99 47.5; 30.8	 Pd-99 66.8; 58.7
 100 47.0; 27.3, -19.0.	 Pd-100 69.3; 22.5; 18.3



95

39.8; 38.2; -38.4



Pd-95

46.8; 38.0; 18.6

With respect to coordination with Pd, Ligand **90** and its P-epimer **85**, 1,2-R,R_p-Fc[P(O)Eph](PPh$_2$) and 1,2-S,S_p-Fc[P(O)Eph](PPh$_2$), present a rather comparable behaviour. The chemical shifts' differences between each phosphorus atom on the ligand and the same atoms on the complex are proportional. This suggests that while the structures may somewhat present different steric and electronic properties they assume a similar coordination mode with the metal. Also with a free phosphine and the phosphine oxide, both presenting significant changes in chemical shift from the ligand to the complex, ligand **99**, 1,2-S,S_p-Fc[P(O)(Eph'PPh$_2$)](Me), seems to establish P-Pd-OP bonds in a six membered ring. In contrast, besides the phosphorus oxide ligand **100**, 1,2-S,S_p-Fc[P(O)(Eph'PPh$_2$)](PPh$_2$), presents two free phosphorus atoms with the coordination occurring at both to form an 8 membered ring. In truth the chemical shift change on these last atoms is in agreement with metal bonding whereas the less significant change on the phosphoryl P(O) chemical shift solely reflects alteration on the ring's electron density. On a diverse case ligand **95**, 1,2-R,R_p-[FcP(O)Eph]$_2$(PPh), presents two phosphoryl O atoms and only one free P atom. Either due to steric constrains and/or due to reluctance on the Cl to be displaced, the Pd center establishes bonds with the free phosphine and only one phosphoryl O. The remaining one practically presents no chemical shift variation.

These simple experiments show that the oxazaphospholidine oxide group has the ability to chelate with Pd, in this case through phosphoryl oxygen (PO-Pd) coordination. When its structure contains only one free phosphine the oxazaphospholidine oxide group may confer hemilabile character to the ligand which acts as a PO ligand, in this case a bis-phosphine monoxide (BPMO). Such is the case of ligands **90**, **85**, **99** and **95**. The oxazaphospholidine oxide phosphoryl O is a hard Lewis base center and a weak restrictive donor, whereas the free phosphine (P), a soft Lewis base center and strong coordinating group.[312,314] Hybrid ligands, with difunctional properties that result from the presence of two basic sites with such distinct donating properties, display exchangeable coordination modes that switch on a sequential activation and stabilization mechanism.[314] This hemilability, or aptitude to block and liberate a coordination site on the metal, confers catalytic activity to the catalyst. It also stabilizes various transition metals in low and high oxidation states.[312,314] Actually by generating stable metal low-valent and unsaturated species this type of “smart ligands” allow low energetic barrier pathways. It favours and activates different stages of the catalytic cycle including key steps such as ligand exchange, isomerization, oxidative addition, migratory insertion, and reductive elimination. Accordingly these ligands may catalyse diverse reactions under unusually mild conditions with very high selectivities. For instance the catalyst oxidative addition with an aryl halide, often the rate-determining-step in various reactions, is expected to undergo directly without requiring reduction or ligand dissociation, hence reducing such energy barriers. Desirable C-Cl and C-F bond activation, sp^3-sp^3 coupling, coupling of sterically hindered substrates, room temperature reactions, and aqueous reactions represent some of the challenges possible to be dealt with by using hemilabile ligands.[312,314] In fact PO ligands have soon shown to be useful in various chemistry areas,[312,315] continuing to attract interest including in catalysis and asymmetric catalysis.[314,316]

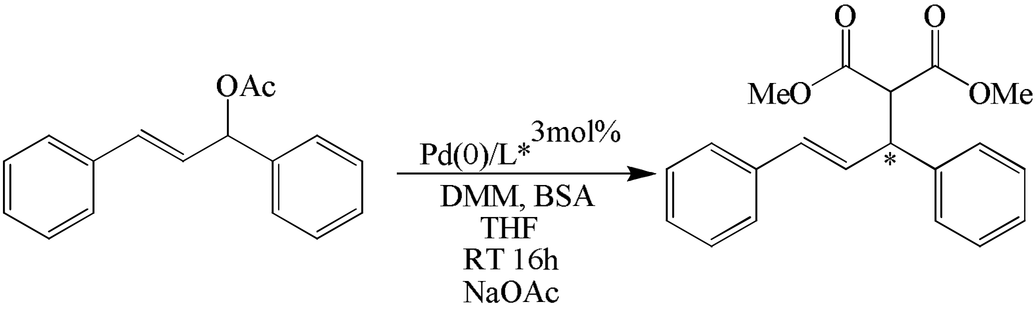
The ligands hemilability depends on several factors such as the metal's oxidation state, coordination environment ensued by the presence of other ligands in the inner sphere, and the concentration and reactivity of substrate/reagent. Plus it depends upon the nature of the counterion if the metal complex is charged, size of the chelate ring, medium polarity, temperature, and so forth.[312] For this reason accurately predicting a ligand's performance becomes challenging. Though, we observed that when two free phosphines are present on the molecule, besides the oxazaphospholidine oxide moiety, the metal coordinates with these performing more as a diphosphine, PP ligand. Such is the case of ligand **100**, 1,2-*S*,S_p-Fc[P(O)(Eph'PPh_2)](PPh_2). For example, adding one equivalent of **90**, 1,2-*R*,R_p-Fc[P(O)Eph](PPh_2), to **Pd-90** would expectedly cause the Pd to bind with both free P atoms, one from each ligand. In other words altering the ratio of Pd/ligand from 1:1 to 1:2 should cause Pd to detach from the phosphoryl O. The ligand would act as unidentate presenting a dangling oxazaphospholidine oxide. In fact this has been observed in other PO ligands.[312-314]

3.5.2 FERROCENYL OXAZAPHOSPHOLIDINE OXIDE PHOSPHINES AND ASYMMETRIC ALLYLIC ALKYLATION

Having reached the above conclusions about the coordination chemistry of our oxazaphospholidine oxide ligands we decided to further test them. We sought to investigate on the ligands catalytic activity and ability to educe enantioselectivity, including on the role of planar chirality. We especially focused on the new ligands with S_p configuration at the ferrocenyl backbone and *S* configuration at the phosphorus oxide. One of the reactions chosen for that purpose was the asymmetric allylic alkylation. Besides its aforementioned importance this reaction has been catalysed by

PO ligands before,[317-319] including ferrocenes[134] and ferrocenyl oxazaphospholidine oxides.[173] Accordingly under typical standard conditions the palladium catalysed allylic substitution of 1,3-diphenyl-2-propenyl acetate by the anion of dimethyl malonate (DMM) was studied, as depicted in the following **Scheme**.

Scheme 44 - Palladium catalysed allylic substitution of 1,3-diphenyl-2-propenyl acetate by DMM.



The catalyst was formed by preparing and stir for 30 minutes a THF solution containing the palladium source, $[C_3H_5PdCl]_2$, and the ligand. Next, a THF solution of rac-1,3-diphenyl-2-propenyl acetate, DMM, *N*,*O*-bis-(trimethylsilyl)acetamide (BSA), and NaOAc were added, and the mixture was stirred at R.T. for 16 hours. Subsequent to aqueous workup and solvent evaporation, the conversion was determined by ^{1}H NMR analysis of the crude mixture. E.e. values were measured by HPLC (Chiralcel-OB). The employed ligands are represented in the next **Figure** together with a **Table** summarizing the results obtained.

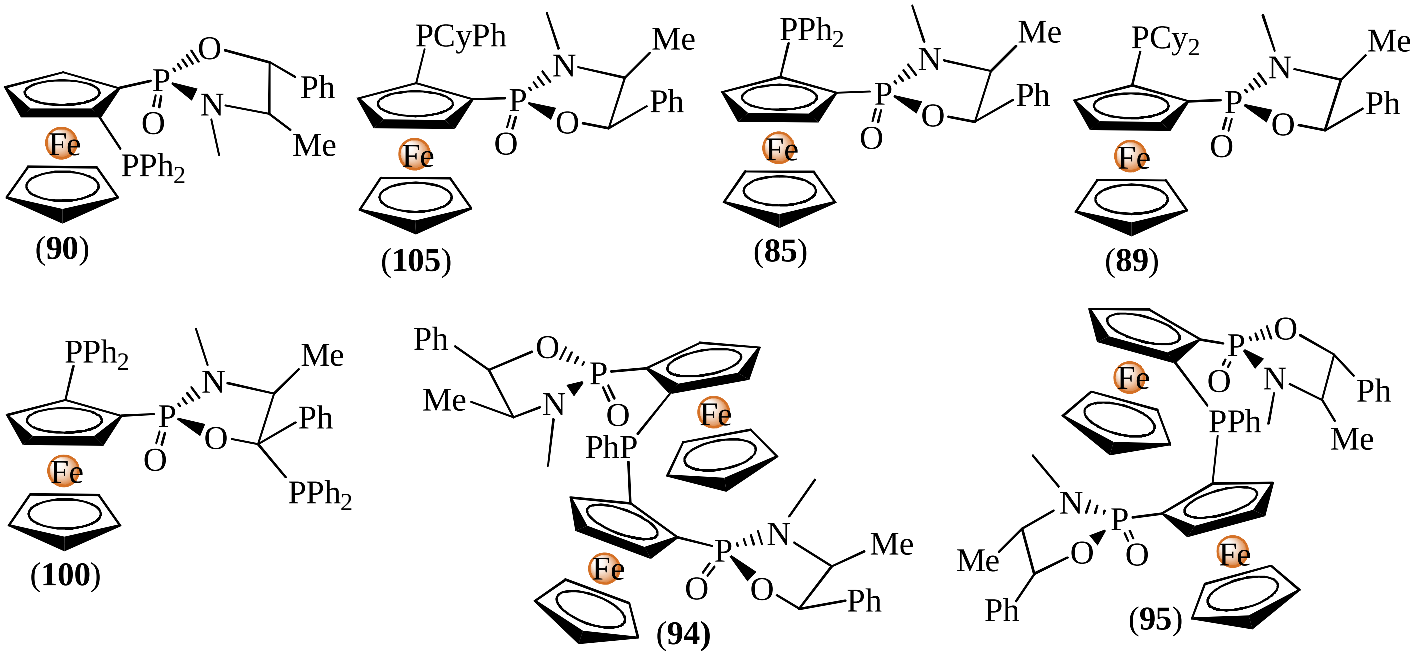


Figure 37 - Selection of ligands tested in this work on AAA.

Table 3 - Results on the application of new ferrocenyl oxazaphospholidine oxide ligands to the palladium catalysed allylic substitution of 1,3-diphenyl-2-propenyl acetate by DMM.

Entry[a]	Ligand	Conversion %[b]	E.e. %[c]	Configuration
1	**85**	>99	25	*S*
2	**89**	>99	8	*S*
3	**105**	>99	27	*S*
4	**100**	>99	23	*R*
5	**90**	>99	70	*R*
6	**95**	>99	0	-
7	**94**	>99	6	*S*

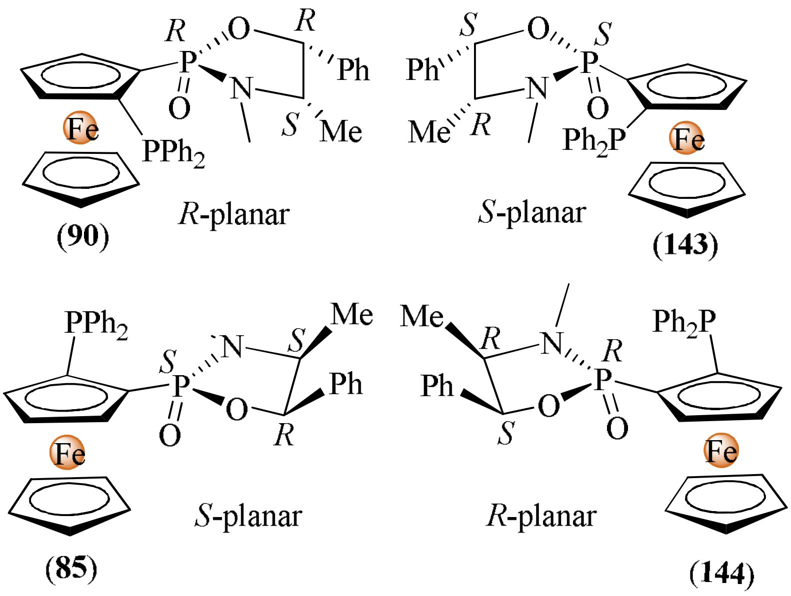
(a) Reaction conditions: 126 mg of 1,3-diphenyl-2-propenyl acetate (0.5 mmol), 250 µL of BSA (1mmol), 15 mg NaOAc (0.18 mmol), 115 µL of DMM (1mmol), room temperature, 5.45 mg of $[C_3H_5PdCl]_2$ (0.015 mmol) and 0.03 mol of ligand in 2 mL of THF at RT during 16 h. (b) The conversion was calculated from the crude reaction mixture by ^{1}H NMR spectroscopy. (c) Determined by HPLC using column DAICEL AD (95/5) Hex/iPrOH).

From the results on **Table** 3 we are able to notice that all the tested ligands display high activity in the studied AAA reaction and under the chosen set of conditions. Entry

1 shows that compound **85**, 1,2-*S*,*S*$_p$-Fc[P(O)Eph](PPh$_2$), induces enantioselectivity with similar chirality, *S*, to the chirogenic *S* oxazaphospholidine oxide P atom and the plane of chirality, *S*. The same happens with ligand **89**, 1,2-*S*,*S*$_p$-Fc[P(O)Eph](PCy$_2$), though whichever for steric and/or electronic reasons the degree of enantioselectivity is minor. We are not able to conclude whether the electron richer and bulkier PCy$_2$ group leads the ligand into acting more as monodentate P ligand than as a bidentade PO one, such as ligand **85**. With a phenyl and a cyclohexyl group, ligand **105**, 1,2-*S*,*S*$_p$-Fc[P(O)Eph](PCyPh), should have steric and electronic properties that are intermediate to those from ligands **85** and **89**. Indeed the result is better than the one from **89** and even from **85**, however it is expected that the presence of the allegedly chiral free phosphine, *R*, also plays a role on the reaction. Therefore, though by comparing these three results it seems that the other elements of chirality in the molecule exert a stronger effect than the free phosphine P chirality, one is not able to take definite conclusions on the matter.

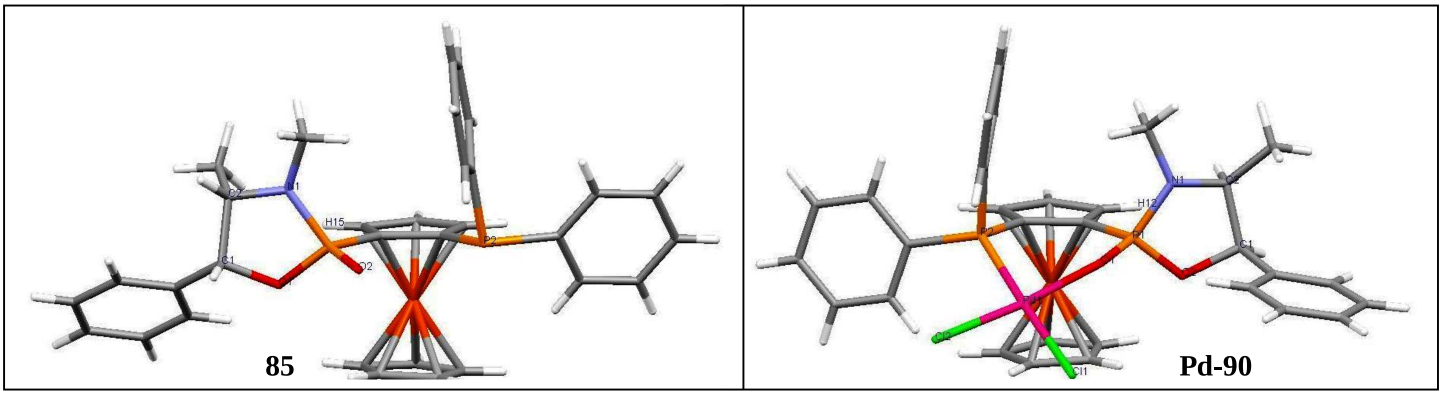
Comparing entries 1 and 4 we can see close e.e.'s albeit with inversion of configuration. Indeed as discussed previously the coordination mode between the two ligands is expected to be different, PO versus PP, and thus also the spatial arrangement and electronic properties around the metal. Going from ligand **85** with an *S*,*S*$_p$ configuration to its P-epimer **90**, 1,2-*R*,*R*$_p$-Fc[P(O)Eph](PPh$_2$), entries 1 and 5 respectively, we observe an inversion of the product's configuration as well as a significant e.e. difference. Clearly planar chirality and P-chirality, at the oxide, play an important role on the reaction outcome. We could discuss how planar chirality plays probably the biggest role, since Pd does not bind directly to the P but to the O and therefore the influence from P-chirality is more secondary. Unfortunately we are not able to evaluate each one of these factors separately, which would have been possible would we have access to diastereomers **96** and **97** with R,S_p and S,R_p configurations, **Figure** 21 in **Chapter** ***2***, page 82. Also having an inversion of configuration however with different e.e.'s is explained by the fact that ligands **85** and **90** are P-epimers but one is not the mirror image of the other, as would be ligands **143** and **144** represented in **Figure** 37.

Figure 37 - Ligands **90**, **85** and their corresponding mirror image representations.



Indeed ligands **85** and **90** present inverted planar and P-chirality, but the same central chirality at C4 and C5 atoms on the oxazaphospholidine ring. In ligand **90** there is probably a better match from all these chiral elements that act synergistically to afford a relatively good enantioselectivity, nevertheless such is not the case with ligand **85**.

In order to rationalize on the above fact we want to consider both X-ray structures for ligand **85**, 1,2-S,S_p-Fc[P(O)Eph](PPh$_2$), and complex **Pd-90**, 1,2-R,R_p-Fc[P(O)Eph](PPh$_2$)PdCl$_2$, in the following **Figure** .



85

Pd-90

Figure 38 - X-ray structures Mercury views of ligand **85** and complex **Pd-90**.

Indeed, apart from having opposite planar chirality, ligands **85** and **90** are also expected to give rise to complexes in which the spatial arrangement around the metal center is dissimilar. Due to their opposite P-chirality, at the oxazaphospholidine oxide, the C4 methyl and C5 phenyl may be pointing towards the phosphoryl group, on complex **Pd-90**, or to the opposite direction, on ligand **85**. Since the metal coordinates with the phosphoryl oxygen, ligand **90** imposes more steric hindrance closer to the coordination sphere. This may confer more rigidity to the way an incoming substrate molecule will bind to the metal, therefore increasing enantiomeric discrimination. Conversely ligand **85** allows for more spatial freedom thus resulting in a minor degree of enantioselectivity.

As suggested on entries 6 and 7, diferrocenyl ligands **95** and **94,** 1,2-R,R_p-[FcP(O)Eph]$_2$(PPh) and 1,2-S,S_p-[FcP(O)Eph]$_2$(PPh), educe none or poor enantioselectivity. Comparing these last ligands with ligands **90** and **85** respectively, 1,2-R,R_p-Fc[P(O)Eph](PPh$_2$) and 1,2-S,S_p-Fc[P(O)Eph](PPh$_2$), we can perceive that they will have different steric and electronic properties. Also the question arises whether the metal favours coordination with only one of the two phosphoryl groups present in ligands **90** and **85**.

Based on **Table** 3 we believe that steric factors, probably more than electronic ones, are important in the reaction. In fact this also is suggested by early results.[173] In addition planar chirality is believed to play an important role on enantioselectivity, with P-chirality, either at the phosphorus oxide or in free phosphines also influencing it.

Thus far, from these preliminary results on the AAA of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate, we conclude that ferrocenyl oxazaphospholidine oxide ligands exert high catalytic activity with ability to educe enantioselectivity up to 70% e.e. It would be important to carry out more studies on the reaction, expecting to obtain better results, and to better be able to rationalize on the ligands performance.

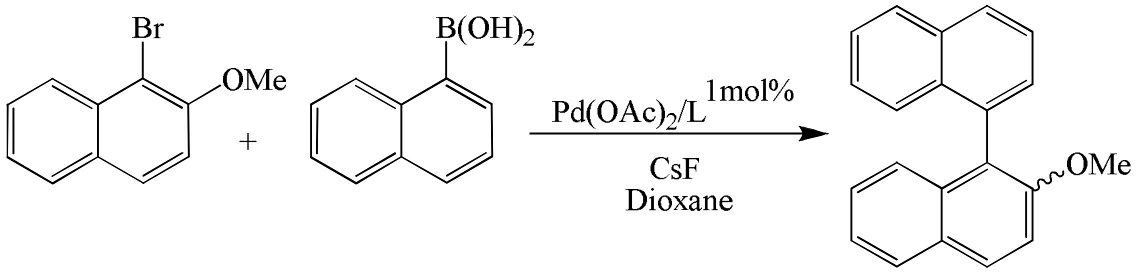
3.5.3 FERROCENYL OXAZAPHOSPHOLIDINE OXIDE PHOSPHINES AND SUZUKI COUPLING

Although studies involving our ligands and AAA unveiled some aspects of their behaviour in asymmetric catalysis all displayed similar catalytic activity, reason why we decided to further test them. Given that the Suzuki-Miyaura cross-coupling has been successfully catalysed by PO ligands,[119,296,313,314,320] we decided to apply our ligands in this reaction, this time the focus of our study being their catalytic activity. Also from that point of view we tried to address questions as how the presence of the oxazaphospholidine group affects the reaction and whether we would notice different activity between P-epimers.

3.5.3.1 Coupling Bromides and Boronic Acids in the Presence of Ferrocenyl Oxazaphospholidine Oxide Ligands

We decided to test our ligands in the palladium catalysed coupling of 2-methoxy naphthyl bromide with naphthyl boronic acid. This choice was based on the relative challenge involved in cross-coupling bulky substrates and on the importance of naphthyl derivatives, especially those with at least three substituents. The reaction is presented in the **Scheme** below.

Scheme 45 - Palladium catalysed Suzuki coupling of 2-methoxy naphthyl bromide with naphthyl boronic acid.



Some of the employed ligands are represented in the following **Figure** together with a **Table** summarizing the results obtained.

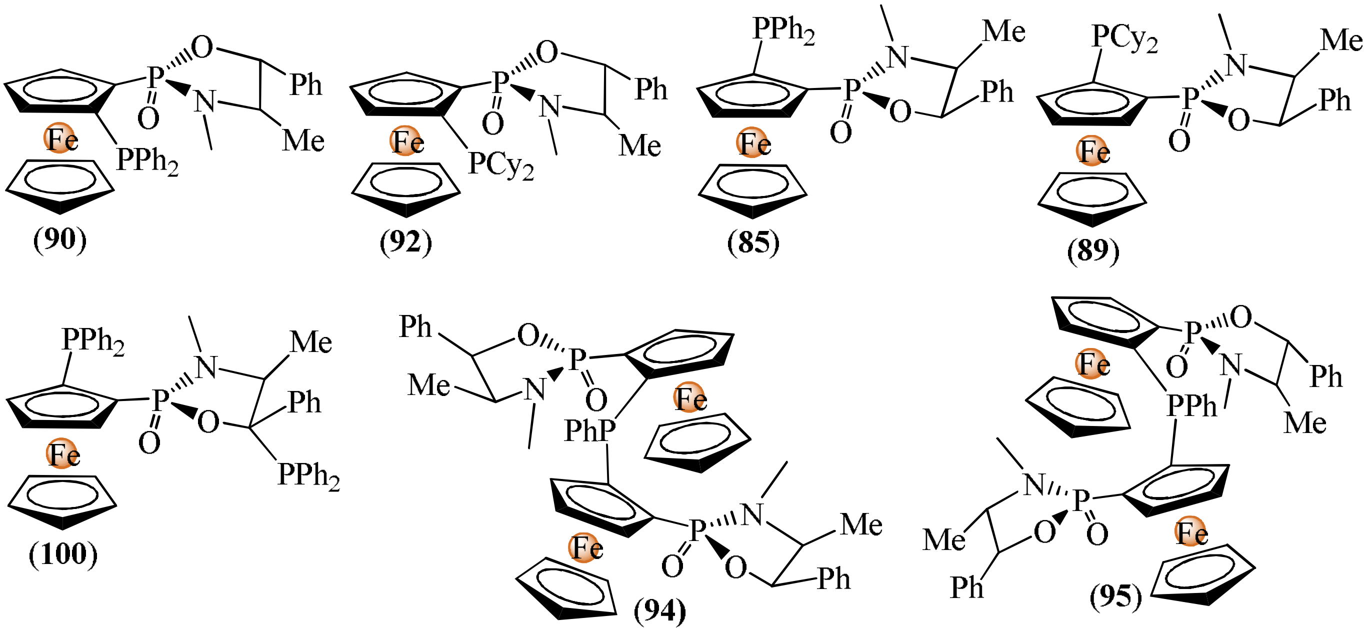


Figure 38 - Selection of ligands tested in this work on the Suzuki-Miyaura cross coupling.

Table 4 - Results obtained while testing our ferrocenyl oxazaphospholidine oxide ligands in the Suzuki coupling of 2-methoxy naphthyl bromide with naphthyl boronic acid.

Entry[a]	**Ligand**	**L/Pd ratio**	**T (°C)**	**Reaction Time (h)**	**Conversion (%)**
1	**90**	1	105	4	81
2	**90**	2	105	4	97
3	**90**	2	105	1	61
4	**90**	2	75	4	94
5	**85**	1	105	4	79
6	**85**	2	105	4	96
7	**85**	2	105	1	64
8	**85**	2	75	4	92
9	**94**	1	105	4	18
10	**94**	2	105	4	33
11	**95**	1	105	4	17
12	**95**	2	105	4	34
13	**100**	1	105	4	87
14	**100**	2	105	4	46
15	$FcPPh_2$	1	105	4	44
16	$FcPPh_2$	2	105	4	88
17	PPh_3	1	105	4	50
18	PPh_3	2	105	4	57
19	$Ph_2PC_6H_4OMe$-*o*	1	105	4	35
20	$Ph_2PC_6H_4OMe$-*o*	2	105	4	39
21	$Ph_2PC_6H_4OH$-*o*	1	105	4	5
22	$Ph_2PC_6H_4OH$-*o*	2	105	4	3

(a) Reaction conditions: 1.0 equiv. of aryl bromide, 1.5 equiv. of boronic acid, 3.0 equiv. of CsF, dioxane, 1 mol% $Pd(OAc)_2$.

A quick observation on **Table** 4 shows how the several tested ferrocenyl oxazaphospholidine oxide ligands exhibit diverse activity in the chosen Suzuki reaction.

In order to better understand the oxazaphospholidine oxide moiety's influence on the ligands' activity we have performed the reaction using a 1 to 1 and a 1 to 2 ligand to Pd ratio. As observed in the majority of cases this ratio affects activity. Comparing entry 1 and 2 we notice that ligand **90**, 1,2-*R*,*R*$_p$-Fc[P(O)Eph](PPh$_2$), displays higher activity at a ligand to palladium ratio of 2:1. The same happens with oxazaphospholidine oxide ligands **85**, **94** and **95**, 1,2-*S*,*S*$_p$-Fc[P(O)Eph](PPh$_2$), 1,2-*S*,*S*$_p$-[FcP(O)Eph]$_2$(PPh) and 1,2-*R*,*R*$_p$-[FcP(O)Eph]$_2$(PPh), on entries 5 and 6, 9 and 10, and 11 and 12 respectively. Comparing these results with the ones achieved by using FcPPh$_2$, entries 15 and 16, we can notice that a similar trend is observed. In this ligand, which is a related version of ligands **90** and **85** but without the oxazaphospholidine oxide moiety, the activity is even more affected by the ligand to Pd ratio. More specifically when using FcPPh$_2$ a 1:1 ratio leads to 44% conversion while a 2:1 ratio to 88%, compared with 81 and 97%, and 79 and 96%, in entries 1 vs. 2, and 5 vs. 6. This suggests a decrease of activity originated by the absence of the oxazaphospholidine oxide which is more relevant when a 1:1 ratio is used. The observation can be rationalized if one considers that the hemilabile oxazaphospholidine oxide group can coordinate to Pd. Especially when a 1:1 ratio is used, ligands **90** and **85** can act as stable bidentade PO ligands in contrast to the less stable monodentade FcPPh$_2$. This must be of particular importance in stabilizing relatively more sensitive Pd(0) species which are often formed subsequent to reductive elimination at the end of each catalytic cycle. When the ligand ratio is doubled both ligand types, with and without the hemilabile group, act more similarly as monodentade ligands on a bisphosphine Pd complex. However the presence of this moiety seems to increase the activity even with a 2 to 1 ligand to Pd ratio. Hypothetically, this is either due to extra coordination and stabilization of the oxazaphospholidine oxide to the Pd (0) species, or due to extra steric hindrance and/or different electronic properties conferred to the catalyst.

As displayed on **Table** 4, despite some structural dissimilarity, P-epimers **90** and **85** show rather similar results the same happening between ligands **94** and **95**. Performing the reaction with the first pair of ligands however reducing its time to 1 hour continues to reveal a similar behaviour, entries 3 and 7, though with an expected decrease in conversion, 61 and 64%. Finally a reaction at lower temperature, 75ºC, still presents similar high activities 94 and 92%, in entries 4 and 8.

Considering the different activity between **90** and **85**, and **94** and **95** we can only relate it with different steric and/or electronic properties. On this matter it could also be interesting to perform the reaction with Fc_2PPh.

Taking notice of entries 13 and 14 we see that when using ligand **100**, 1,2-*S*,S_p-Fc[P(O)(Eph'PPh_2)](PPh_2), the best result is achieved by using a 1:1 ratio. This is not so odd bearing in mind that the ligand is supposed to act as a bidentade bisphosphine. In fact entry 13 presents a somewhat similar result to entry 16, 87 and 88% respectively, in which two monodentade phosphine molecules, $FcPPh_2$, are expected to coordinate with one Pd atom. When two equivalents of **100** are used conversion drops to half. Possibly the metal atom binds with both molecules forming a stable saturated 18 electrons tetra-coordinated complex which slows the reaction rate. Interestingly entries 14 and 15 present close conversions, 46 and 44%. However in entry 15 likely an unstable low-valent unsaturated 12 electrons complex is formed. In both cases the catalytic cycle is affected however probably it is so at different stages.

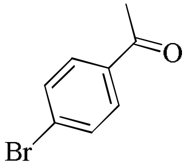
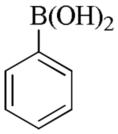
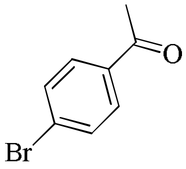
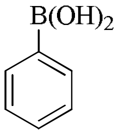
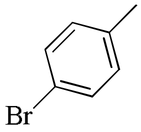
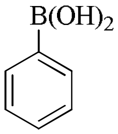
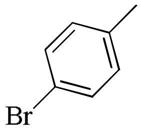
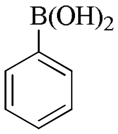
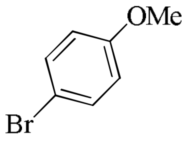
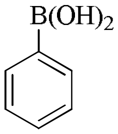
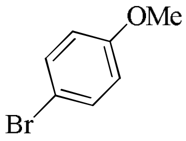
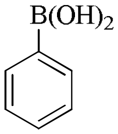
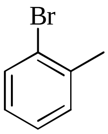
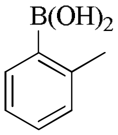
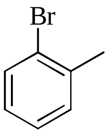
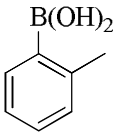
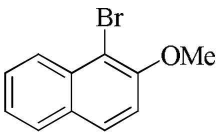
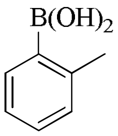
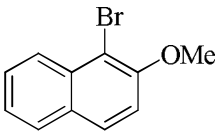
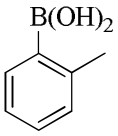
Ligand **92**, 1,2-*R*,R_p-Fc[P(O)Eph](PCy_2), has also shown to perform better under a 1:1 ligand to Pd ratio resulting in more than 99% conversion in this case, while in 55% when the ligand amount was doubled.[198] Ligand **89**, 1,2-*S*,S_p-Fc[P(O)Eph](PCy_2), is expected to have a similar behaviour, however it seems to be more air and moisture sensitive than the PPh_2 derivative **85**, which may affect the reaction outcome. In fact a related bulky monophosphine, PCy_3, allowed an 87% conversion at a 1:1 ratio and 32% at 2:1 ratio. Likely while the metal complex is more active when binding to two molecules of **85** and **90**, the PPh_2 derivatives, it is more active when binding to only one molecule of **92**. The steric hindrance and electron density that the PCy_2 group provides is responsible for this distinct behaviour.

With the purpose to draw more conclusions on the influence of a hemilabile coordinating site in the ligand we have also tested PPh_3, $Ph_2PC_6H_4OMe$-*o* and $Ph_2PC_6H_4OH$-*o*. The synthesis of these last two ligands is described in **Chapter 5**. The results on entries 17 to 22 imply a week dependence on the ligand to Pd ratio as well as lower activity provided by the presence of the extra *ortho* binding site. In the light of the previous results obtained with the ferrocenyl oxazaphospholidine oxide ligands, it is revealed how each case is very specific and how challenging ligand design may be. Factors, like the rigidity of the molecule and the proximity between the two binding sites are suspected to play an important role on the results.

3.5.3.1.1 Further testing the ligands

Thus far P-epimers **85** and **90**, 1,2-*S,S*$_p$-Fc[P(O)Eph](PPh_2) and 1,2-*R,R*$_p$-Fc[P(O)Eph](PPh_2), have shown close behaviour, for this reason we tested them varying electronic and steric conditions on the bromide and the boronic acid. The results are shown in **Table** 5.

Table 5 - Results obtained while testing our ferrocenyl oxazaphospholidine oxide ligands in the Suzuki coupling of several bromides with boronic acids.

Entry[a]	ArBr	$RB(OH)_2$	Ligand	Conversion (%)
1			**85**	>99
2			**90**	> 99
3			**85**	>99
4			**90**	>99
5			**85**	>99
6			**90**	>99
7			**85**	>99
8			**90**	>99
9			**85**	>99
10			**90**	>99

(a) Reaction conditions: 1.0 equiv. of aryl bromide, 1.5 equiv. of boronic acid, 3.0 equiv. of CsF, dioxane, 1 mol% $Pd(OAc)_2$, 105ºC.

In the presented cases both ligands are again equally active, especially revealing little dependence on electronic factors. How it would be expected when coupling bulky substrates to afford tetra-substituted biaryls the conversion drops.[198]

3.5.3.2 Coupling Chlorides and Boronic Acids in the Presence of Ferrocenyl Oxazaphospholidine Oxide Ligands

Owing to the availability and lower prices of chlorides, the Suzuki coupling with this type of substrates is of great interest. Due to a relatively stronger C-Cl bond, coupling such substrates is generally more challenging. This factor gives importance to the design of effective ligands for the reaction. Hence we have compared our ligands behaviour in the coupling of *p*-chloroacetophenone with phenyl boronic acid. The reaction is depicted in **Scheme** 46 and the results are summarized in **Table** 6.

Scheme 46 - Palladium catalysed Suzuki coupling of *p*-chloroacetophenone with phenyl boronic acid.

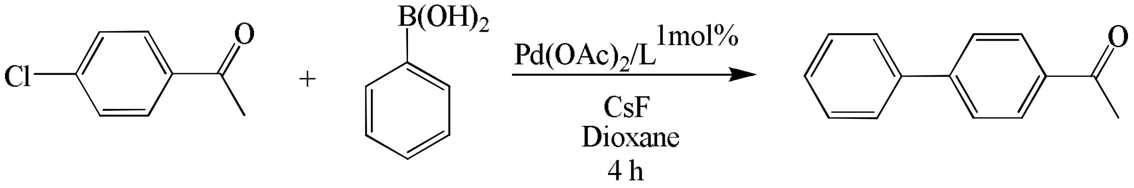


Table 6 - Results obtained while testing our ferrocenyl oxazaphospholidine oxide ligands in the Suzuki coupling of *p*-chloroacetophenone with phenyl boronic acid.

Entry[a]	Ligand	L/Pd ratio	T (°C)	Conversion (%)
1	**85**	2	105	65
2	**90**	2	105	63
3	**89**	1	105	96
4	**92**	1	105	>99
5	**94**	2	105	28
6	**95**	2	105	23
7	**100**	1	105	51

8	$FcPPh_2$	2	105	93
9	PCy_3	1	105	>99
10	PPh_3	2	105	8
11	$Ph_2PC_6H_4OMe$-*o*	2	105	26
12	$Ph_2PC_6H_4OH$-*o*	2	105	37

(a) Reaction conditions: 1.0 equiv. of aryl chloride, 1.5 equiv. of boronic acid, 3.0 equiv. of CsF, dioxane, 1 mol% $Pd(OAc)_{2,}$, 4h.

Table 6 shows how among the several tested ferrocenyl oxazaphospholidine oxide ligands only **89** and **92**, 1,2-*S*,S_p-Fc[P(O)Eph](PCy_2) and 1,2-*R*,R_p-Fc[P(O)Eph](PCy_2), entries 3 and 4, are capable to catalyse the reaction more effectively. Ligands **85**, **90** and **100**, 1,2-*S*,S_p-Fc[P(O)Eph](PPh_2), 1,2-*R*,R_p-Fc[P(O)Eph](PPh_2) and 1,2-*S*,S_p-Fc[P(O)(Eph'PPh_2)](PPh_2), entries 1, 2 and 7, could probably afford higher conversions than the ones presented, would the reaction time be extended. Nevertheless it is not expected that they would be effective with more demanding non-activated and bulky substrates as ligand **92** has revealed to be.[198] In fact ligands **92** and **89** have shown comparable results to the ones in which the bulky electron rich phosphine PCy_3 was used, entry 9.

Once again P-epimers pairs present similar behaviour as seen with pairs **85**/**90**, **89**/**92** and **94**/**95**, 1,2-*S*,S_p-$[FcP(O)Eph]_2$(PPh)/1,2-*R*,R_p-$[FcP(O)Eph]_2$(PPh). Comparison between entries 1, 2 and 8 reveals an, at a first glance, unanticipated result. Indeed it shows higher conversion achieved by the monodentade phosphine $FcPPh_2$ than by ligands **85** and **90**. This leads us into thinking that in this particular reaction the oxazaphospholidine oxide moiety stabilizes the catalyst however lowering the reaction rate. Extending the reaction time could better elucidate on the matter.

Another interesting set of results on entries 10, 11 and 12 shows how in this reaction the presence of an extra *ortho*-coordinating site, compared with $PPh_{3,}$ is important to increase the reaction rate. In this case the stronger chelating $Ph_2PC_6H_4OH$-*o* ligand exerts better activity. Comparing these results with the ones achieved by the same three ligands, while coupling 2-methoxy naphthyl bromide with naphthyl boronic acid, entries 18, 20 and 22 on **Table** 4, we can notice an inversion on the ligands' reactivity. Presumably this implies that the action of a specific hemilabile moiety, present in a specific ligand, affects different catalytic steps in a different manner, with the influence upon the rate determining step being more important. For instance, in the chloride reaction, coordination of the hemilabile group to the metal should increase its electron density. This could facilitate oxidative addition, the rate determining step, which has been described as similar to an aromatic nucleophilic substitution by the Pd complex.[321] On the other hand the transmetalation step during the bromide reaction may be of greater importance, and is probably not favoured by the presence of the hemilabile group. In fact this step is believed to proceed more accordingly to an S_E2 concerted mechanism.[321] Though the different results for ligands PPh_3, $Ph_2PC_6H_4OMe$-*o* and $Ph_2PC_6H_4OH$-*o* may found reasoning in the above remarks, the same is not said to the opposite trends observed with ligands **85**, **90** and $FcPPh_2$ in both reactions. Once again, while in both cases we are trying to infer on the influence of a hemilabile group on a ligand's structure the fact is that each ligand exerts a different influence on the catalytic cycle in such a way that predicting its catalytic activity is not linear.

In conclusion the oxazaphospholidine oxide moiety exerts clear influence on the ligands performance, both its activity and its ability to educe chirality. **85** and **90** are effective ligands in the Suzuki reaction between several aryl bromides and aryl boronic acids, while ligands **89** and **92** are especially useful to couple chlorides. Ligand **90** also revealed significant potential to induce chirality on a standard test AAA reaction.

3.6 CONCLUDING REMARKS

The ferrocenyl oxazaphospholidine oxides prepared on **Chapter *2*** have been investigated in terms of their chemical coordination towards palladium and in terms of their chemical activity and ability to educe enantioselectivity in asymmetric catalysis. **Pd-90**, a palladium complex containing ligand **90**, 1,2-R,R_p-Fc[P(O)Eph](PPh_2), was prepared and isolated. Its X-ray structure resolution demonstrated coordination with palladium both at the diphenylphosphine and the phosphoryl oxygen atom. 1 To 1 mixtures of other ferrocenyl oxazaphospholidine oxides with a Pd source were prepared and analysed by ^{31}P NMR. The data from these solutions and the corresponding free ligands ^{31}P NMR, together with the data from **Pd-90**, suggests that the oxazaphospholidine oxide moiety has the ability to coordinate to palladium via the phosphoryl oxygen. However, normally this coordination occurs only providing that other stronger coordinating atoms, such as free phosphines, are not occupying all the metal’s coordination sites.

Ferrocenyl oxazaphospholidine oxides have displayed high activity and ability to educe enantioselectivity. Among several ligands tested on AAA all displayed high activity however leading to different enantioselectivities. Ligand **90**, presenting (R,R_p) configuration educed the highest enantioselectivity, 70% ee, which is probably due optimal combination of steric and electronic factors all together with a configuration that allows for more rigidity. Being tested in Suzuki-Miyaura coupling, the several tested ligands have displayed dissimilar activity. Ligands **90** and **85**, 1,2-R,R_p-Fc[P(O)Eph](PPh_2) and 1,2-S,S_p-Fc[P(O)Eph](PPh_2), displayed high activity with naphthyl bromides while the corresponding PCy_2 derivative **92**, 1,2-R,R_p-Fc[P(O)Eph](PCy_2), shown better activity towards reaction with chlorides.

4

Heteroaromatic, Tetrazolyl and Benzisothiazolyl, Phenyl Ethers as Intermediates for Suzuki-Miyaura Cross-Coupling of Phenols

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Expanding the scope of a specific reaction or synthetic process by using attractive substrates is of interest. Herein the possibility to use tetrazolyl and benzisothiazolyl phenolic ethers as intermediates for Suzuki-Miyaura cross-coupling of phenols will be discussed.

Chapter 4

4.1 INTRODUCTION

Thus far we have focused on the importance of developing new ligands, able to be successfully applied in important useful catalytic processes, as a way to bring them to be more economic, environment friendly, and asymmetric. Conversely, when trying to achieve some of these goals, rather from looking just from the catalyst perspective, one may consider to tackle the issue from others aspects of the catalytic process. Such are the substrate, the solvent, the presence of additives, the use of microwaves technology et cetera. An example of that is the use of chlorides in the Suzuki-Miyaura coupling, which has attracted much attention due to their higher stability and availability, as well as lower prices, when compared to bromides and especially iodides.[279] In fact expanding the reaction scope of a catalytic process is normally taken as an advantage, not only because of possible economic gain, but also from a synthetic point of view. Accordingly to this line of thought, the Suzuki-Miyaura cross-coupling reaction involving phenols, derivatized into tetrazolyl and benzisothiazolyl ethers, has been considered. The envisaged strategy will be clarified revealing the reason for the choice of phenols, tetrazoles and benzisothiazoles.

4.2 PHENOLS - IMPORTANCE, CHARACTERISTICS AND DERIVATIZATION

Following, some relevant aspects about phenols will be presented including the reason why these are attractive starting materials in organic synthesis.

4.2.1 PHENOLS - THEIR IMPORTANCE

At an industrial level, phenols are attractive starting materials, with important biological activity and wide abundance. They are responsible for the flavour, aroma and colour of many foods, often presenting antioxidant activity. The presence of a phenolic fraction is a physiological characteristic of all plant tissues, with phenols playing a significant role in the protection and normal development of plants.[322] These compounds occur also in algae, fungus and bacteria where they can display antibiotic activity.[322] Finally phenols are considerable petrochemical derivatives.

4.2.2 PHENOLS - STRUCTURAL ASPECTS

On phenolic compounds, the hydroxide group is directly attached to the benzene ring, resulting in conjugation between the ring's π system and the electron lone pairs orbitals belonging to the oxygen atom. As a consequence the C-OH bond becomes stronger and the species more acidic. As a matter of fact, the phenolic C-OH bond has a partial double bond nature with a bond order of around 1.3 to 1.4 and a length close to 1.37 Å in between a single C-O bond, 1.43 Å, and a double one C=O, 1.23 Å.[323] On **Figure** 39 bond dissociation energies of several aryl compounds are compared.

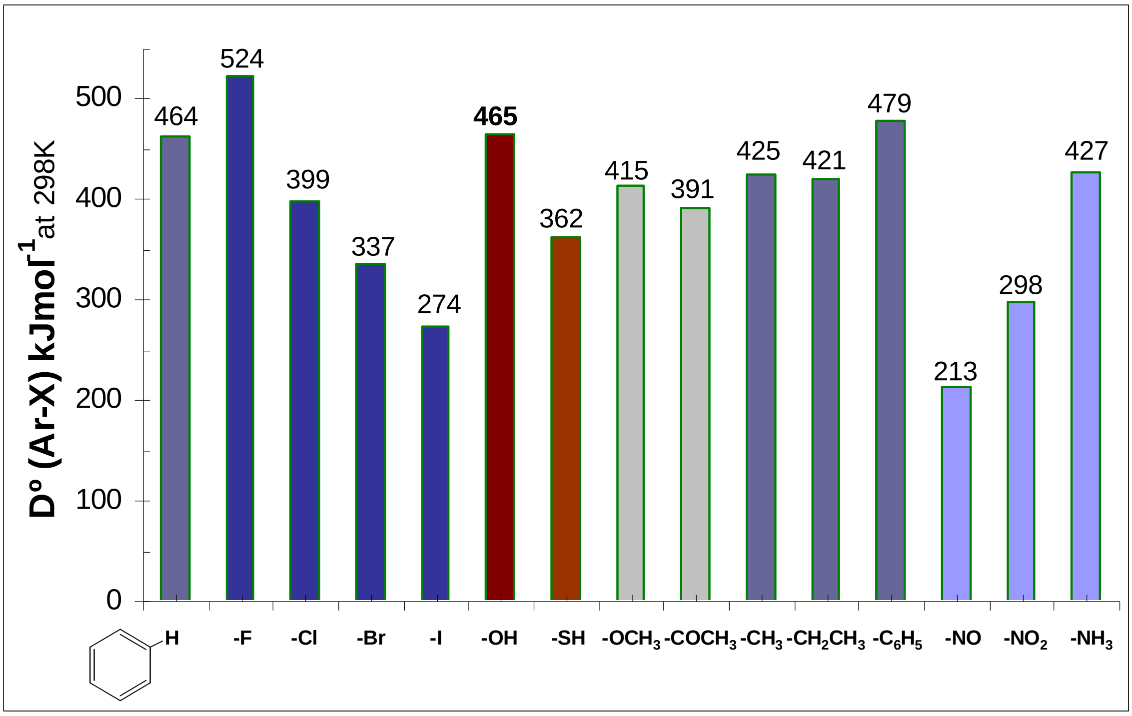


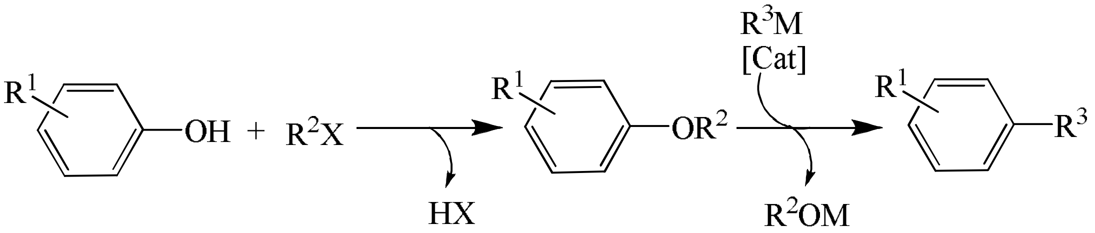
Figure 39 - Bond dissociation energies of selected aryl compounds.[324,325]

The phenolic C-OH bond is very strong, its dissociation energy surpassing even the one from chlorobenzene. In the halogen series it is only inferior to the one from fluorobenzene. Expectedly, directly breaking the C-OH phenolic bond, as a means to undergo *ipso*-substitution of the hydroxide group by other groups, is a very challenging task especially in a selective fashion involving few steps and mild reaction conditions.

4.2.3 PHENOLS - ACTIVATING THE C-O BOND WITH CONVENTIONAL DERIVATIZING AGENTS

A way to by-pass the above difficulty is to derivatize the phenolic compound, weakening and thus activating the C-O bond as depicted in the **Scheme** below.

Scheme 47 - Phenolic ether mediated *ipso*-substitution of the hydroxy phenolic group via metal catalysed cross-coupling reaction.



Traditionally this strategy has been achieved by converting phenols into triflates.[326-332] Instead, fluorosulfonates,[333] tosylates[334-339] and other arenesulfonates,[340-344] mesylates,[345-346] as well as phosphates[347] have also been used in a variety of reactions involving Zn, Sn, Mg, Cu, Si and B organometallic compounds. Nonetheless none of these derivatizing agents has gain sufficient interest and widespread application, especially at an industrial level. Really, the synthesis of aryl triflates involves the use of hazardous triflic acid or triflic anhydride, with their use also resulting in undesired by-products. Time consuming and cost ineffective, chromatographic purification is necessary in order to afford generally non-crystalline, thermally labile, base sensitive compounds. Even mesylates, tosylates and other arylsulfonates, are also non-crystalline leading to the formation of acidic by-products. Plus these last suffer from low reactivity towards the oxidative addition step. Finally, in regards to phosphates long reaction times and large nucleophile excess are often required. In addition these ethers are normally syrups which have to be purified by vacuum distillation.[340,345,347,348]

Though some progress has been done to improve the reactivity of tosylates and mesylates towards the Suzuki cross-coupling reaction,[334,340-343,345,346] there is still a need to develop an all together more attractive alternative to triflates, that will still allow to explore the advantage of coupling phenols with organoboranes.

4.2.4 Phenols - Activating the C-O Bond with Tetrazolyl and Benzisothiazolyl Derivatives

The concept involved in the use of tetrazolyl and benzisothiazolyl ethers is to obtain derivatives in which the electronic density is pulled away from the C-O bond we intend to break, towards the newly introduced fragment. This is similar to the case of triflates and other mentioned phenolic intermediates. Such fact has been confirmed in tetrazolyl and benzisothiazolyl phenolic ethers[323] as it is shown in **Figure** 40.

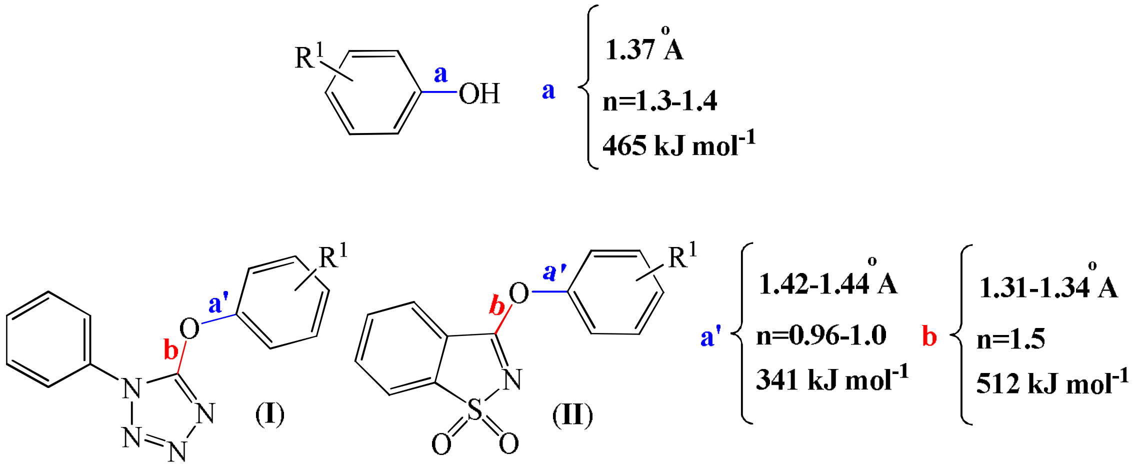


Figure 40 - Structural data on phenols, 5-aryloxy-1-phenyl-1H-tetrazoles (**I**) and 3-aryloxy-1,2-benzisothiazole 1,1-dioxides (**II**).[323]

Remarkably, in both tetrazolyl and benzisothiazolyl ethers, **I** and **II** respectively, C-O bonds **a'** and **b** are dissymmetrical. The first is as weak as, or weaker then, a C-O aliphatic ether bond, n=1, 1.43 Å, 347 kJ mol^{-1}, and the second is a lot stronger even more than a typical phenol C-O one, **a**. The ether C-O-C bond angle is close to 120º typical of sp^2 hybridization at the oxygen atom. In fact, from **a** to **a'**, the original phenolic C-O bond has lost its partial double bond character, the oxygen atom no longer being p-conjugated with the aryl group. Instead conjugation occurs with the heteroaromatic fragment forming a new C-O bond with partial double bond character. Expectedly, in order to have such a result the benzisothiazolyl and tetrazolyl fragments ought to be sufficiently electrowithdrawing. Experiments with ethers presenting both fragments reveal an electronegativity of 3.76 for the benzisothiazolyl system, parallel to the one from fluoride, and an even higher electronegativity of 3.81 for the tetrazolyl system. However it should be noticed that while electronegativity might be a necessary characteristic for a good derivatizing agent, per se, it might not be a sufficient condition for optimal reactivity.[323]

In addition to these attractive features application of benzisothiazolyl and tetrazolyl phenolic ethers to catalysis leads to the formation of saccharin or 5-phenyltetrazolone. These by-products act as good nucleofuges, are water soluble and thus easily separated from the products via extraction,[349] and theoretically could also be recycled. Finally, tetrazolyl and benzisothiazolyl phenolic ethers have been successfully employed in catalytic hydrogenolysis with hydrogen gas[350] or suitable hydrogen donors.[352,353] This together with Ni and/or Pd catalysed cross-coupling reactions involving Zn, Sn and Mg organometallics.[349,353,354]

4.2.5 Synthesis of Phenolic Tetrazolyl and Benzisothiazolyl Ethers

Phenolic tetrazolyl and benzisothiazolyl ethers are easily formed. They are obtained by respectively reacting 5-chloro-1-phenyl-1*H*-tetrazole (**III**) or 3-chloro-1,2-benzisothiazole 1,1-dioxide (**IV**) with phenols to afford generally highly crystalline stable compounds. Both the tetrazol chloride and the more economical pseudosaccharyl chloride are shown on **Figure** 41.

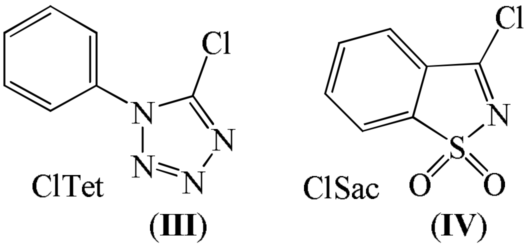


Figure 41 - 5-Chloro-1-phenyl-1*H*-tetrazole (**III**) and 3-chloro-1,2-benzisothiazole 1,1-dioxide (**IV**).

The synthesis of tetrazolyl and benzisothiazolyl phenolic ethers has been established for a variety of phenols presenting electron-withdrawing and/or donating groups.[323,350-352,355-362] Benzylic[363] and allylic[364] alcohols may also be used, hence reflecting the wide scope involved in the derivatization of alcohols into tetrazolyl and benzisothiazolyl heteroaromatic ethers. The derivatization of phenols into tetrazolyl ethers requires previous formation of the corresponding phenoxide as a means to increase its nucleophilic character. Indeed the reaction between the phenoxide and 5-chloro-1-phenyl-1*H*-tetrazole is suggested as proceeding in a bimolecular S_N2 type mechanism in which the reaction rate is dependent and proportional to the phenoxide nucleophilic strength. Thus, whilst the formation of the alkoxide might not be so vigorous when electron rich phenols are used, its reaction with the chloride is normally favoured when compared with electron poor ones. Different base and solvent combinations have been used for the reaction, namely acetone and K_2CO_3,[350,356] THF and NaH,[363,364] or DMF and ^{t}BuOK,[323,351,359,360] the last one often being more efficient.[351] **Figure** 42 presents the formation of tetrazolyl ethers from a phenol alkoxide and tetrazol chloride in the presence of DMF.

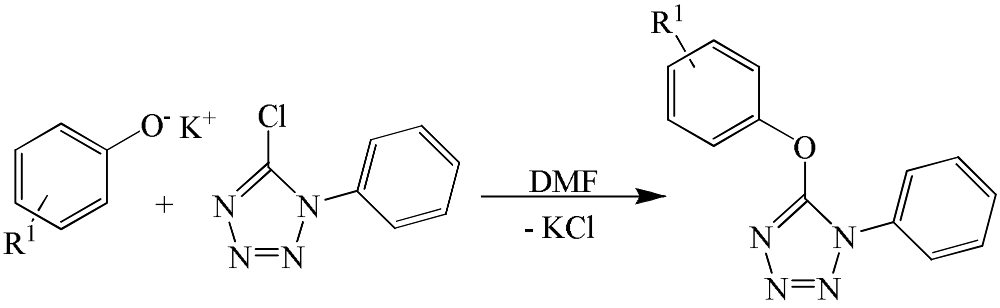


Figure 42 - Synthesis of 5-aryloxy-1-phenyl-1*H*-tetrazoles.

Regarding the synthesis of benzisothiazolyl ethers, as mentioned before, it involves 3-chloro-1,2-benzisothiazole 1,1-dioxide (**IV**) which presents the disadvantage of not being commercially available. Its synthesis however is well known and accordingly with **Figure** 43, consisting on the halogenation of sacharine (**V**) with phosphorus pentachloride, PCl_5.[360,365]

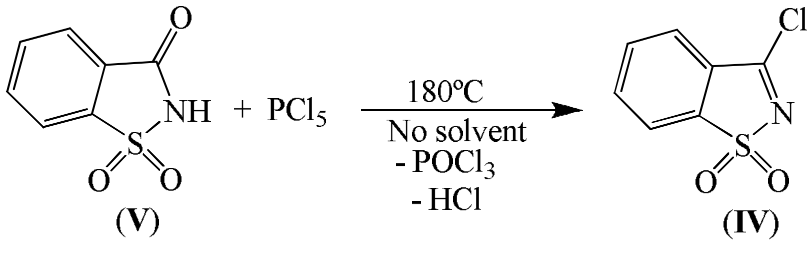


Figure 43 - Synthesis of 3-chloro-1,2-benzisothiazole 1,1-dioxide from saccharine.

In a heteroaromatic nucleophilic substitution mechanism and in the presence of triethylamine the chloride reacts with the alcohol forming the desired ether. Also a hydrochloride salt, which easily precipitates in the apolar solvent used, toluene, is originated according to **Figure** 44.

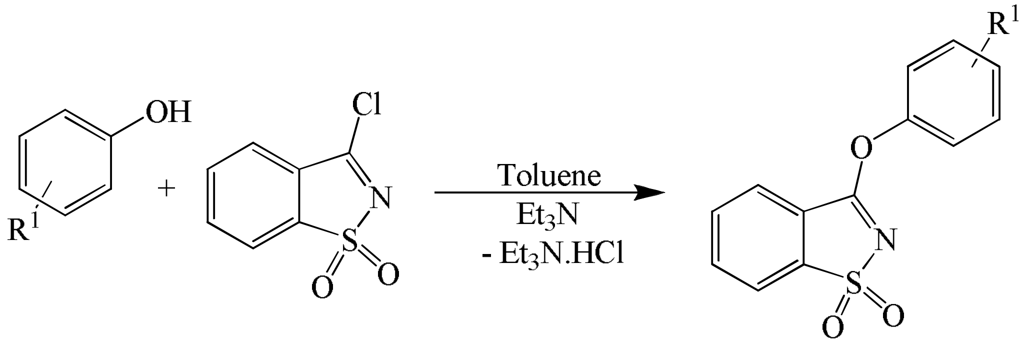


Figure 44 - Synthesis of 3-aryloxy-1,2-benzisothiazole 1,1-dioxides.

4.3 RESULTS AND DISCUSSION

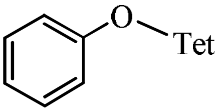
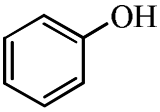
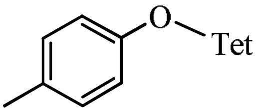
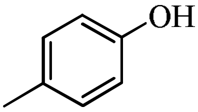
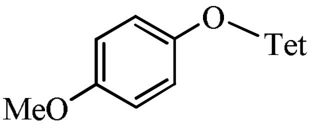
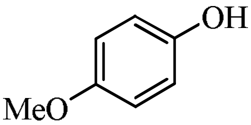
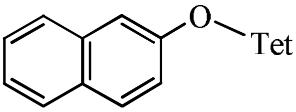
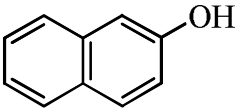
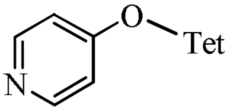
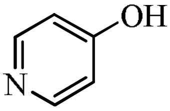
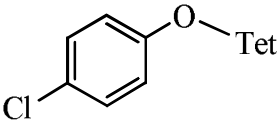
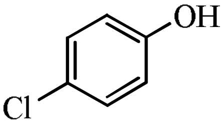
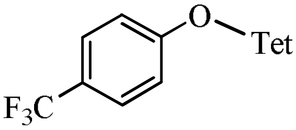
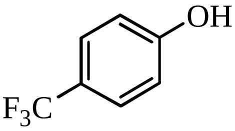
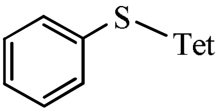
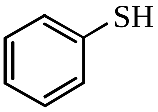
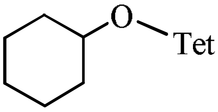
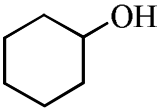
4.3.1 PHENOLIC TETRAZOLYL AND BENZISOTHIAZOLYL ETHERS SYNTHESIZED IN THIS WORK

Accordingly with the above considerations we have set the goal to investigate on the use of tetrazolyl and benzisothiazolyl phenolic ethers as intermediates for the Suzuki cross-coupling of phenols. For that reason we have synthesized various tetrazolyl and benzisothiazolyl phenolic ethers.

4.3.1.1 Phenolic Tetrazolyl Ethers Synthesized in this Work

The tetrazolyl ethers synthesized in the present work were prepared by utilizing two systems, namely the ones involving THF and NaH, or DMF and ^{t}BuOK. Accordingly with the employed alcohol, different temperatures and reaction times were used, however without optimization. The structures of several tetrazolyl ethers prepared in this work are presented on **Table** 7.

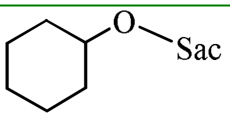
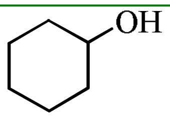
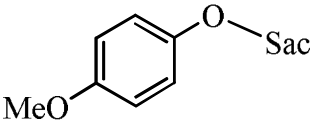
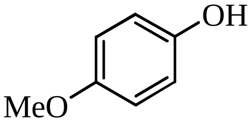
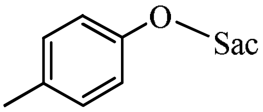
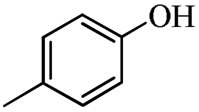
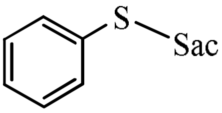
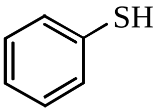
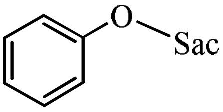
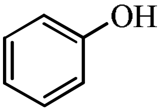
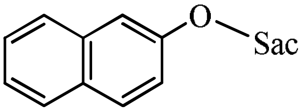
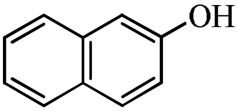
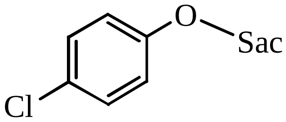
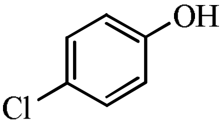
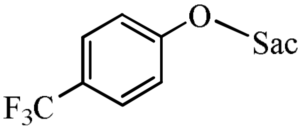
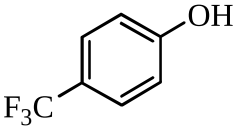
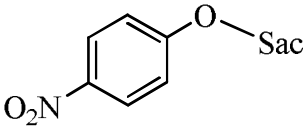
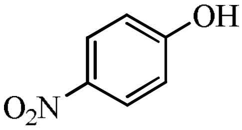
Table 7 - Tetrazolyl ethers prepared in this work.

Tetrazolyl Ether	Alcohol	Temperature	Melting Point (ºC)	Yield (%)
		R.T.	127.0-129.4	92.3
		R.T.	86.0-89.8	84.2
		R.T.	77.4-80.2	85.7
		R.T.	138.2-142.4	91.9
		R.T.	219.8-222.6	77.5
		Reflux (THF)	99.0-101.9	73.7
		70ºC	68.0-71.2	80.2
		R.T.	58.1-62.4	25.3
		80ºC	73.5-75.4	66.3

4.3.1.2 Phenolic Benzisothiazolyl Ethers Synthesized in this Work

To prepare benzisothiazolyl ethers we have reacted the phenol and the pseudo-saccharyl chloride in toluene and in the presence of a base. Again different temperatures and reaction times were used according to the alcohol. **Table** 8 displays the benzisothiazolyl ethers formed.

Table 8 - Benzisothiazolyl ethers prepared in this work.

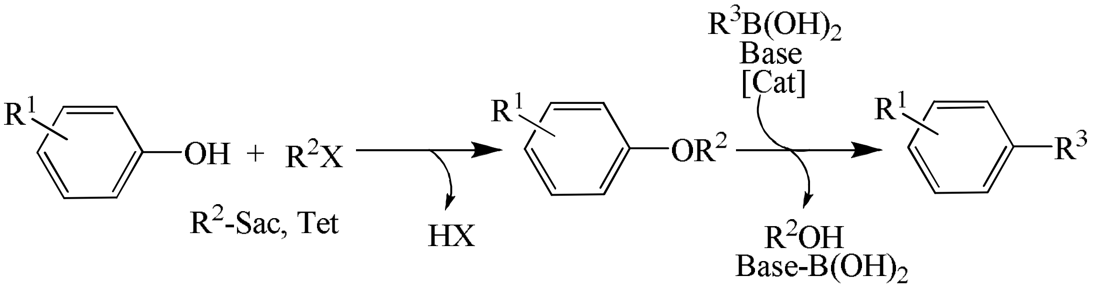
Benzisothiazolyl Ether	Alcohol	Temperature	Melting Point (ºC)	Yield (%)
		R.T.	105.9-110.8	67.2
		R.T.	167.4-169.1	86.9
		R.T.	173.4-175.5	95.9
		R.T.	224.8-228.0	90.7
		R.T.	183.0-184.2	87.2
		70ºC	257.0-259.3	85.2
		70ºC	257.0-259.3	83.0
		80ºC	140.9-142.7	73.0
		Reflux	250.1-252.4	71.4

Once again we point to the broad scope of alcohols able to be derivatized into tetrazolyl and benzisothiazolyl ethers pointing to the need for higher temperatures and longer periods of time when electron-poor phenols are used. The different reactivity displayed in the formation of both types of ethers may lead us to take them as complementary strategies.

4.3.2 TESTING PHENOLIC TETRAZOLYL AND BENZISOTHIAZOLYL ETHERS IN THE SUZUKI-MIYAURA REACTION

According to the discussion above and to **Scheme** 48 the feasibility of using 5-chloro-1-phenyl-1*H*-tetrazole and the 3-chloro-1,2-benzisothiazole 1,1-dioxide on the first step of our methodology has been already well established. We thus turned our attention to the second step, the application of tetrazolyl and benzisothiazolyl ethers on the Suzuki-Miyaura cross-coupling.

Scheme 48 - Phenolic ether mediated *ipso*-substitution of the hydroxy phenolic group via metal catalysed Suzuki-Miyaura cross-coupling reaction.



The number of parameters involved in the Suzuki reaction that may be adjusted, as a way to educe better results, ought to be noticed. Among them we can count the electrophile, nucleophile, base, catalytic system, solvent and temperature. Having these into account, and remembering that tetrazolyl and benzisothiazolyl phenolic ethers have not previously been applied to the Suzuki cross-coupling, the possible difficulty involved in the development of suitable reaction conditions is well perceived. As a matter of fact evaluating each one of the reaction's parameters separately may become a time consuming endeavour. Consequently we set the purpose to tryout some of them more superficially in order to infer as to whether tetrazolyl and benzisothiazolyl phenolic ethers are prone to undergo catalytic coupling with boron derivatives or not.

To do so reaction conditions early employed while using aryl halogens and triflates, as the electrophile, have been considered as a starting platform. Also reaction conditions used when coupling tetrazolyl and benzisothiazolyl phenolic ethers with organometallics other than boron ones were regarded. However this has been done bearing in mind that extrapolating conditions from one reaction system to another may not always lead to a satisfying outcome. Accordingly with the results that were obtained along the way we sought to draw conclusions and perform experiments that in our reasoning would result better or give us more insight regarding the reaction.

Typical reaction proceedings have been used during our study. In most cases dried solvents and controlled atmosphere conditions were used. The addition of the several reagents in the reaction slightly varied according to factors such as the use or not of additives, whereas the base was a solid or a liquid, etc. Gas chromatography (GC) monitoring of the reactions was performed using an internal standard compound, usually durene, in order to calculate conversions. Identification of products was done by gas chromatography-mass spectrometry (GC-MS) analysis and when possible also by comparing retention times from our reaction samples with samples of the pure compound. Various samples were taken along the reaction, of which we have chosen to present the results at the end of approximately 1 and 24 hours. At a certain point of our study we observed that boronic acid homocoupling could be a significant competitive reaction, reason that took us to also perform reactions with substrates in which the cross-coupling product (P) and the homo-coupling by-product (H_c) could be distinguished. When possible both values were registered.

For the sake of better understanding the effect of each variable separately from the others, we have tried to organize the results in **Tables** focusing more specially in one variable at the time. In some cases we have presented the same result in more than one **Table**. The typical reaction that we have studied is depicted on the **Figure** below.

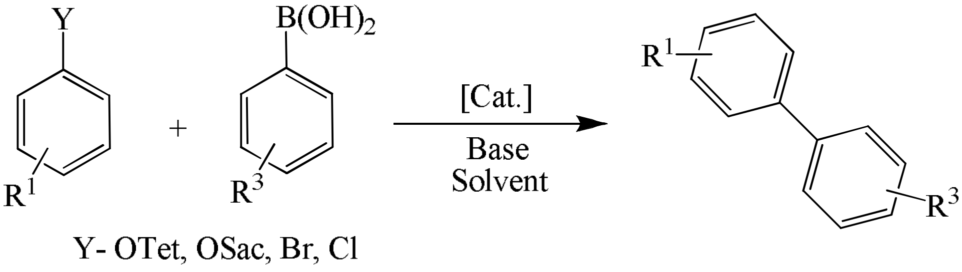
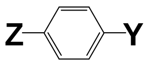


Figure 45 - Coupling reaction between tetrazolyl and benzisothiazolyl ethers with boron organometallics.

Next, different catalytic systems with different combinations of metal, ligand and even sometimes of additives are compared.

4.3.2.1 The Catalytic System

Table 9 - Results from Suzuki coupling reactions with tetrazolyl ethers - the catalytic system.

#[a]			Borane	Catalytic system	Base	Solvent	P% 1h	P% 24h	H_c% 1h	H_c% 24h
1	H	OTet	1.5 $PhB(OH)_2$	$Pd(OAc)_2$,4 PPh_3	2.5 Na_2CO_3	Toluene	0	0	-	-
2	H	OTet	1.3 $PhB(OH)_2$	$PdCl_2(PPh_3)_2$, 4 BuLi	4 Et_3N	DMF	2.5	4.9	-	-
3	H	OTet	2 $PhB(OH)_2$	$PdCl_2$dppf	4 Et_3N	DMF	3.5	5.5	-	-
4	H	OTet	2 $PhB(OH)_2$	$PdCl_2$	4 Et_3N	DMF	1.1	3.0	-	-
5	H	OTet	2 $PhB(OH)_2$	Pd/C 10%	4 Et_3N	DMF	0	0	-	-
6	H	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$	4 Et_3N	DMF	10.3	10.7	-	-
7	H	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$, 21 mol%	4 Et_3N	DMF	17.1	17.4	-	-
8	H	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$[b]	4 Et_3N	DMF	9.1	9.5	-	-
9	CF_3	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$	4 Na_2CO_3	DMF	3.6	4.4	5.8	5.8
10	CF_3	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$, 4 PPh_3	4 Na_2CO_3	DMF	0	1.4	7.0	15.4
11	NaphtylOTet[c]		2 $PhB(OH)_2$	$Pd(OAc)_2$, 4 PPh_3	4 K_3PO_4	Toluene	0	0	22.7	24.7
12	NaphtylOTet[c]		2 $PhB(OH)_2$	$Pd(OAc)_2$[d]	4 K_3PO_4	Toluene	1.5	0.8	19.9	32.5
13	H	OTet	1.5 $PhB(OH)_2$	$NiBr_2$dppp	2.5 KF	Toluene	0	0	-	-
14	H	OTet	1.3 $PhB(OH)_2$	$NiCl_2$dppf, 4 BuLi	4 Et_3N	DMF	4.3	4.3	-	-
15	H	OTet	1.3 $PhB(OH)_2$	$NiCl_2(PPh_3)_2$	4 Et_3N	DMF	3.6	3.6	-	-
16	H	OTet	1.3 $PhB(OH)_2$	$NiCl_2(PPh_3)_2$, 17.2 Zn	4 Et_3N	DMF	3.4	3.4	-	-
17	H	OTet	1.3 $PhB(OH)_2$	$NiCl_2(PPh_3)_2$, 4 BuLi	4 Et_3N	DMF	8.6	8.6	-	-
18	H	OTet	1.3 $PhB(OH)_2$	$NiCl_2(PPh_3)_2$, 4 BuLi, 5 LiCl	4 Et_3N	DMF	4.7	4.7	-	-
19	H	OTet	1.3 $PhB(OH)_2$	$NiCl_2(PPh_3)_2$, 4 BuLi[b]	4 Et_3N	DMF	9.7	9.7	-	-
20	NaphtylOTet[c]		2 $PhB(OH)_2$	$Ni(PPh_3)_4$	4 K_3PO_4	Toluene	0	0	0	0
21	NaphtylOTet[c]		2 $PhB(OH)_2$	$Ni(OAc)_2$	4 K_3PO_4	Toluene	0	0	0	0

P - cross-coupling product: biphenyl on entries 1 to 8 and 13 to 19; 4-(trifluoromethyl)biphenyl on entries 9 and 10; 2-phenylnapthalene on entries 11,12, 20 and 21. H_c - homocoupling by-product: biphenyl in all entries. (a) 100ºC, 1 mmol of electrophile, 7 mol% of catalyst, reaction under N_2 atmosphere. (b) Room temperature. (c) Apparently 5-phenoxi-1*H*-phenyltetrazol was formed. (d) Reaction under open air.

An analysis to **Table** 9 sadly reveals poor results obtained when trying to cross-couple tetrazolyl phenolic ethers with phenyl boronic acid using usual catalytic systems.

The use of PPh_3 and the more bulky electron rich bisphosphine dppf failed to produce good results either when Pd or Ni catalysts were used, entries 1 to 3, 10, 11, and 14 to 20, the same happening with dppp, entry 13. Even the use of additives such as BuLi and Zn, which had the purpose to improve the formation of active Pd (0) and Ni (0) species, or salts such as LiCl, to facilitate ligand exchange, did not have sufficient impact on the reaction. Entries 15 and 16 show no amelioration by using Zn powder. BuLi did help the Ni catalysed reaction, to some extent, entries 15 and 17. However adding LiCl hindered the reaction, entries 17 and 18.

Diverse Pd sources were used without addition of extra ligands, entries 4 to 9, and 12. Under the conditions presented, entry 5, Pd/C proved to be ineffective, even in face of good results that this catalyst shows in the hydrogenolysis of tetrazolyl and benzisothiazolyl phenolic ethers,[350-352] and of its prior utilization on Suzuki coupling.[366] Entries 3 and 4 reveal an apparent slight improvement in the reaction when $PdCl_2$dppf was used instead of sole $PdCl_2$, the same being observed with $PdCl_2(PPh_2)_2$, entry 2. Interestingly, in contrast, reactions in which $Pd(OAc)_2$ was used by itself led to better results than the ones in which four equivalents of PPh_3 were used, entries 9 vs. 10, 11 vs. 12, and also suggested in 1 vs. 6. The only difference between entries 4 and 6 is the palladium source, from $PdCl_2$ to $Pd(OAc)_2$, which suggests that the acetate anion may play a role in the reaction. In fact this last catalyst has been used in the Suzuki reaction without the presence of other ligands before.[279] Furthermore in 1994 Wallow and Novak have demonstrated how phosphine ligands could play a role in reaction inhibition thus limitating the catalyst performance in the Suzuki coupling.[279,367]

In fact the result on entry 6 was the best in several reactions, reason why we focused some attention on its conditions with the purpose to obtain better results and understanding of the reaction. Entry 7 shows that a three fold increase in the amount of

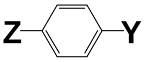
$Pd(OAc)_2$ did not yield the same increase of product. Comparison between yields after 1 and 24 hours on entries 6 and 7 suggest that the reaction generally takes place within the first hour, involving a few minutes, then coming to a halt. Indeed changes in the reaction colour and formation of a black deposit in the reaction flask was often observed, which we believe could be palladium sintering. The catalytic system is probably rather unstable, and the reaction could occur in a burst kinetic fashion. Reaction 8 and 19 were performed at R.T. instead of being submitted to warming, 100ºC, as in reaction 6 and 17 respectively. In the first case, using Pd, no significant decrease in yield was registered. When using Ni, the yield was slightly higher at R.T. probably due to higher catalyst's stability. Both cases revealed little dependence on temperature.

Regarding reactions in which the cross-coupling product could be distinguished from the homocoupling by-product, entries 9 to 12, 20 and 21, it is shown how usually homocoupling occurs in palladium catalysed reactions. Its extension varies accordingly to the conditions used. Often we have noticed a trend for homocoupling to be favoured by less polar solvents, the use of K_3PO_4, the presence of PPh_3 and of an oxygen source. Entries 11 and 12 reveal how this undesirable parallel reaction occurs with considerable extension confirming early observations made by several authors, regarding the presence of oxygen and PPh_3.[279] However under those conditions the transmetalation step is sufficiently fast, thus not being the step causing the catalytic cycle to be interrupted.

Other competitive processes may be taking place, for when 5-(naphthalen-2-yloxy)-1-phenyl-1*H*-tetrazole was used 5-phenoxy-1-phenyl-1*H*-tetrazole seemed to be formed, entries 11, 12, 20 and 21. Though this fact was not further investigated, apparently oxidative addition and transmetalation could be taking place however prior to reductive elimination the formation of 5-phenoxy-1-phenyl-1*H*-tetrazole occurs.

4.3.2.2 The Base

Table 10 - Results from Suzuki coupling reactions with tetrazolyl ethers - the base.

#[a]			Borane	Catalytic system	Base	Solvent	P% 1h	P% 24h	H_c% 1h	H_c% 24h
1	H	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$	4 Et_3N	DMF	10.3	10.7	-	-
2	H	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$	-	DMF	7.1	9.1	-	-
3	H	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$	4 $Ba(OH)_2$	DMF	18.6	28.1	-	-
4	H	OTet	2 $PhB(OH)_2$	Pd(OAc)2	4 Na_2CO_3, 2M	DMF	16.7	18.9	-	-
5	H	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$	4 K_3PO_4	DMF	8.7	11.1	-	-
6	H	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$	4 K_3PO_4	Toluene	13.3	20.8	-	-
7	H	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$	4 Et_3N	Toluene	14.0	15.6	-	-
8	H	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$[d]	4 K_3PO_4	Toluene	17.5	49.3	-	-
9	CF_3	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$	4 Et_3N	DMF	15.6	22.6	3.1	3.5
10	CF_3	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$	-	DMF	0	0.7	3.2	4.2
11	CF_3	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$	4 Na_2CO_3	DMF	3.6	4.4	5.8	5.8
12	NaphtylOTet[c]		2 $PhB(OH)_2$	$Pd(OAc)_2$[d]	4 K_3PO_4	Toluene	1.5	1.5	19.9	32.5
13	NaphtylOTet[c]		2 $PhB(OH)_2$	$Pd(OAc)_2$[d]	4 KOAc	Toluene	0	0	10.5	26.4
14	NaphtylOTet[c]		2 $PhB(OH)_2$	$Pd(OAc)_2$[d]	4 Na_2CO_3	Toluene	0	1.4	17.8	17.8
15	NaphtylOTet		0.5 Ph_4BNa	$Pd(OAc)_2$	4 Na_2CO_3	DMF/ H_2O[e]	2.1	6.8	15.7	27.9
16	NaphtylOTet		0.5 Ph_4BNa	$Pd(OAc)_2$	4 K_3PO_4	Toluene	1.1	2.4	3.9	16.4
17	H	OTet	2 $PhB(OH)_2$	Pd/C 10%	4 Et_3N	DMF	0	0	-	-
18	H	OTet	2 $PhB(OH)_2$	Pd/C 10%	4 K_3PO_4	Toluene	2.8	10.2	-	-
19	H	OTet	1.3 $PhB(OH)_2$	$NiCl_2(PPh_3)_2$, 4 BuLi	4 Et_3N	DMF	8.6	8.6	-	-
20	H	OTet	1.3 $PhB(OH)_2$	$NiCl_2(PPh_3)_2$, 4 BuLi	4 K_3PO_4	DMF	7.2	7.4	-	-

P- cross-coupling product: biphenyl on entries 1 to 8 and 17 to 20; 4-(trifluoromethyl)biphenyl on entries 9 to 11; 2-phenylnapthalene on entries 12 to 16. H_c- homocoupling by-product: biphenyl in all entries. (a) 100ºC, 1 mmol of electrophile, 7 mol% of catalyst, reaction under N_2 atmosphere. (c) Apparently 5-phenoxi-1*H*-phenyltetrazol was formed. (d) Reaction under open air. (e) (2:1), 90ºC.

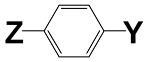
Accordingly to **Table** 10 the base effect on the reaction was investigated with different bases and reaction conditions. Comparing a reaction performed with and without base, entries 1 vs. 2, seems to reveal a weak dependence on the reaction upon the base. Yet entries 9 vs. 10 contradict this fact showing the reaction to be seriously hindered by the absence of base. This result is clearer since we are able to distinguish the desired product from the homocoupling by-product. Base dependence is in line with what is normally observed on the Suzuki coupling, which associates the base with boron nucleophile activation.[279,368]

Comparing reaction 1 using Et_3N with reactions 3 to 5, employing $Ba(OH)_2$, aqueous Na_2CO_3, and K_3PO_4 respectively, we notice that $Ba(OH)_2$ led to what seems to be a better result. In effect the literature points to the pH as influencing the reaction outcome, with pH values higher than 9 facilitating the transmetalation step due to formation of trihydroxyphenylborate, $PhB(OH)_3^-$.[279,368] Nevertheless homocoupling could be the reaction being favoured. Na_2CO_3 also led to a better result however when comparing entry 4 with 9 vs. 11 it appears as if water is playing an important role on the first one. Accordingly kinetic studies have been made suggesting that water does improves boronic acid activation.[279,368] On the other hand K_3PO_4 performed in a rather similar way as to Et_3N, entries 1 vs. 5. Again entries 6 and 7 present very similar yields within the first hour, still after a longer period of time K_3PO_4 conduces to higher yield. When performed in open air the yield increases more, especially after 24 hours, entry 8. Comparison between these results with the one on entry 12 reveals that homocoupling is involved, apparently favoured by the presence of oxygen. Because of poor results entries 12, 13 and 14 are inconclusive. Entries 14 to 16 vary in more than one parameter transpiring how variation of one parameter affects the effect of another one, highlighting the difficulty to study each parameter individually and to find an optimal set of reaction conditions. Reactions 17 and 18 suggest that even if cross-coupling is taking place at all, in reaction 18, homocoupling is probably taking place in the reaction. As aforementioned, cross-coupling frequently occurs within the first minutes. On the other hand the homocoupling reaction carries on throughout the time. Apparently at some stage of the reaction oxidative addition of the ethers becomes inefficient. Hypothetically this is due to strong chelation of tetrazolyloxy and saccharyl leaving groups to palladium, which would change the electronic and steric properties around the metal center and hinder oxidative addition. Though this is not the case when these ethers are being coupled with other substrates such as Grignard reagents, we consider whether the presence of a base in Suzuki coupling could lead to it. Another partial explanation is that both ethers may undergo hydrolysis into the corresponding original alcohols. Finally entries 19 and 20, performed with a Ni catalyst, present only a slightly better performance when Et_3N is the base in opposition to K_3PO_4.

We have early mentioned how the presence of some anions, like the acetate one, could impact the reaction. To this respect we wish also to add that one should also have into account that any present cations may be more than spectators. This becomes of more significance when trying to understand the effect of a given base upon the reaction.

4.3.2.3 The Solvent

Table 11 - Results from Suzuki coupling reactions with tetrazolyl ethers - the solvent.

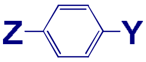
#[a]			Borane	Catalytic system	Base	Solvent	P% 1h	P% 24h	H_c% 1h	H_c% 24h
1	H	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$	4 Et_3N	DMF	10.3	10.7	-	-
2	H	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$	4 Et_3N	CH_3CN^f	10.4	12.4	-	-
3	H	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$	4 Et_3N	Toluene	14.0	15.6	-	-
4	H	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2{}^d$	4 K_3PO_4	Toluene	17.5	49.3	-	-
5	H	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2{}^d$	4 K_3PO_4	T/E/W	21.1	21.1	-	-
6	CH_3	Br	0.5 Ph_4BNa	$Pd(OAc)_2$	4 K_3PO_4	Toluene	1.3	3.5	3.4	7.0
7	CH_3	Br	0.5 Ph_4BNa	$Pd(OAc)_2$	3 Na_2CO_3	DMF/ H_2O^e	80.2	92.4	11.1	18.0
8	NaphtylOTet[c]		2 $PhB(OH)_2$	$Pd(OAc)_2{}^d$	4 K_3PO_4	Toluene	1.5	1.5	19.9	32.5
9	NaphtylOTet[c]		2 $PhB(OH)_2$	$Pd(OAc)_2$	4 K_3PO_4	THF^h	3.2	5.49	7.8	8.0
10	CF_3	OTet	1.3 $PhB(OH)_2$	$Pd(OAc)_2$	3 K_2CO_3	DMF/ H_2O^i	17.1	21.0	18.1	19.5
11	CF_3	OTet	1.3 $PhB(OH)_2$	$Pd(OAc)_2$	3 K_2CO_3	Toluene/ H_2O^j	8.9	21.2	6.9	32.6

P- cross-coupling product: biphenyl on entries 1 to 5; 4-methylbiphenyl on entries 6 and 7; 2-phenylnapthalene on entries 8 and 9; 4-(trifluoromethyl)biphenyl on entries 10 and 11. H_c- homocoupling by-product: biphenyl in all entries. (a) 100ºC, 1 mmol of electrophile, 7 mol% of catalyst, reaction under N_2 atmosphere. (c) Apparently 5-phenoxi-1*H*-phenyltetrazol was formed. (d) Reaction under open air.(e) (2:1), 90ºC. (f) 80ºC. T/E/W-Toluene/Ethanol/Water. (h) Reflux. (i) 5:2, 1.3 mmol of TPAB. (j) 7:1, 2 mmol of TPAB.

Different polar and apolar solvents were tested. Thought at different temperatures reactions 1 and 2 occurred on polar solvents, DMF and acetonitrile, leading to very close yields. Changing to a less polar solvent apparently increased the yield nonetheless we are not sure whether this was due to cross- or homo-coupling. Entries 4 and 5 compare an apolar solvent, with a biphasic system formed by toluene as well, in addition to ethanol and water. This last solvent system seems to perform better initially. In contrast the reaction in toluene presents higher yield after 24 hours. As discussed above we believe that homocoupling is involved, at least in this last case. Theoretically a biphasic system could help the reaction, the water favouring transmetalation and dissociation of the tetrazolyloxy and saccharyl fragments from the metal centre. The influence of each parameter in entries 6 and 7 is not clear though these reactions involving bromides show how changing two parameters may increase the yield dramatically. Entries 8 and 9, Toluene vs. THF, suggest better performance when polar solvents are used, showing a lesser extension on the homocoupling reaction. Finally entries 10 and 11 compare two solvent systems, the first containing water and a polar solvent DMF, the second also containing water however with an apolar solvent, toluene. Apparently the initial reaction rate is favoured in the first case whereas in the second one, in which there is a clear biphasic system, the reaction is initially slower. Though tetrapropylammonium bromide (TPAB), a phase transfer agent, was used in both cases there probably is slower interaction between the several reagents in the toluene/water system. In regards to this type of additive it is expected that its use when the solvent is polar or especially when biphasic systems are used may benefit the reaction. As a matter of fact it has previously been effectively combined with $Pd(OAc)_2$ without any ligand, being believed to stabilize anionic palladium species.[369] Nonetheless we have not independently focused our study on their effect.

4.3.2.4 The Substrate and the Boron Nucleophile

Table 12 - Results from Suzuki coupling reactions with tetrazolyl and benzisothiazolyl ethers - the substrate and the boron organometallic.

#[a]			**Borane**	**Catalytic system**	**Base**	**Solvent**	**P% 1h**	**P% 24h**	**H_c% 1h**	**H_c% 24h**
1	H	OTet	2 $PhB(OH)_2$	$PdCl_2dppf$	4 Et_3N	DMF	3.5	5.5	-	-
2	H	OSac	2 $PhB(OH)_2$	$PdCl_2dppf$	4 Et_3N	DMF	2.2	2.6	-	-
3	H	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$	4 Et_3N	CH_3CN^f	10.4	12.4	-	-
4	H	OSac	2 $PhB(OH)_2$	$Pd(OAc)_2$	4 Et_3N	CH_3CN^f	3.1	10.3	-	-
5	H	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$	4 Et_3N	DMF	10.3	10.7	-	-
6	CF_3	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$	4 Et_3N	DMF	15.6	22.6	3.1	3.5
7	H	Br	2 $PhB(OH)_2$	$Pd(OAc)_2$	4 Et_3N	DMF	26.0	27.2	-	-
8	H	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2^d$	4 K_3PO_4	Toluene	17.5	49.3	-	-
9	CH_3	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2^d$	4 K_3PO_4	Toluene	0	0.4	15.1	35.5
10	OCH_3	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2^d$	4 K_3PO_4	Toluene	0	0	16.7	53.4
11	-	-	2 $PhB(OH)_2$	$Pd(OAc)_2^d$	4 K_3PO_4	Toluene	-	-	12.0	23.9[l]
12	CH_3	Cl	2 $PhB(OH)_2$	$Pd(OAc)_2^d$	4 K_3PO_4	Toluene	0.8	1.1	11.2	18.2
13	CH_3	Br	2 $PhB(OH)_2$	$Pd(OAc)_2^d$	4 K_3PO_4	Toluene	70.2	92.7	8.6	21.3
14	CH_3	Br	0.5 Ph_4BNa	$Pd(OAc)_2$	4 K_3PO_4	Toluene	1.3	3.5	3.4	7.0
15	CF_3	OTet	0.5 Ph_4BNa	$Pd(OAc)_2$	4 Na_2CO_3	DMF	11.1	10.2	16.5	25.6
16	CF_3	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$	4 Na_2CO_3	DMF	3.6	4.4	5.8	5.8
17	H	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$	4 K_3PO_4	Toluene	13.3	20.8	-	-
18	CF_3	OTet	2 $PhB(OH)_2$	$Pd(OAc)_2$	4 K_3PO_4	Toluene	0	0.8	9.6	16.0
19	NaphtylOTet		0.5 Ph_4BNa	$Pd(OAc)_2$	4 K_3PO_4	Toluene	1.1	2.4	3.9	16.4
20	NaphtylOTet[c]		2 $PhB(OH)_2$	$Pd(OAc)_2^d$	4 K_3PO_4	Toluene	1.5	1.5	19.9	32.5
21	NaphtylOSac		2 $PhB(OH)_2$	$Pd(OAc)_2^d$	4 K_3PO_4	Toluene	0	0	19.8	24.2
22	H	OSac	1.3 $PhB(OH)_2$	$NiCl_2(PPh_3)_2$, 4 BuLi[b]	4 Et_3N	DMF	5.3	6.3	-	-
23	H	OTet	1.3 $PhB(OH)_2$	$NiCl_2(PPh_3)_2$, 4 BuLi[b]	4 Et_3N	DMF	9.7	9.7	-	-
24	H	OTet	0.5 Ph_4BNa	$NiCl_2(PPh_3)_2$, 4 BuLi	4 Et_3N	DMF	4.9	6.2	-	-
25	H	OTet	1.3 PhCB	$NiCl_2(PPh_3)_2$, 4 BuLi	4 K_3PO_4	DMF	3.1	3.1	-	-

26	H	OSac	1.3 $PhB(OH)_2$	$NiCl_2(PPh_3)_2$, 4 BuLi	4 Et_3N	DMF	2.8	2.8	-	-
27	H	OTet	1.3 $PhB(OH)_2$	$NiCl_2(PPh_3)_2$, 4 BuLi	4 Et_3N	DMF	8.6	8.6	-	-
28	H	OTet	1.3 $PhB(OH)_2$	$NiCl_2(PPh_3)_2$, 4 BuLi[b, m]	4 Et_3N	DMF	9.5	9.5	-	-
29	H	OTet	1.3 $PhB(OH)_2$	$NiCl_2(PPh_3)_2$, 4 BuLi [b, n]	4 Et_3N	DMF	8.8	9.4	-	-

P - cross-coupling product: biphenyl on entries 1 to 5, 7, 8, 17, and 22 to 29; 4-(trifluoromethyl)biphenyl on entries 6, 15, 16 and 18; 4-methylbiphenyl on entries 9 and 12 to 14; 4-methoxylbiphenyl on entry 10; 2-phenylnapthalene on entries 19 to 21. Hc - homocoupling by-product: biphenyl in all entries. (a) 100ºC, 1 mmol of electrophile, 7 mol% of catalyst, reaction under N2 atmosphere. (b) Room temperature. (c) Apparently 5-phenoxi-1H-phenyltetrazol was formed. (d) Reaction under open air. (f) 80ºC. (h) Reflux. (l) 70%-140 h. (m) The borane was first added followed by the ether after 15 min. (n) The ether was first added followed by the borane after 1 h. PhCB - phenyl catechol borane.

Accordingly to **Table** 12, along with tetrazolyl phenolic ethers, benzisothiazolyl ones, aryl bromides and chlorides have also been tested as a way to compare their reactivity. In addition different boron species have been used. Without exception tetrazolyl ethers led to better results than the benzisothiazolyl ones as perceived by comparing entries 1 vs. 2, 3 vs. 4, 20 vs. 21, 22 vs. 23, and 26 vs. 27. Besides an apparent dissimilar reactivity between both types of ethers another drawback presented by benzisothiazolyl phenolic ethers is associated with higher hydrolysis rates. Indeed the presence of a base, together with high temperatures favours the hydrolysis of the ether into the original phenol. This was actually the reason why we focused more on studying the tetrazolyl ethers reactivity.

Tetrazolyl ethers presenting varied substituents were compared. Entries 5 and 6 show an improvement when going from 5-phenoxi-1*H*-phenyltetrazol, Z=H, to 5-(4-(trifluoromethyl)phenoxy)-1*H*-phenyltetrazol, Z=CF_3. The reason why this is so does not seem to be so clear. In fact an electrowithdrawing group in aryl halogens is normally associated with favoured oxidative addition due to a weaker carbon-halogen bond. However the corresponding bond in tetrazolyl ethers is apparently not affected by electron donating and withdrawing groups.[323] If this is so then oxidative addition is not expected to suffer any gain by the presence of electron-withdrawing groups. Indeed from our studies we are prone to consider that factors other than inductive electronic effects may play a role. The reaction is not expected to undergo a linear dependence to Hammett's σ_x parameter.[370] Entries 8 to 10, 17 and 18 involve substrates with different substituents however the results are inconclusive. Entry 11 is consistent with boronic acid homocoupling. Entries 5 vs. 7 and 9 vs. 13 reveal that in those conditions bromides react better then tetrazolyl ethers. In the last case, even in open air cross-coupling is sufficiently fast to compete with homocoupling leading to high yield. Expectedly chlorides led also to worst results than bromides, entries 12 and 13. In the case of chlorides we expect the problem to be involved with slow oxidative addition unable to sustain the catalytic cycle. In the case of tetrazolyl ethers this is not so clear.

The influence of different boron compounds upon the reaction was tested. In the set of conditions involving entries 13 and 14, partially due to solubility issues, $PhB(OH)_2$ acts a lot better than Ph_4BNa. On entries 15 and 16, now with other conditions, the situation is inverted. On entries 19 and 20 the results are close showing that the choice of boron derivative ought to match with the reaction conditions.

Comparison of different substrates was also performed when using Ni catalysts. Though with some variation in the reaction conditions, reactions 23 to 25 show that among $PhB(OH)_2$, Ph_4BNa and phenyl catechol borane the first led to the best result while the last to the worst.

With reactions 23, 28 and 29 we intended to verify the possible influence that the order in which the reagents were added would have upon reactivity. In a more typical reaction, 23, the borane and the ether were added together to a solution of catalyst. On a second case, 28, the borane was first added followed by the ether after 15 min. Finally in a third case, 29, the ether was first added followed by the borane after 1 h. The results show small variation on the reaction yields suggesting little influence on the reagents order of addition.

4.3.2.5 Rationalizing on the Preliminary Results

Until this point our study has allowed us to take these main conclusions:

- Both palladium and nickel catalysts displayed some degree of activity therefore both being susceptible to be employed in the reaction;
- Ligand free catalysts reveal activity however not being stable enough to sustain the catalytic cycle;
- When combined with the metal, common phosphine ligands did not lead to sufficiently active catalysts resulting in poor yields;
- The temperature does not seem to have great impact in the cross-coupling reaction;
- The presence of a base in the reaction is vital;
- The reaction may be pH sensitive;
- The use of base favours the hydrolysis of both phenolic ether types especially the benzisothiazolyl ones;
- The right choice of solvent, base, and organoboranes is important and challenging;
- The substituent in the ether seems to influence the reaction;
- Boronic acid homocoupling is an important competitive reaction.

In order to tackle some of the preview issues we have considered the next possible solutions:

- The use of bulky electron rich ligands may benefit the reaction by improving both oxidative addition and reductive elimination thus maintaining the catalytic cycle.[291]

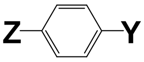
  If indeed in those basic conditions the tetrazolyloxy and saccharyl groups are less prompted to be detached from the metal center, a bulky and strongly coordinating ligand may play a positive role;

- By reducing the reaction time, the use of a very active catalyst may reduce the extension of the hydrolysis and homocoupling reactions;
- The use of alternative nucleophiles that do not need activation may avoid the ethers hydrolysis;
- An appropriate choice of solvent and base may reduce the extension of the hydrolysis, and homocoupling reactions;
- Slow addition of organoborane may reduce the homocoupling reaction extension.

4.3.2.6 Carrying on With the Study

According with these possible ways to improve our reaction we decided to investigate the effect of using bulkier and electron richer ligands than those early used. We have early mentioned how dialkylbiaryl phosphines or trialkylphosphines have successfully catalysed Suzuki cross-coupling with chlorides. In addition they have been applied to catalyse the same reaction with other demanding substrates instead. An example is Buchwald's ligand XPhos used together with $Pd(OAc)_2$ to cross-couple aryl tosylates,[340] PCy_3 used with nickel pre-catalysts to cross-couple aryl tosylates[334,341,342] and aryl mesylates,[342] and ferrocenyl ligands also combined with nickel to cross-couple aryl tosylates.[343] Based on these reports we carried out our investigations this time trying PCy_3 and our ligand **90**, 1,2-*R*,*R*$_p$-Fc[P(O)Eph](PPh_2). The results are shown in the following **Table**.

Table 13 - Results from Suzuki coupling reactions with tetrazolyl and benzisothiazolyl ethers - using PCy$_3$ and ligand **90**.

#[a]			Borane	Catalytic system	Base	Solvent	P%
1	MeO	OTet	1.5 PhB(OH)$_2$	NiCl$_2$(PCy$_3$)$_2$ 4 PCy$_3$	2.5 K$_3$PO$_4$	Dioxane	23
2	MeO	OSac	1.5 PhB(OH)$_2$	NiCl$_2$(PCy$_3$)$_2$ 4 PCy$_3$	2.5 K$_3$PO$_4$	Dioxane	0
3	MeO	OTet	1.5 PhB(OH)$_2$	NiCl$_2$(COD)$_2$ 4 PCy$_3$	2.5 K$_3$PO$_4$	Dioxane	34*
4	MeCO	OTet	1.5 PhB(OH)$_2$	NiCl$_2$(COD)$_2$ 4 PCy$_3$	2.5 K$_3$PO$_4$	Dioxane	27
5	MeCO	OSac	1.5 PhB(OH)$_2$	NiCl$_2$(COD)$_2$ 4 PCy$_3$	2.5 K$_3$PO$_4$	Dioxane	0
6	MeCO	OTet	1.5 PhB(OH)$_2$	NiCl$_2$(COD)$_2$ 4 **90**	2.5 K$_3$PO$_4$	Dioxane	28
7	MeCO	OTet	1.5 PhB(OH)$_2$	Pd(OAc)$_2$ 1.2 PCy$_3$	2.5 K$_3$PO$_4$	Dioxane	40
8	MeCO	OTet	1.5 PhB(OH)$_2$	Pd(OAc)$_2$ 2 **90**	2.5 K$_3$PO$_4$	Dioxane	47

P - cross-coupling product; (a) 105ºC, 0.5 mmol of ether, 3 mol% of Ni catalyst or 5 mol % of Pd catalyst, 2 ml of dioxane, reaction under N$_2$ atmosphere, 24 h. *Isolated yield.

According with **Table** 13, both Pd and Ni were tested in a set of conditions based on the early mentioned pertinent publications.[334,340-343] Dioxane, a relatively polar solvent that seems to favour our reaction was used. Although in our early studies K$_3$PO$_4$ did not appear as the ideal base for the reaction, we have employed it again. Although we considered that in this system it could exert a more positive effect we lowered the number of equivalents from 3 to 2.5 relatively to the ether.

Entries 1 and 2 involve tetrazolyl and benzisothiazolyl ethers presenting an electrondonating methoxy group, Z. The catalyst involves NiCl$_2$(PCy$_3$)$_2$ together with 4 equivalents of extra PCy$_3$. Based on ^{1}H NMR entry 1 presented a 23% conversion while entry 2 did not lead to the formation of the desired product. In entries 3 to 5 NiCl$_2$(COD)$_2$ was used as the metal source instead, again combined with 4 equivalents of PCy$_{3.}$ This system led to better results when tetrazolyl ethers were used, with the benzisothiazolyl one still failing to react. It is not clear whether the stated improvement reflects an ideal proportion between the ligand and the metal,[341,343] the presence of 1,5-cyclooctadiene (COD) in the reaction media, or both. Entry 3 presents one of the best results obtained in our study so far, the amount of product isolated corresponding to 34% yield. Entry 4 however presents a conversion of 27% while involving an ether with a more electrowithdrawing group. More results are needed to confirm and allow a better understanding of this result. Nevertheless it is important to note that this result is not surprising if we consider that oxidative addition is not necessarily the rate determining step especially when Ni is used. Reaction 6 was performed with ligand **90** showing a similar result to the one with PCy_3 on reaction 4.

Finally Pd metal was tested with 1.2 equivalents of PCy_3 and with 2 equivalents of ligand **90**. As with the Ni metal, both ligands improve our Pd catalyzed reaction leading to conversions of 40 and 47%. We did not carry further studies by changing the reaction conditions.

As previously mentioned we wonder if the tetrazolyloxy and saccharyl fragments formed after oxidative addition would strongly coordinate to the Pd center and thus hinder the catalytic cycle. Trying to take conclusions on the matter we decided to react a bromide, *p*-bromotoluene, in the presence of 10 mol% of the corresponding tetrazolyl or benzisothiazolyl ether, or in the presence of the same amount of tetrazolone or saccharine. The reaction is presented in the **Figure** below.

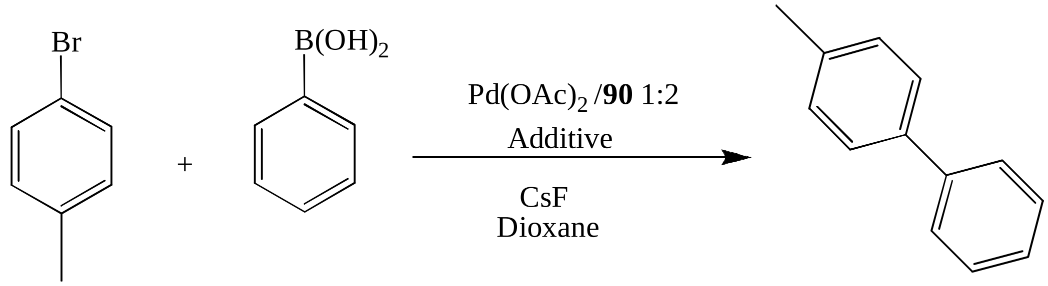
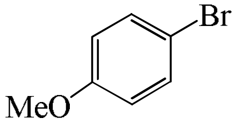
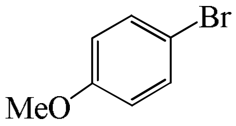
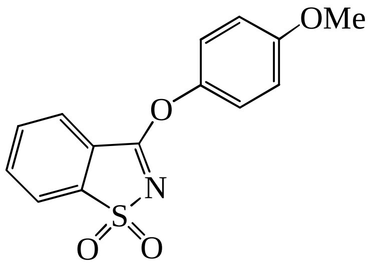
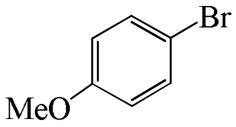
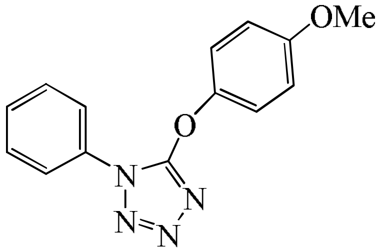
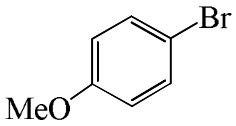
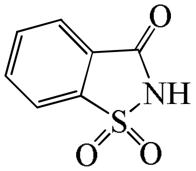
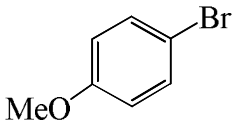
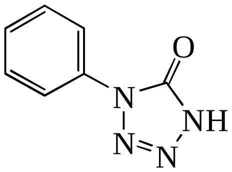


Figure 46 - Cross-coupling reaction between tetrazolyl and benzisothiazolyl ethers with boron organometallics.

The results obtained using the different additives are displayed on **Table** 14.

Table 14 - Results on the influence of tetrazolyl and benzisothiazolyl derivatives upon the Suzuki coupling reaction of *p*-bromotoluene with phenylboronic acid.

#[a]	Substrate	Additive[b]	Conversion
1		-	>99 %
2			>99 %
3			>99 %
4			>99 %
5			>99 %

(a) 105ºC, 0.5 mmol of p-bromotoluene, 0.75 mmol of phenyl boronic acid, 1.5 mmol of CsF, 1 mol% of $Pd(OAc)_2$, 2 mol % of ligand **90**, 2 ml of dioxane, reaction under N_2 atmosphere, 4 h. (b) 10 mol % of additive added.

Entry 1 shows the reaction between *p*-bromotoluene with phenylboronic acid catalysed by $Pd(OAc)_2$ in the presence of 2 equivalents of ligand **90**, 1,2-R,R_p-Fc[P(O)Eph](PPh_2). Under those conditions the conversion was superior to 99%. As displayed in the **Table** adding the tetrazole or benzisothiazole derivatives did not seem to affect the result. This suggests that either there was no oxidative addition of the ethers, due to competitive addition of the bromide, or the removal of the tetrazolyloxy and saccharyl fragments does not impose a problem under these reaction conditions. We realize that the same experiment could be done in conditions that led to good conversions when bromides were used without any ligand. Namely using $Pd(OAc)_2$, K_3PO_4, and toluene, as on **Table** 12 entry 13. This could be more enlightening than the previous experiment.

4.4 CONCLUDING REMARKS

On this chapter we have studied the Suzuki coupling involving tetrazolyl and benzisothiazolyl phenolic ethers, as an indirect means to substitute the hydroxide group on phenols by aryl groups on boronic acids. Accordingly the synthesis of several tetrazolyl and benzisothiazolyl phenolic ethers was performed.

With respect to their use in Suzuki coupling, we have seen that the reaction is indeed possible especially with the first type of ethers. Nevertheless finding optimal reaction conditions have proved challenging with hydrolysis of both types of ethers and boronic acids homocoupling representing undesired reactions to be avoided. Bulky electron rich phosphines ligands seem however to disclose the possibility to attain better results. In fact we believe that further studies and improvements on the reaction conditions could well lead to higher yields and better performance. To this matter a recent paper on the Suzuki coupling of boronic acids and 5-chloro-1-phenyl-1*H*-tetrazole, although not being exactly similar to our system, discloses possible suggestions. In their case bulky and electron rich phosphine ligands presenting extra-coordinating groups, together with the use of microwaves heating, provided respectable results.[371]

5

Experimental

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*The present **Chapter** describes the synthesis for all new compounds presented in this thesis, including the corresponding experimental analytical data. The analytical techniques applied for each compound varied according with the compound and the availability of the resources.*

Chapter 5

5.1 GENERAL CONDITIONS

The experimental work presented in this thesis was done at the University of Liverpool - LCMC and at the Universidade do Algarve - FCT (University of the Algarve). Generally new compounds were fully characterized and known compounds were prepared according with reported procedures and partially characterized.

At the University of Liverpool reactions were normally carried out under a nitrogen atmosphere with standard Schlenk techniques. All glassware was oven-dried for a minimum of two hours before use. THF, dioxane and Et_2O were distilled under nitrogen atmosphere from a deep blue solution of sodium-benzophenone prior to use. Toluene, DCM, and NEt_3 were freshly distilled over powdered CaH_2 prior to use. Flash-chromatography was performed using silica gel 60 Å (37-70 nm). Analytical TLC was carried out utilizing 0.25 mm pre-coated plates (silica gel 60 UV_{254}). For NMR-spectroscopy samples were dissolved in $CDCl_3$ and run at room temperature. ^1H (400 MHz), ^{13}C (100 MHz) and ^{31}P (162 MHz) NMR spectra were recorded on a Bruker 400 Avance spectrometer. Chemical shifts for protons were reported using TMS (0.05%) as internal reference (δ 0). Carbon signals were referenced to the shift from the ^{13}C signal of $CDCl_3$ (δ 77.0). The following abbreviations were used to define the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The coupling constants (*J*) are measured in Hertz (Hz). Mass spectra were measured at 70 eV (EI). Elemental analyses were performed by the Microanalysis Laboratory, Department of Chemistry, University of Liverpool. Melting points were reported as their uncorrected values.

At the Universidade do Algarve glassware was oven-dried for a minimum of two hours before use. All solvents were dried before use and stored over type 4 Å zeolites. THF, dioxane and Et_2O were distilled under nitrogen atmosphere from a deep blue solution of sodium-benzophenone prior to use. Toluene, acetonitrile, and NEt_3 were freshly distilled over powdered CaH_2 prior to use. DMF was dried by azeotropic distillation with toluene and then with type 4 Å zeolites.

Analytical TLC was carried out utilizing 0.25 mm pre-coated plates (silica gel 60 UV_{254}) normally using toluene/acetone [5:1] or DCM as eluent. IR spectra were recorded on a Mattson 1000 FTIR UNICAM spectrometer. Melting points were measured on a Melting Point Apparatus, SMP 3, Bibby Stuart Scientific, and reported as their uncorrected values. Elemental analyses, NMR-spectroscopy and Mass spectrometry were, kindly, performed at the Department of Chemistry, University of Liverpool.

Reaction monitoring was performed by means of analytical TLC, gas chromatography, and also, for further identification of the products, by gas chromatography - mass spectrometry (GC-MS).

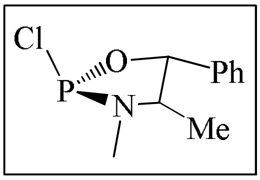
Gas chromatography was performed on a CHROMPACK CP 9001 apparatus, equipped with a FID detector, splitter and Supelco SPB-1 (30m x 0.2 mm, 0,2 μm) or Optima-5 (25 m x 0.25 mm, 0.25 μm) columns. Nitrogen was used as the carrier gas with a pressure of 50 kPa.

GC-MS spectra were measured on a Hewlett Packard, 5890 SERIES II Gas Chromagraph.

5.2 EXPERIMENTAL PROCEDURE FOR CHAPTER 2

SYNTHESIS OF OXAZAPHOSPHOLIDINES

(2*R*,4*S*,5*R*)-2-Chloro-3,4-dimethyl-5-phenyl-[1,3,2]-oxazaphospholidine (80)

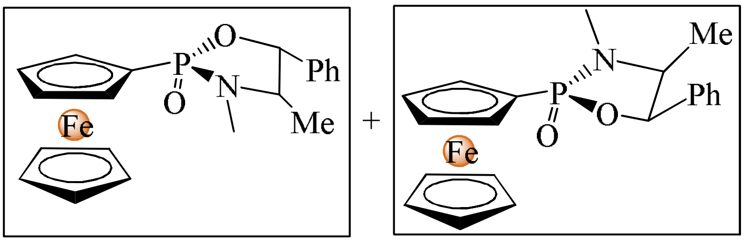


$C_{10}H_{13}ClNOP$

Mol. Wt.: 229.64

A 1 L Schlenk flask, equipped with magnetic stirrer bar and septum, was charged with toluene (250 mL) and *N*-methylmorpholine (26.6 mL, 242.0 mmol). Addition of PCl_3 (10.5 mL, 121 mmol) was smoky and resulted in a cloudy solution that was subsequently cooled to -78 °C. A second Schlenk flask, equipped with a magnetic stirrer bar and septum, was charged with (1*R*,2*S*)-(-)-ephedrine (20 g, 121 mmol) and 150 mL of toluene and the solution was transferred via cannula to the first Schlenk flask. The reaction was allowed to reach room temperature overnight and the mixture was then filtered from the morpholine hydrochloride salt and washed with 50 mL of dry toluene. The yellowish solution was then evaporated under vacuum and the resulting oil solidified upon overnight cooling in the freezer (-30°C). The desired product was recovered as a yellowish waxy solid in 93% yield (25.60 g, 111.48 mmol). No further purification of the product was necessary before being used for the next step. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm): 0.71 (3H, d, *J*=6.5 Hz, CH_3), 2.69 (3H, d, *J*=15.9 Hz, NMe), 3.59-3.67 (1H, dq, *J*=6.6 Hz, CHMe), 5.82 (1H, d, *J*=6.6 Hz, CHPh), 7.14-7.36 (5H, m, Ar). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 14.88, 29.51, 88.20, 127.0, 128.7, 136.9. **^{31}P NMR** ($CDCl_3$, 162 MHz) δ (ppm): 172.4.[372]

(2*R*,4*S*,5*R*)-3,4-Dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (31) and (2*S*,4*S*,5*R*)-3,4-Dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (81)



$C_{20}H_{22}FeNO_2P$

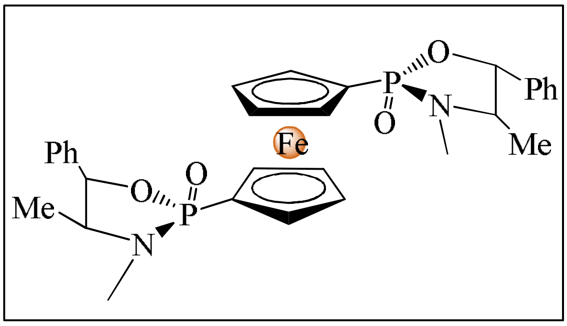
Mol. Wt.: 395.21

A Schlenk flask (250 mL) equipped with magnetic stirrer bar and septum was charged with ferrocene (13.5 g, 72.6 mmol) and ^{t}BuOK (1.3 g, 11.6 mmol). The powder mixture was degassed using vacuum-nitrogen cycles before dry THF (150 mL) was added. The flask was cooled to –78 °C with a bath of dry ice and acetone and then ^{t}BuLi (47.0 mL, 79.8 mmol) was added. The reaction was allowed to stir for around 10 minutes and the bath was removed in order to allow the mixture to reach room temperature. After 1 hour stirring at room temperature a fine red-brick precipitate was formed. The slurry was cooled back to -78ºC and then carefully divided via syringe into two other Schlenk flasks (250 mL), also equipped with magnetic stirrer bar and septum, each containing a solution of oxazaphospholidine chloride (**80**) (12.50 g, 54.4 mmol) in dry THF (75 mL). One of them (A) was previously cooled with an ice bath for 30 min. and then 2h30 with a dry ice/acetone bath (-78ºC). The other reaction (B) was at room temperature during 3 hours. Reaction A was allowed to slowly reach room temperature. After overnight stirring the mixtures were cooled to 0 °C with an ice bath and ^{t}BuOOH (10 mL, 55 mmol) was added to each of the reactions. After 1 hour the baths were removed and the mixtures stirred at room temperature for 3 hours, then the mixtures were washed with a saturated solution of $Na_3S_2O_3$, extracted with EtOAc and dried over $MgSO_4$. The solutions were filtrated from the salt on a sintered funnel and the solvent evaporated under vacuum. The crude mixtures were then purified by flash chromatography on silica gel using EtOAc as eluent. Upon purification the products were crystallized by being dissolved in warm EtOAc slowly crystallizing into brown crystals on cooling. Compound's **81** crystals allowed the resolution of the compound's X-Ray structure (for more structural details see the appendix). In both reactions (2*R*,4*S*,5*R*)-3,4-dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide **31** and (2*S*,4*S*,5*R*)-3,4-dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide **81** were afforded but in different proportions. Reaction A: **31** (6.70 g, 16.95 mmol, 46.5%); **81** (2.63 g, 6.65 mmol, 18.3%) and Reaction B: **31** (3.59 g, 9.08 mmol, 24.9% yield); **81** (5.32 g, 13.46 mmol, 36.9%).

31: Mp: 160-162 °C. **^{1}H NMR** ($CDCl_3$) δ (ppm): 0.82 (3H, d, *J*=6.4 Hz, CH_3), 2.56 (3H, d, *J*=10.2 Hz, NMe), 3.59 (1H, ddq, *J*=6.4 Hz, *J'*=10.8 Hz, CHMe), 4.34 (5H, s, Cp), 4.35 (1H, m, subst. Cp), 4.43 (2H, m, subst. Cp), 4.70 (1H, m, subst. Cp), 5.47 (1H, t (dd), *J*=6.7 Hz, CHPh), 7.31-7.50 (5H, m, Ph). **^{13}C NMR** ($CDCl_3$) δ (ppm): 14.96, 29.20, 59.22, 70.29, 71.60, 71.74, 74.22, 82.62, 127.12, 128.59, 128.75, 137.04. **^{31}P NMR** ($CDCl_3$) δ (ppm): 40.80. **$[\alpha]^{20}_D$**= 140° (c=1 $CHCl_3$). **HRMS,** calc. for $C_{20}H_{22}FeNO_2P$, [M+Na]: 418.0635. Found: 418.0644. **EA** calculated for $C_{20}H_{22}FeNO_2P$: C (60.78%), H (5.61%), N (3.54%); found: C (60.62%), H (5.66%), N (3.49%).[173]

81: Mp: 175-176 °C. **^{1}H NMR** ($CDCl_3$) δ (ppm): 0.72 (3H, d, *J*=6.6 Hz, CH_3), 2.70 (3H, d, *J*=9.1 Hz, NMe), 3.74 (1H, dq, *J*=6.2 Hz, *J'*=6.6 Hz, CHMe), 4.40 (5H, s, Cp), 4.41 (1H, m, subst. Cp), 4.46 (2H, m, subst. Cp), 4.73 (1H, m, subst. Cp), 5.88 (1H, d, *J*=6.1 Hz, CHPh), 7.32-7.44 (5H, m, Ph). **^{13}C NMR** ($CDCl_3$) δ (ppm): 14.34, 29.66, 61.32, 66.35, 70.54, 71.82, 71.95, 72.26, 72.39, 74.72, 74.89, 80.33, 125.97, 128.39, 128.89, 137.13. **^{31}P NMR** (CDCl$_3$) δ (ppm): 37.89. **[α]$^{20}_{D}$=** -320º (c=1.0 CHCl$_3$). **HRMS,** calculated for $C_{20}H_{22}FeNO_2P$, [M+H]: 396.0816; found: 396.0813. [M+Na]: 418.0635; found: 418.0606. **EA** calculated for $C_{20}H_{22}FeNO_2P$: C (60.78%), H (5.61%), N (3.54%); found: C (61.06%), H (5.76%), N (3.95%).

1,1'-bis((*2R,2R',4R,4R',5S,5S'*)-3,4-dimethyl-5-phenyl-[1,3,2]-oxazaphospholidin-2-oxide-2-yl)ferrocene (82), 1,1'-bis((*2S,2R',4R,4R',5S,5S'*)-3,4-dimethyl-5-phenyl-[1,3,2]-oxazaphospholidin-2-oxide-2-yl)ferrocene (83) and 1,1'-bis((*2S,2S',4R,4R',5S,5S'*)-3,4-dimethyl-5-phenyl-[1,3,2]-oxazaphospholidin-2-oxide -2-yl)ferrocene (84)



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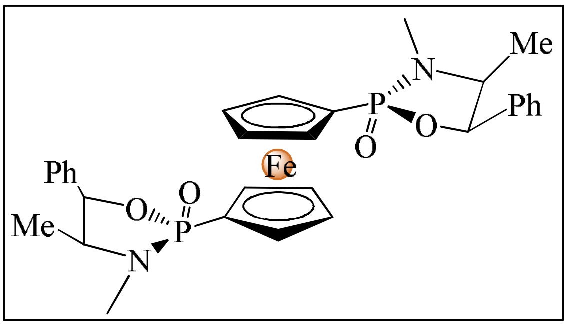

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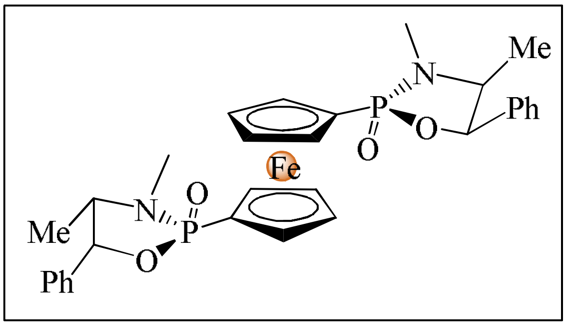


$C_{30}H_{34}FeN_2O_4P_2$

Mol. Wt.: 604.32

A Schlenk flask (500 mL) equipped with magnetic stirrer bar and septum was charged with dry hexane (15 mL) and TMEDA (6.5 mL, 43.5 mmol). A solution of ^{n}BuLi (2.5 M) (17.4 mL, 43.5 mmol) was added and the mixture, which turned yellow, was allowed to stir for 15 min. at room temperature. Subsequently a solution of ferrocene (3.28 g, 17.64 mmol) in hexane (150 mL) was added and after 6h stirring at room temperature the orange mixture was added to a solution of oxazaphospholidine chloride (12.15 g, 52.9 mmol) in dry THF (200 mL) at 0°C.

After overnight stirring the mixture was cooled to 0 °C with an ice bath and ^{t}BuOOH (9.7 mL, 53 mmol) was added. After 1 hour the bath were removed and the mixture stirred at room temperature for 3 hours, then washed with a saturated solution of $Na_3S_2O_3$, extracted with EtOAc and dried over $MgSO_4$. The solution was filtrated from the salt on a sintered funnel and the solvent evaporated under vacuum. The crude mixture was then purified by flash chromatography on silica gel initially using EtOAc as eluent and then increasing polarity with mixtures of EtOAc and MeOH.

Among the several fractions some ferrocene was recovered as well as the monolithiated products (2*R*,4*S*,5*R*)-3,4-dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (**31**) and (2*S*,4*S*,5*R*)-3,4-dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (**81**).

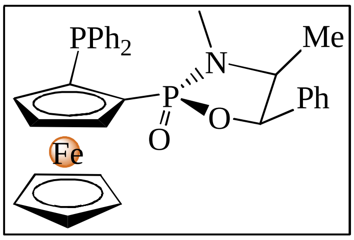
The products were mostly collected as a mixture of three different diastereomers (6.74 g, 11.15 mmol, 63.2% yield). In one of the first fractions one less polar compound was isolated pure **82**: **^{1}H NMR** ($CDCl_3$) δ (ppm): 0.74 (6H, d, *J*=6.5 Hz, CH_3), 2.48 (6H, d, *J*=10.5 Hz, NMe), 3.51 (2H, m, CHMe), 4.58 (2H, s, subst. Cp), 4.65 (2H, s, subst. Cp), 4.73 (2H, s, subst. Cp), 4.79 (2H, s, subst. Cp), 5.35 (2H, t, *J*=6.9 Hz, CHPh), 7.25-7.40 (10H, m, Ph). **^{31}P NMR** ($CDCl_3$) δ (ppm): 38.64. **HRMS,** calculated for $C_{30}H_{34}FeN_2O_4P_2$, [M+Na]: 627.1241; found: 627.1244. **EA** calculated for $C_{30}H_{34}FeN_2O_4P_2$: C (59.62%), H (5.67%), N (4.63%); found: C (59.14%), H (5.57%), N (4.52%).

82+**83**: **^{1}H NMR** ($CDCl_3$) δ (ppm): 0.68 (3H, d, *J*=6.6 Hz, CH_3) 0.72 (3H, d, *J*=6.5 Hz, CH_3) and 0.82 (3H, d, *J*=6.5 Hz, CH_3), 2.48 (3H, d, *J*=10.6 Hz, NMe), 2.50 (3H, d, *J*=10.5 Hz, NMe) and 2.68 (3H, d, *J*=9.3 Hz, NMe), 3.52 (1H, m, CHMe), 3.62 (1H, m, CHMe) and 3.75 (1H, m, CHMe), 4.51 (1H, s, subst. Cp), 4.58 (1H, s, subst. Cp), 4.65 (1H, s, subst. Cp), 4.73 (1H, s, subst. Cp), 4.74 (1H, s, subst. Cp), 4.79 (1H, s, subst. Cp), 4.88 (1H, s, subst. Cp) and 4.92 (1H, s, subst. Cp), 5.33 (1H, t, *J*=6.7 Hz, CHPh), 5.59 (1H, t, CHPh) and 5.90 (1H, d, *J*=5.9 Hz, CHPh), 7.30-7.55 (5H, m, Ph). **^{13}C NMR** ($CDCl_3$) δ (ppm): 15.02, 15.16, 29.05, 29.49, 58.80, 59.02, 61.48, 68.07, 69.92, 72.00, 72.28, 73.81, 74.57, 74.64, 74.78, 75.22, 75.38, 82.82, 83.2, 125.9, 127.34, 128.65, 128.78, 136.70, 136.94. **^{31}P NMR** ($CDCl_3$) δ (ppm): 35.25, 38.59.

84: **^{1}H NMR** ($CDCl_3$) δ (ppm): 0.70 (6H, d, CH_3), 2.70 (6H, d, NMe), 3.70 (2H, dq, CHMe), 4.59 (2H, s, subst. Cp), 4.70 (2H, s, subst. Cp), 4.75 (2H, s, subst. Cp), 4.79 (2H, s, subst. Cp), 5.80 (2H, d, CHPh), 7.20-7.50 (10H, m, Ph). **^{31}P NMR** ($CDCl_3$) δ (ppm): 36.72. **HRMS,** calculated for $C_{30}H_{34}FeN_2O_4P_2$, [M+Na]: 627.1241; found: 627.1237.

Typical Procedure for the Ortho-Lithiation Reactions

(2*S*,4*S*,5*R*)-3,4-Dimethyl-2-(α-(*S*$_p$)-diphenyl-phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (*S*$_p$-85)



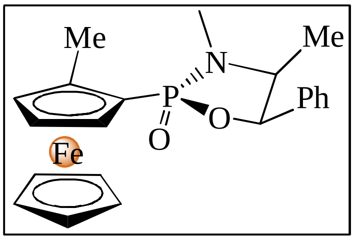
$C_{32}H_{31}FeNO_2P_2$

Mol. Wt.: 579.39

A Schlenk tube, equipped with magnetic stirrer bar and septum, was charged with (2*S*,4*S*,5*R*)-3,4-dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (1.00 g, 2.53 mmol). The tube was degassed using vacuum-nitrogen cycles and then THF was added. The mixture was cooled to –78 °C with a bath of dry ice and acetone for 30 minutes before ^{t}BuLi (1.7 M) (2.4 mL, 4.0 mmol, 1.6 eq.) was added. The reaction was stirred at –78 °C for another hour before chlorodiphenylphosphine (0.7 mL, 3.9 mmol, 1.5 eq.) was added. After overnight stirring at room temperature, analysis of the reaction mixture by TLC (EtOAc) revealed the presence of a new compound. The crude product was analyzed with ^{1}H and ^{31}P NMR, extracted with EtOAc (3 x 75 mL), washed with brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure and purification by flash chromatography using EtOAc as eluent on silica gel afforded the pure product as an orange solid in 60.7% yield (0.89 g, 1.54 mmol). The product was crystallized by being dissolved in warm EtOAc slowly crystallizing into brown crystals on cooling. Compound's **85** crystals allowed the resolution of the compound's X-Ray structure (for more structural details see the appendix).

Mp: 190-191°C. **^{1}H NMR** ($CDCl_3$) δ (ppm): 0.63 (3H, d, *J*=6.6 Hz, CH_3), 2.04 (3H, d, *J*=9.3 Hz, NMe), 3.55 (1H, dq, *J*=6.2 Hz, *J'*=6.3 Hz, CHMe), 3.90 (1H, s, subst. Cp), 4.38 (5H, s, Cp), 4.51 (1H, m, subst. Cp), 4.66 (1H, m, subst. Cp), 5.82 (1H, d, *J*=5.9 Hz, CHPh), 7.24-7.57 (15H, m, Ph). **^{13}C NMR** ($CDCl_3$) δ (ppm): 14.5, 29.5, 61.9, 71.6, 72.8, 75.2, 75.9, 79.9, 125.9, 128.5, 128.6, 129.2, 133.9, 134.1, 135.0, 135.2, 137.2, 137.3, 138.64, 138.8, 140.7, 140.8. **^{31}P NMR** ($CDCl_3$) δ (ppm): -19.8, 35.9. **$[\alpha]^{20}_D$**= -80° (c=1.0 $CHCl_3$). **HRMS,** calculated for $C_{32}H_{31}FeNO_2P_2$, $[M+H]^+$: 580.1258; found: 580.1252. **EA** calculated for $C_{32}H_{31}FeNO_2P_2$: C (66.34%), H (5.27%), N (2.31%); found: C (66.16%), H (5.46%), N (2.38%).

(2*S*,4*S*,5*R*)-3,4-Dimethyl-2-(α-(*S$_p$*)-methyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (*S$_p$*-86)



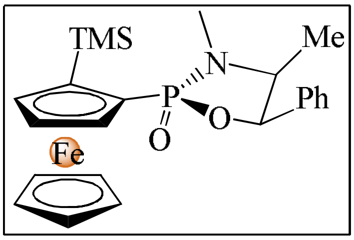
$C_{21}H_{24}FeNO_2P$

Mol. Wt.: 409.24

(2*S*,4*S*,5*R*)-3,4-Dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (2.50 g, 6.33 mmol), ^{t}BuLi (1.7 M) (6.3 mL, 9.5 mmol, 1.5 eq.) and iodomethane (0.8 mL, 12.65 mmol, 2.0 eq.) were used in this reaction.

The compound was purified by flash chromatography using EtOAc/Hexane (3:1) and the pure product was recovered as an orange oil in 46.4% yield (1.19 g, 2.93 mmol). **^{1}H NMR** ($CDCl_3$) δ (ppm): 0.58 (3H, d, *J*=6.4 Hz, CH_3), 2.22 (3H, s, CH_3), 2.56 (3H, d, *J*=9.3 Hz, NMe); 3.57-3.66 (1H, dq, *J*=6.4 Hz, *J'*=6.3 Hz, CHMe), 4.19 (2H, m, subst. Cp), 4.23 (5H, s, Cp), 4.26 (1H, m, subst. Cp), 5.79 (1H, d, *J*=5.9 Hz, CHPh), 7.20-7.40 (5H, m, Ph). **^{13}C NMR** (CDCl$_3$) δ (ppm): 12.50, 13.43, 27.99, 59.92, 64.27, 66.16, 68.67, 69.35, 69.45, 72.38, 78.86, 89.36, 124.48, 126.80, 127.50, 135.79. **^{31}P NMR** (CDCl$_3$) δ (ppm): 37.7. **[α]$^{20}_{D}$**= -320° (c=1.0 CHCl$_3$). **HRMS,** calculated for $C_{21}H_{24}FeNO_2P$, [M+Na]$^+$: 432.0792; found: 432.0788. **EA** calculated for $C_{21}H_{24}FeNO_2P$: C (61.63%), H (5.91%), N (3.42%); found: C (61.18%), H (6.12%), N (3.20%).

(2*S*,4*S*,5*R*)-3,4-Dimethyl-2-(α-(*S$_p$*)-trimethylsylanylferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (*S$_p$*-87)



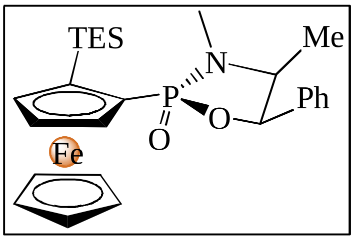
$C_{23}H_{30}FeNO_2PSi$

Mol. Wt.: 467.39

(2*S*,4*S*,5*R*)-3,4-Dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine-oxide (2.00 g, 5.06 mmol), ^{t}BuLi (1.7 M) (4.5 mL, 7.6 mmol, 1.5 eq.) and chloro-trimethylsilane (1.3 mL, 10.00 mmol, 2.0 eq.) were used in this reaction. The compound was purified by flash chromatography using EtOAc/Hexane (3:1) and the pure product was recovered as an orange solid in 46.5% yield (1.10 g, 2.35 mmol). The product was crystallized by being dissolved in warm EtOAc slowly crystallizing into brown crystals on cooling which allowed the resolution of the compound's X-Ray structure (for more structural details see the appendix).

Mp: 118-119ºC. **^{1}H NMR** ($CDCl_3$) δ (ppm): 0.41 (9H, s, TMS), 0.76 (3H, d, *J*=6.7 Hz, CH_3), 2.63 (3H, d, *J*=9.3 Hz, NMe), 3.67-3.76 (1H, dq, *J*=6.6 Hz, *J'*=6.5 Hz, CHMe), 4.38 (5H, s, Cp), 4.44 (1H, m, subst. Cp), 4.53 (1H, m, subst. Cp), 4.58 (1H, m, subst. Cp), 5.87 (1H, d, *J*=5.9 Hz, CHPh), 7.33-7.54 (5H, m, Ph). **^{13}C NMR** ($CDCl_3$) δ (ppm): 0.0, 13.2, 28.3, 60.2, 68.9, 72.4, 72.6, 73.5, 73.7, 88.7, 124.6, 126.9, 127.5, 135.8, 135.9. **^{31}P NMR** ($CDCl_3$) δ (ppm): 38.8. **$[\alpha]^{20}_D$**= 400º (c=1.0 $CHCl_3$). **HRMS,** calculated for $C_{23}H_{30}FeNO_2PSi$, $[M+H]^+$: 468.1211; found: 468.1209. $[M+Na]^+$: 490.1031 found: 490.1036. **EA** calculated for $C_{23}H_{30}FeNO_2PSi$: C (59.10%), H (6.47%), N (3.00%); found: C (59.30%), H (6.65%), N (2.73%).

(2*S*,4*S*,5*R*)-3,4-Dimethyl-2-(α-(*S$_p$*)-triethylsylanylferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (*S$_p$*-88)



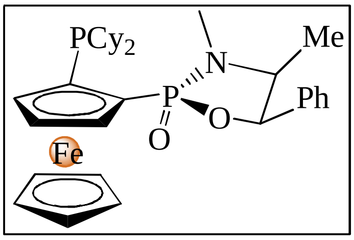
$C_{26}H_{36}FeNO_2PSi$

Mol. Wt.: 509.47

(2*S*,4*S*,5*R*)-3,4-Dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (2.10 g, 5.31 mmol), ^{t}BuLi (1.7 M) (4.4 mL, 7.4 mmol, 1.4 eq.) and chloro-triethylsilane (1.3 mL, 7.7 mmol, 1.45 eq.) were used in this reaction.

The compound was purified by flash chromatography using EtOAc/Hexane (3:1) and the pure product was recovered as an orange solid in 47.0% yield (1.27 g, 2.50 mmol). Mp: 68-69ºC. **^{1}H NMR** ($CDCl_3$) δ (ppm): 0.68 (3H, d, *J*=6.6 Hz, CH_3), 0.78-1.1 (15H, m, TES), 2.53 (3H, d, *J*=9.3 Hz, NMe), 3.58-3.68 (1H, dq, *J*=6.6 Hz, *J'*=6.5 Hz, CHMe), 4.30 (5H, s, Cp), 4.35 (1H, m, subst. Cp), 4.45 (1H, m, subst. Cp), 4.54 (1H, m, subst. Cp), 5.79 (1H, d, *J*=6.2 Hz, CHPh), 7.25-7.38 (5H, m, Ph). **^{13}C NMR** ($CDCl_3$) δ (ppm): 4.0, 7.08, 13.4, 28.2, 60.2, 69.0, 72.7, 72.8, 73.4, 73.6, 78.2, 78.3, 78.5, 124.6, 126.9, 127.5, 135.8, 135.9. **^{31}P NMR** ($CDCl_3$) δ (ppm): 40.6. **$[\alpha]^{20}_D$** = -380° (c=1.0 $CHCl_3$). **HRMS,** calculated for $C_{26}H_{36}FeNO_2PSi$, $[M+Na]^+$: 532.1500; found: 532.1476. **EA** calculated for $C_{26}H_{36}FeNO_2PSi$: C (61.29%), H (7.12%), N (2.75%). Found: C (61.01%), H (7.22%), N (2.59%).

(2*S*,4*S*,5*R*)-3,4-Dimethyl-2-(α-(*S*$_p$)-dicyclohexyl-phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (*S*$_p$-89)



$C_{32}H_{43}FeNO_2P_2$

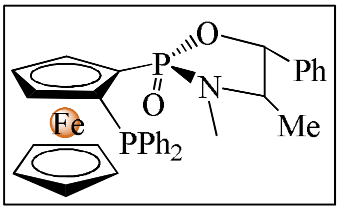
Mol. Wt.: 591.48

(2*S*,4*S*,5*R*)-3,4-Dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (0.87 g, 2.20 mmol), ^{t}BuLi (1.7 M) (1.9 mL, 3.3 mmol, 1.5 eq.) and chloro-dicyclohexylphosphine (0.5 mL, 2.26 mmol, 1.0 eq.) were used in this reaction.

The compound was purified by flash chromatography using EtOAc as eluent and the pure product was recovered as an orange solid in 49.2% yield (0.64 g, 1.08 mmol).

Mp: 77-78°C. **^{1}H NMR** ($CDCl_3$) δ (ppm): 0.73 (3H, d, *J*=6.6 Hz, CH_3), 1.13-2.41 (22H, m, Cy), 2.78 (3H, d, *J*=9.3 Hz, NMe), 3.64-3.76 (1H, dq, *J*=6.4 Hz, *J'*=5.9 Hz, CHMe), 4.40 (6H, s, Cp), 4.55 (2H, m, subst. Cp), 5.88 (1H, d, *J*=5.9 Hz, CHPh), 7.26-7.45 (5H, m, Ph). **^{13}C NMR** ($CDCl_3$) δ (ppm): 14.7, 26.9, 27.9, 62.1, 71.6, 73.2, 79.8, 126.0, 128.3, 128.9.**^{31}P NMR** ($CDCl_3$) δ (ppm): -9.2, 37.4. **$[\alpha]^{20}_D$**= -80º (c=1.0 $CHCl_3$). **HRMS,** calculated for $C_{32}H_{43}FeNO_2P_2$, $[M+H]^+$: 592.2197; found 592.2213. **EA** calculated for $C_{32}H_{43}FeNO_2P_2$: C (64.98%), H (7.33%), N (2.37%); found: C (64.63%), H (7.42%), N (2.28%).

(2*R*,4*S*,5*R*)-3,4-Dimethyl-2-(α-(*R$_p$*)-diphenyl-phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (*R$_p$*-90)



$C_{32}H_{31}FeNO_2P_2$

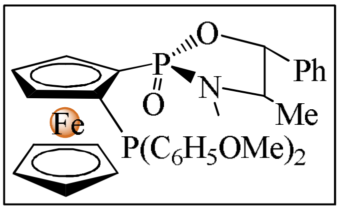
Mol. Wt.: 579.39

(2*R*,4*S*,5*R*)-3,4-Dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (7.00 g, 17.71 mmol), ^{t}BuLi (1.7 M) (15.1 mL, 25.7 mmol, 1.45 eq.) and chloro-diphenylphosphine (4.8 mL, 26.6 mmol, 1.50 eq.) were used in this reaction. The compound was purified by flash chromatography using EtOAc as eluent and the pure product was recovered as an orange solid in 71.9% yield (7.38 g, 12.74 mmol).

^{1}H NMR ($CDCl_3$) δ (ppm): 0.74 (3H, d, *J*=6.5 Hz, CH_3), 2.82 (3H, d, *J*=10 Hz, NMe), 3.35 (1H, ddq, *J*=6.5 Hz, *J'*=22.1 Hz, CHMe), 3.89 (1H, m, subst. Cp), 4.27 (5H, s, Cp), 4.47 (1H, m, subst. Cp), 4.58 (1H, m, CHPh), 4.90 (1H, m, subst. Cp), 7.00-8.08 (15H, m, Ph). **^{13}C NMR** ($CDCl_3$) δ (ppm): 14.6, 29.7, 59.3, 71.5, 73.5, 75.8, 75.9, 77.1, 80.7, 126.5, 128.7, 128.4, 128.5, 128.6, 128.8, 128.9, 128.9, 129.0, 129.5, 133.3, 133.5, 135.2, 135.4, 137.0, 138.2, 140.8. **^{31}P NMR** ($CDCl_3$) δ (ppm): -19.4, 41.0. **HRMS,** calculated for $C_{32}H_{31}FeNO_2P_2$, $[M+H]^+$: 580.1258; found: 580.1284. **EA**

calculated for $C_{32}H_{31}FeNO_2P_2$: C (66.34%), H (5.39%), N (2.42%); found: C (66.34%), H (5.27%), N (2.31%).[173]

(2*R*,4*S*,5*R*)-3,4-Dimethyl-2-(α-(*R*$_p$)-bis(4-methoxyphenyl)phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (*R*$_p$-91)



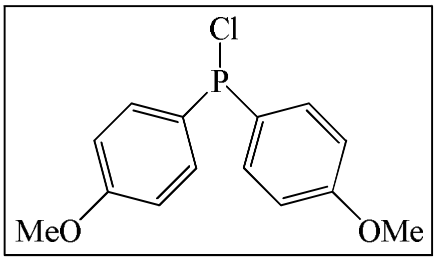
$C_{34}H_{35}FeNO_4P_2$

Mol. Wt.: 639.44

(2*R*,4*S*,5*R*)-3,4-Dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (1.77 g, 4.50 mmol), ^{t}BuLi (1.7 M) (4.2 mL, 7.1 mmol, 1.58 eq.) and chlorobis(4-methoxyphenyl)phosphine (2.14 g, 7.6 mmol, 1.50 eq.) were used in this reaction. The compound was purified by flash chromatography using EtOAc as eluent and the pure product was recovered as an orange solid in 29.9% yield (0.86 g, 1.35 mmol).

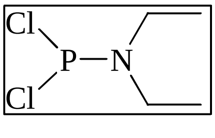
^{1}H NMR ($CDCl_3$) δ (ppm): 0.69 (3H, d, *J*=6.5 Hz, CH_3), 2.75 (3H, d, *J*=10.4 Hz, NMe), 3.27 (1H, ddq, *J*=6.5 Hz, CHMe), 3.61 (3H, s, OMe), 3.74 (3H, s, OMe), 4.05 (1H, m, subst. Cp), 4.19 (5H, s, Cp), 4.34 (1H, m, subst. Cp), 4.56 (1H, dd, CHPh), 4.82 (1H, m, subst. Cp), 6.74 (2H, d, Ar), 6.86 (2H, d, Ar), 6.95 (2H, d, Ar), 7.10-7.23 (5H, m, Ph), 7.44 (2H, m, Ar). **^{31}P NMR** ($CDCl_3$) δ (ppm): -24.3, 37.4. **MS** (CI+(NH_3)) m/z 640 $[M+H]^+$.[173]

Chlorobis(4-methoxyphenyl)phosphine



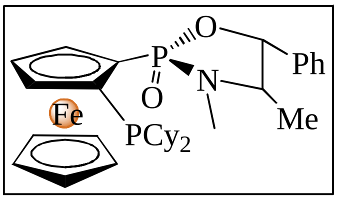
To a suspension of Mg (3.89g, 0.16 mol) and I_2 (a small crystal) in THF at 0ºC, bromoanisol (0.15 mol, 19 mL) was added. After a while the ice bath was removed and the temperature allowed rising with the mixture becoming dark brown. The mixture was refluxed during 2h, cooled, and then slowly added to a solution of Et_2NPCl_2 (8.5 mL, 0.07 mol) at 0ºC. The mixture was stirred for 3h at R.T., the solvent being removed under vacuum. Cyclohexane was added to the mixture to cause precipitation of Mg salts. After filtration a solution of HCl (2M) in Et_2O (75 mL, 0.15 mL) leading to the formation of a yellow precipitate. After standing for 2h the mixture was filtrated and the salt washed with cyclohexane. Evaporation afforded a yellow oil which solidified unto a yellow solid under vacuum (7.69g, 0.027 mol, 47.7%). **^{1}H NMR** ($CDCl_3$) δ (ppm): 3.75 (s, 6H), 6.85 (m, 4H), 7.45 (m, 4H). **^{13}C NMR** ($CDCl_3$) δ (ppm): 54.3, 66.1, 113.3, 128.4, 132.1. **^{31}P NMR** ($CDCl_3$) δ (ppm): 84.2.[373]

1,1-dichloro-N,N-diethylphosphinamine



To a solution of PCl_3 (29 mL, 0.33 mol) in Et_2O (200 mL) at -78ºC, Et_2NH (69 mL, 0.66 mol) was slowly added in a dropwise fashion. The formation of a white mixture was immediate. After about 1h30 stirring at low temperature the bath was removed and the solution stirred at R.T. for another 4h30. The precipitate salt was filtered off and the solution was evaporated to afford a yellow oil. Distillation under reduced pressure was performed using a bath at 50ºC, and a pressure of 0.5 torr. A transparent non-coloured product was distilled (around 23ºC) (37.47g, 0.22 mol, 65.3%). **^{1}H NMR** ($CDCl_3$) δ (ppm):1.12 (t, *J*=7.1 Hz, 6H); 3.28 (dq, *J*=7.1 Hz, 4H). **^{31}P NMR** ($CDCl_3$) δ (ppm): 162.3.[374]

(2*R*,4*S*,5*R*)-3,4-Dimethyl-2-(α-(*R_p*)-dicyclohexyl-phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (*R_p*-92)



$C_{32}H_{43}FeNO_2P_2$

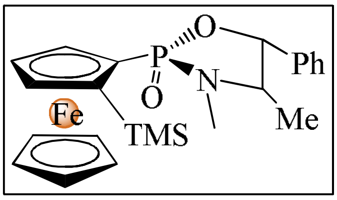
Mol. Wt.: 591.48

(2*R*,4*S*,5*R*)-3,4-Dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (1.79 g, 4.53 mmol), ^{t}BuLi (1.7 M) (4.0 mL, 6.8 mmol, 1.5 eq.) and chloro-dicyclohexylphosphine (1.0 mL, 4.53 mmol, 1.00 eq.) were used in this reaction.

The compound was purified by flash chromatography using EtOAc as eluent and the pure product was recovered as an orange solid in 40.1% yield (1.07 g, 1.82 mmol). **^{1}H NMR** ($CDCl_3$) δ (ppm): 0.84 (3H, d, *J*=6.5 Hz, CH_3), 0.99-2.36 (22H, m, Cy), 2.73 (3H, d, *J*=10.0 Hz, NMe), 3.73-3.82 (1H, m, CHMe), 4.34 (5H, s, Cp), 4.41 (1H, m, subst. Cp), 4.58 (1H, m, subst. Cp), 4.63 (1H, m, subst. Cp), 5.58 (1H, t, *J*=6.7 Hz, CHPh), 7.30-7.49 (5H, m, Ph). **^{13}C NMR** ($CDCl_3$): δ 15.7, 26.9, 71.3, 72.7, 74.0, 74.1, 75.6, 75.7, 82.1, 127.1, 128.4, 128.7, 137.5. **^{31}P NMR** ($CDCl_3$) δ (ppm): -10.8, 39.5.

HRMS, calculated for $C_{32}H_{43}FeNO_2P_2$, $[M+H]^+$: 592.2197; found 592.2210. **EA** calculated for $C_{32}H_{43}FeNO_2P_2$: C (64.98%), H (7.33%), N (2.37%); found: C (64.93%), H (7.37%), N (2.42%).[173]

(2*R*,4*S*,5*R*)-3,4-Dimethyl-2-(α-(*R*$_p$)-trimethylsylanylferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (*R*$_p$-93)



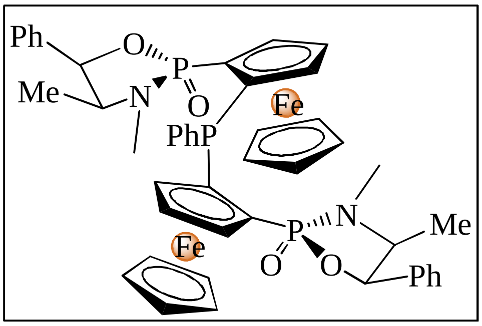
$C_{23}H_{30}FeNO_2PSi$

Mol. Wt.: 467.39

(2*R*,4*S*,5*R*)-3,4-Dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (1.66 g, 4.20 mmol), ^{t}BuLi (1.7 M) (3.7 mL, 6.3 mmol, 1.5 eq.) and chloro-trimethylsilane (1.1 mL, 8.4 mmol, 2.00 eq.) were used in this reaction.

The compound was purified by flash chromatography using EtOAc/Hexane (1:1) as eluent and the pure product was recovered as an orange solid in 65.2% yield (1.28 g, 2.74 mmol). **^{1}H NMR** ($CDCl_3$) δ (ppm): 0.41 (9H, s, TMS), 0.83 (3H, d, *J*=6.5 Hz, CH_3), 2.48 (3H, d, *J*=10.3 Hz, NMe), 3.61-3.70 (1H, m, CHMe), 4.30 (s, 5H, Cp), 4.42 (1H, m, subst. Cp), 4.49 (1H, m, subst. Cp), 4.56 (1H, m, subst. Cp), 5.57 (1H, t, *J*=6.5 Hz, CHPh), 7.33-7.54 (5H, m, Ph). **^{13}C NMR** ($CDCl_3$) δ (ppm): 0.0, 13.6, 27.9, 58.2, 69.0, 72.4, 73.5, 77.7, 78.2, 81.7, 125.9, 127.3, 127.5, 135.9. **^{31}P NMR** ($CDCl_3$) δ (ppm): 42.7. **HRMS,** calculated for $C_{23}H_{30}FeNO_2PSi$, $[M+Na]^+$: 490.1031; found: 490.1033. **EA** calculated for $C_{23}H_{30}FeNO_2PSi$: C (59.10%), H (6.47%), N (3.00%); found: C (58.95%), H (6.53%), N (2.91%).[173]

(*2S,2S',4S,4'S,5R,5'R*)-(2-(*S$_p$*),2'-(*S$_p$*)-(phenylphosphinediyl)bis(ferrocen-2,1-diyl))bis(3,4-dimethyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide) (*S$_p$,S$_p$*-94)



$C_{46}H_{47}Fe_2N_2O_4P_3$

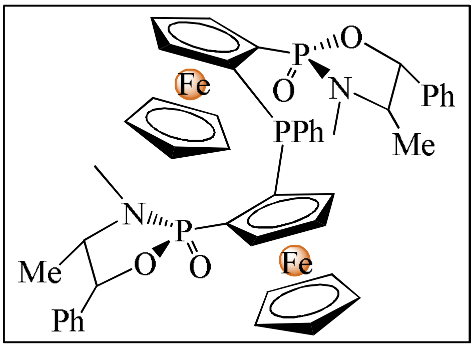
Mol. Wt.: 896.49

(2*S*,4*S*,5*R*)-3,4-Dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (2.00 g, 5.06 mmol, 2.1 eq.), ^{t}BuLi (1.7 M) (3.9 mL, 6.6 mmol, 1.3 eq.) and chloro-diphenylphosphine (0.33 mL, 2.45 mmol) were used in this reaction.

The compound was purified by flash chromatography using EtOAc as eluent and the pure product was recovered as an orange solid in 56.7% yield (1.24 g, 1.39 mmol).

Mp: 145-146ºC. **^{1}H NMR** ($CDCl_3$) δ (ppm): 0.51 (3H, d, *J*=6.6 Hz, CH_3), 0.82 (3H, d, *J*=6.6 Hz, CH_3), 1.89 (3H, d, *J*=9.3 Hz, NMe), 3.07 (3H, d, *J*=9.9 Hz, NMe), 3.49 (1H, dq, *J*=6.5, *J'*=6.3, CHMe), 3.75 (1H, dq, *J*=6.3, *J'*=5.7, CHMe), 3.95 (5H, s, Cp), 4.35 (5H, s, Cp), 4.49-4.78 (6H, m, subst. Cp), 5.75 (1H, d, *J*=5.7 Hz, CHPh), 5.89 (1H, d, *J*=5.7 Hz, CHPh); 7.27-7.40 (15H, m, Ph). **^{13}C NMR** ($CDCl_3$) δ (ppm): 14.3, 15.3, 29.5, 62.1, 71.6, 79.9, 80.4, 125.9, 126.5, 128.1, 128.2, 128.3, 128.8, 128.9, 135.1, 135.3, 137.2. **^{31}P NMR** ($CDCl_3$) δ (ppm): -37.2, 35.9, 38.8. **$[\alpha]^{20}_D$**= -40º (c=1.0 $CHCl_3$). **HRMS,** calculated for $C_{46}H_{47}Fe_2N_2O_4P_3$, $[M+Na]^+$: 919.1345. Found: 919.1305.

(*2R,2R',4S,4'S,5R,5'R*)-(2-(*R_p*),2'-(*R_p*)-(phenylphosphinediyl)bis(ferrocen-2,1-diyl))bis(3,4-dimethyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide) (*R_p*,*R_p*-95)



$C_{46}H_{47}Fe_2N_2O_4P_3$

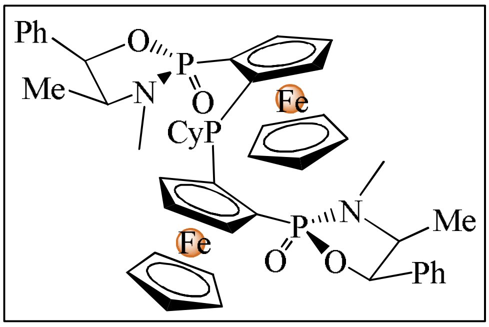
Mol. Wt.: 896.49

(2*R*,4*S*,5*R*)-3,4-Dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (2.00 g, 5.06 mmol, 2.0 eq.), ^{t}BuLi (1.7 M) (4.0 mL, 6.8 mmol, 1.35 eq.) and dichlorophenylphosphine (0.3 mL, 2.5 mmol) were used in this reaction.

The compound was purified by flash chromatography using EtOAc as eluent and the pure product was recovered as an orange solid in 66.1% yield (1.55 g, 1.73 mmol).

Mp: 146-147ºC. **^{1}H NMR** ($CDCl_3$) δ (ppm): 0.68 (3H, d, *J*=6.6 Hz, CH_3), 0.98 (3H, d, *J*=6.6 Hz, CH_3), 2.23 (3H, d, *J*=10.4 Hz, NMe), 3.07 (3H, d, *J*=11.2 Hz, NMe), 3.35 (1H, ddq, *J*=6.4, *J'*=6.6, CHMe), 3.87 (5H, s, Cp), 4.18 (5H, s, Cp), 4.24 (1H, ddq, *J*=6.6 Hz, *J'*=6.4 Hz, CHMe), 4.57-4.70 (6H, m, subst. Cp), 4.92 (1H, m, CHPh), 6.30 (1H, m, CHPh), 7.26-7.37 (10H, m, Ph), 7.67-7.78 (5H, m, Ph). **^{13}C NMR** ($CDCl_3$) δ (ppm): 16.0, 29.1, 30.0, 59.0, 59.3, 60.7, 71.4, 72.6, 73.4, 81.5, 127.0, 127.1, 128.0, 128.3, 128.6, 129.3, 134.4, 134.7, 137.4, 137.9, 142.7. **^{31}P NMR** ($CDCl_3$) δ (ppm): -38.4, 38.3, 39.8. **$[\alpha]^{20}_D$**= -240º (c=1.0 $CHCl_3$). **HRMS,** calculated for $C_{46}H_{47}Fe_2N_2O_4P_3$, $[M+Na]^+$: 919.1345; found: 919.1310. **EA** calculated for $C_{46}H_{47}Fe_2N_2O_4P_3$: C (61.63%), H (5.28%), N (3.12%); found: C (61.48%), H (5.34%), N (3.08%).

Attempting the synthesis of (*2S,2S',4S,4'S,5R,5'R*)-(2-(*S$_p$*),2'-(*S$_p$*)-(cyclohexylphosphinediyl)bis(ferrocen-2,1-diyl))bis(3,4-dimethyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide)



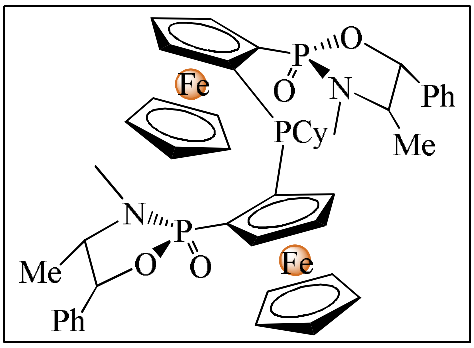
$C_{46}H_{53}Fe_2N_2O_4P_3$

Mol. Wt.: 902.54

(2*S*,4*S*,5*R*)-3,4-Dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (2.00 g, 5.06 mmol, 2.1 eq.), ^{t}BuLi (1.7 M) (3.9 mL, 6.6 mmol, 1.3 eq.) and chloro-dicyclohexylphosphine (0.45 g, 0.39ml, 2.40 mmol) were used in this reaction.

The compound was purified by flash chromatography using EtOAc as eluent and the product was recovered as an orange solid. Although the product was not recovered pure ^{1}H NMR and ^{31}P NMR on one of the fractions suggest that the product was synthesized. **^{31}P NMR** ($CDCl_3$) δ (ppm): -33.0, 36.2, 37.9 ppm.

Attempting the synthesis of (*2R,2R',4S,4'S,5R,5'R*)-(2-(*R_p*),2'-(*R_p*)-(cyclohexylphosphinediyl)bis(ferrocen-2,1-diyl))bis(3,4-dimethyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide)



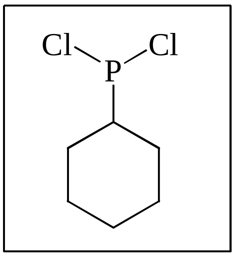
$C_{46}H_{53}Fe_2N_2O_4P_3$

Mol. Wt.: 902.54

(2*R*,4*S*,5*R*)-3,4-Dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (2.00 g, 5.06 mmol, 2.1 eq.), ^{t}BuLi (1.7 M) (4.1 mL, 6.7 mmol, 1.3 eq.) and chloro-dicyclohexylphosphine (0.46 g, 0.40 mL, 2.50 mmol) were used in this reaction.

The compound was purified by flash chromatography using EtOAc as eluent and the product was recovered as an orange solid. Although the product was not recovered pure ^{1}H NMR and ^{31}P NMR on one of the fractions suggest that the product was synthesized. **^{31}P NMR** ($CDCl_3$) δ (ppm): -33.2, 36.4, 41.9 ppm.

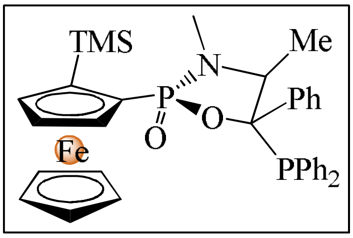
Dichlorocyclohexylphosphine (103)



To a suspension of Mg (2.139g, 0.09 mol) and I_2 (a small crystal) in THF at 0°C, cyclohexylbromide (9.85 mL, 0.080 mol) was added. After a while the ice bath was removed and the temperature allowed rising. The mixture was refluxed during 2h, cooled, and then slowly added to a solution of $(Et_2N)_2PCl$ (10.82g, 0.051 mL, 0.07 mol) at 0ºC. The mixture was stirred for 3h at R.T., the solvent being removed under vacuum. Cyclohexane was added to the mixture to cause precipitation of Mg salts. After filtration a solution of HCl (4M) in dioxane (35 mL, 0.15 mol) leading to the formation of a precipitate. After standing for 2h the mixture was filtrated and the salt washed with cyclohexane. Evaporation afforded an oil (10.9, 42.0 mmol, 60.0%). **^{1}H NMR** ($CDCl_3$) δ (ppm): 0.8-2.0 (11H, m). **^{31}P NMR** ($CDCl_3$) δ (ppm): 196.2 ppm.

Attempting a Second Ortho-Lithiation Reaction at the Ferrocenyl ring

((2*S*,4*S*,5*S*)-3,4-Dimethyl-2-(α-(*S$_p$*)-trimethylsilanyl-ferrocenyl)-5-phenyl-5-diphenyl-phosphanyl-[1,3,2]-oxazaphospholidine 2-oxide (*S$_p$*-98)

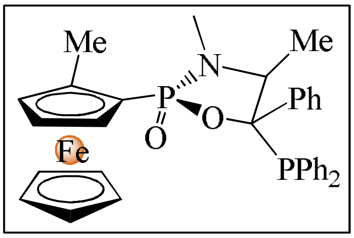


$C_{35}H_{39}FeNO_2P_2Si$

Mol. Wt.: 651.57

A Schlenk tube, equipped with magnetic stirrer bar and septum, was charged with (2*S*,4*S*,5*R*)-3,4-Dimethyl-2-(α-(*S$_p$*)-trimethylsylanylferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (0.805 g, 1.72 mmol). The tube was degassed using vacuum-nitrogen cycles and then THF was added. The mixture was cooled to –78 °C with a bath of dry ice and acetone for 30 minutes before ^{t}BuLi (1.5 mL, 2.58 mmol, 1.5 eq.) was added. The reaction was stirred at –78 °C for another hour and following chlorodiphenylphosphine (0.6 mL, 3.4 mmol, 2.0 eq.) was added. After overnight stirring at room temperature, analysis of the reaction mixture by TLC (EtOAc/Hexane 1:1) revealed the presence of a new compound. The crude product was analyzed with ^{1}H and ^{31}P NMR, extracted with EtOAc (2 x 50 mL), washed with brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure and purification by flash chromatography using EtOAc/Hexane (1:1) as eluent on silica gel afforded the pure product as an orange oil in 90% yield (1.01g, 1.55mmol). **^{1}H NMR** ($CDCl_3$) δ (ppm): 0.32 (9H, s, TMS), 1.75 (3H, d, *J*=7.2 Hz, CH_3), 2.65 (3H, d, *J*=9.7 Hz, NMe), 4.28 (5H, s, Cp), 4.40 (1H, s, subst. Cp), 4.56 (1H, s, subst. Cp), 4.89 (1H, s, subst. Cp), 6.05 (1H, dd, *J*=6.6 Hz, *J'*=7.0 Hz, CHMe), 7.13-7.60 (15H, m, Ph). **^{13}C NMR** ($CDCl_3$) δ (ppm): 12.3, 27.6, 31.0, 68.9, 71.6, 71.7, 74.6, 77.2, 108.6, 126.9, 127.4, 127.5, 128.0, 131.1, 131.3, 131.8, 132.0. **^{31}P NMR** ($CDCl_3$) δ (ppm): 29.4 (P(O)Eph, J_{PP}=76.3 Hz), 46.4 (PPh_2, J_{PP}=75.3 Hz). **$[\alpha]^{20}_D$**= -100° (c=1.0 $CHCl_3$). **HRMS,** calculated for $C_{35}H_{39}FeNO_2P_2Si$, $[M+H]^+$: 652.1653; found: 652.1627. **EA** calculated for $C_{35}H_{39}FeNO_2P_2Si$: C (64.52%), H (6.03%), N (2.15%); found: C (64.68%), H (6.08%), N (2.20%).

(2*S*,4*S*,5*S*)-3,4-Dimethyl-2-(α-(*S*$_p$)-methyl-ferrocenyl)-5-phenyl-5-diphenyl-phosphanyl-[1,3,2]-oxazaphospholidine 2-oxide (*S*$_p$-99)



$C_{33}H_{33}FeNO_2P_2$

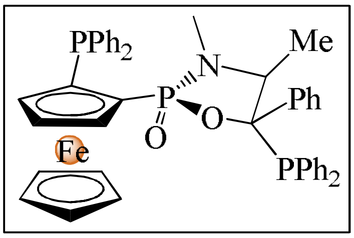
Mol. Wt.: 593.41

(*2S,4S,5R*)-3,4-Dimethyl-2-(α-(S_p)-methyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (S_p-**88**) (0.74 g, 1.81 mmol), ^{t}BuLi (1.7 M) (1.6 mL, 2.7 mmol, 1.5 eq.) and chloro-diphenylphosphine (0.6 mL, 3.1 mmol, 1.7 eq.) were used in this reaction.

The compound was purified by flash chromatography using EtOAc/Hexane (1:1) and the pure product was recovered as an orange oil in 85.7% yield (0.92 g, 1.55 mmol).

^{1}**H NMR** ($CDCl_3$) δ (ppm): 1.65 (3H, d (dd), *J*=7.2 Hz, J_{PH} =1.3 Hz, CH_3), 1.98 (3H, s, CH_3), 2.45 (3H, d (dd), *J*=10.2 Hz, *J'*=2.3 Hz, NMe), 4.13 (1H, s, subst. Cp), 4.14 (5H, s, Cp), 4.18 (1H, s, subst. Cp), 4.38 (1H, s, subst. Cp), 5.88-5.95 (1H, dq, *J*=7.2 Hz, *J'*=6.7 Hz, J_{PH} =2.3 Hz CHMe), 7.09-7.40 (15H, m, Ph). ^{13}**C NMR** ($CDCl_3$) δ (ppm): 12.2, 13.0, 30.7, 69.5, 71.9, 72.0, 86.3, 86.4, 109.5, 109.6, 126.9, 127.0, 127.1, 128.0, 130.1, 131.0, 132.0, 132.2, 133.7, 134.0, 135.1, 135.3, 145.1, 145.2. ^{31}**P NMR** ($CDCl_3$) δ (ppm): 30.0 (P(O)Eph, J_{PP}=81.3 Hz), 48.4 (PPh_2, J_{PP}=83.2 Hz). $\mathbf{[\alpha]^{20}_{D}}$= -60° (c=1.0 $CHCl_3$). **HRMS,** calculated for $C_{33}H_{33}FeNO_2P_2$, $[M+H]^+$: 594.1414; found: 594.1440. $[M+Na]^+$: 616.1234, found: 616.1204. **EA** calculated for $C_{33}H_{33}FeNO_2P_2$: C (66.79%), H (5.61%), N (2.36%); found: C (66.73%), H (5.64%), N (2.31%).

(*2S,4S,5S*)-3,4-Dimethyl-2-(α-(S_p)-diphenyl-phosphanyl-ferrocenyl)-5-phenyl-5-diphenyl-phosphanyl-[1,3,2]-oxazaphospholidine 2-oxide (S_p-100)



$C_{44}H_{40}FeNO_2P_3$

Mol. Wt.: 763.56

(*2S,4S,5R*)-3,4-Dimethyl-2-(α-(S_p)-diphenyl-phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (S_p-100) (0.74 g, 1.81 mmol), ^{t}BuLi (1.7 M) (1.6 mL, 2.7 mmol, 1.5 eq.) and chloro-diphenylphosphine (0.6 mL, 3.1 mmol, 1.7 eq.) were used in this reaction.

The compound was purified by flash chromatography using EtOAc/Hexane (1:1) and the pure product was recovered as an orange solid in 53.1 % yield (0.92 g, 1.55 mmol).

Mp: 58-60°C. **^{1}H NMR** ($CDCl_3$) δ (ppm): 1.58 (3H, d, *J*=7.2 Hz, CH_3), 2.04 (3H, d, *J*=10.1 Hz, NMe), 3.89 (1H, s, subst. Cp), 4.06 (5H, s, Cp), 4.40 (1H, d, *J*=2.3 Hz subst. Cp), 4.89 (1H, s, subst. Cp), 5.97-6.03 (1H, dq, *J*=7.2 Hz, *J'*=7.4 Hz, J_{PH}=1.9 Hz CHMe), 6.74-7.51 (25H, m, Ph). **^{13}C NMR** ($CDCl_3$) δ (ppm): 12.3, 13.0, 30.2, 70.2, 71.1, 80.3, 86.4, 126.5, 126.8, 127.0, 127.4, 127.8, 128.1, 130.2, 131.0, 131.2, 131.7, 131.9, 132.4, 132.6, 133.9, 134.2, 135.1, 135.3, 137.9, 138.1, 139.5, 139.6, 145.3, 145.4. **^{31}P NMR** ($CDCl_3$) δ (ppm): -19.0 (PPh_2 (Cp)), 27.6 (P(O)Eph, J_{PP}=77.3 Hz), 47.3 (PPh_2 (C(PPh_2)Ph), J_{PP}=75.3 Hz). **$[\alpha]^{20}_D$**= +120° (c=1.0 $CHCl_3$). **HRMS** calculated for $C_{44}H_{40}FeNO_2P_3$ $[M+Na]^+$: 786.1519; found: 786.1522. **EA** calculated for $C_{44}H_{40}FeNO_2P_3$: C (69.21%), H (5.28%), N (1.83%); found: C (68.73%), H (5.37%), N (1.59%).

Performing lithiation at a mixture of compounds 82 and 83, the 1,1'-bisubstituted analogues to 31 and 81

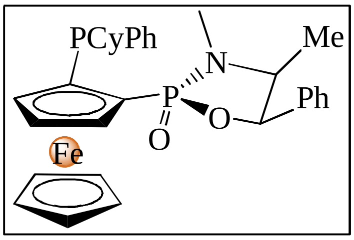
A Schlenk tube, equipped with magnetic stirrer bar and septum, was charged with a mixture of 1,1'-bis((*2R,2R',4R,4R',5S,5S'*)-3,4-dimethyl-5-phenyl-[1,3,2]-oxazaphospholidin-2-oxide-2-yl)ferrocene (**82**) and 1,1'-bis((*2S,2R',4R,4R',5S,5S'*)-3,4-dimethyl-5-phenyl-[1,3,2]-oxazaphospholidin-2-oxide-2-yl)ferrocene (**83**) (0.60 g, 0.99

mmol). The tube was degassed using vacuum-nitrogen cycles and then THF was added. The mixture was cooled to –78 °C with a bath of dry ice and acetone for 30 minutes before ^{t}BuLi (1.7 M) (0.8 mL, 1.4 mmol, 1.4 eq.) was added. The reaction was stirred at -78 °C for another hour before chloro-diphenylphosphine (0.2 mL, 1. mmol, 1.5 eq.) was added. After overnight stirring at room temperature, analysis of the reaction mixture by TLC (EtOAc) revealed the presence of a new compound. The crude product was analyzed with ^{1}H and ^{31}P NMR, extracted with EtOAc (3 x 75 mL), washed with brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded an orange solid. Purification was performed by flash chromatography using EtOAc as eluent on silica gel. One fraction suggested that a lithiation product was formed.

^{31}P NMR (CDCl$_3$) δ (ppm): -20.0; 29.1; 37.8; 49.5. **HRMS,** calculated for $C_{54}H_{52}FeN_2O_4P_4$, $[M+H]^+$: 973.2305; found: 973.2331.

Synthesis of P-chiral ligands

(2*S*,4*S*,5*R*)-3,4-Dimethyl-2-(α-(*S$_p$*)-phenyl-cyclohexyl-phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (*S$_p$*-105)



$C_{32}H_{37}FeNO_2P_2$

Mol. Wt.: 585.43

A Schlenk tube, equipped with magnetic stirrer bar and septum, was charged with (2*S*,4*S*,5*R*)-3,4-dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide

(2.00 g, 5.06 mmol). The tube was degassed using vacuum-nitrogen cycles and then THF was added. The mixture was cooled to -78°C with a bath of dry ice and acetone for 30 minutes before ^{t}BuLi (1.7 M) (4.0 mL, 6.8 mmol, 1.35 eq.) was added. The reaction was stirred at –78 °C for another hour before it was added to a solution of dichlorophenylphosphine (1.0 mL, 7.6 mmol, 1.50 eq.) also at -78ºC.

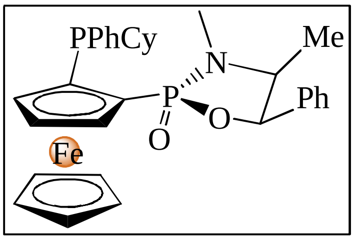
After stirring for 10 min at -78ºC, the mixture was allowed to slowly warm to room temperature, and stirred for approximately 2 h. Then the mixture was cooled to -78ºC again, and a solution of cyclohexylmagnesium bromide in THF [prepared from cyclohexyl bromide (2.5 mL, 20.2 mmol) and magnesium (0.54 g, 22.3 mmol) at 0ºC during addition and then at room temperature during approximately 4h] was added via a syringe at -78ºC. The mixture was warmed to room temperature overnight.

The reaction was quenched with saturated NH_4Cl solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with brine and dried over $MgSO_4$.

Evaporation of the solvent under reduced pressure and purification by flash chromatography using EtOAc as eluent on silica gel afforded the pure product as an orange solid in 37.1% yield (1.10 g, 1.88 mmol).

Mp: 82-83ºC. **^{1}H NMR** ($CDCl_3$) δ (ppm): 0.62 (3H, d, *J*=6.3 Hz, CH_3), 1.10-1.56 (11H, m, Cy), 2.76 (3H, d, *J*=9.3 Hz, NMe), 3.64 (1H, ddq, *J*=6.1 Hz, *J*=5.9 Hz, CHMe), 3.83 (5H, s, Cp), 4.36-4.51 (3H, m, subst. Cp), 5.78 (1H, d, *J*=5.1 Hz, CHPh), 7.49-7.08 (10H, m, Ph). **^{13}C NMR** ($CDCl_3$) δ (ppm): 14.2, 26.5, 27.2, 43.0, 62.0, 71.3, 79.7, 100.1, 125.5, 125.7, 127.9, 128.5. **^{31}P NMR** ($CDCl_3$) δ (ppm): -19.9, 36.0. **$[\alpha]^{20}_{D}$**= +60º (c=1.0 $CHCl_3$). **HRMS**, calculated for $C_{32}H_{37}FeNO_2P_2$, $[M+Na]^+$: 608.1547; found: 608.1545.

(2*S*,4*S*,5*R*)-3,4-Dimethyl-2-(α-(S_p)-cyclohexyl-phenyl-phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (S_p-106)



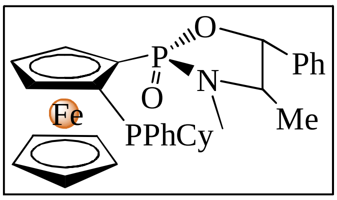
$C_{32}H_{37}FeNO_2P_2$

Mol. Wt.: 585.43

(2*S*,4*S*,5*R*)-3,4-Dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (2.00 g, 5.06 mmol), ^{t}BuLi (1.7 M) (4.0 mL, 6.8 mmol, 1.35 eq.), dichlorocyclohexylphosphine (1.36 g, 1.15 mL, 7.34 mmol, 1.50 eq.) and phenylmagnesium bromide in THF (prepared from bromobenzene (2.13 mL, 20.2 mmol) and magnesium (0.54 g, 22.3 mmol) at 0ºC during addition and then at room temperature during approximately 3h) were used in this reaction. The pure product was recovered as an orange solid in 31.4% yield (0.93 g, 1.59 mmol).

Mp: 159-160ºC. ^{1}**H NMR** ($CDCl_3$) δ (ppm): 0.57 (3H, d, *J*=6.6 Hz, CH_3), 1.49 (3H, d, *J*=9.2 Hz, NMe), 1.10-1.99 (11H, m, Cy), 3.48 (1H, ddq, *J*=6.3 Hz, CHMe), 4.43 (5H, s, Cp), 4.50 (1H, s, subst. Cp), 4.67-4.72 (2H, m, subst. Cp), 5.82 (1H, d, *J*=6.0 Hz, CHPh), 7.13-7.42 (10H, m, Ph). ^{13}**C NMR** ($CDCl_3$) δ (ppm): 14.3, 26.9, 27.4, 38.0, 62.0, 72.0, 74.0, 79.6, 100.1, 125.8, 128.2, 128.8, 128.9, 134.9, 135.1. ^{31}**P NMR** ($CDCl_3$) δ (ppm): -16.2, 36.0. **$[\alpha]^{20}_D$**= -220º (c=1.0 $CHCl_3$). **HRMS**, calculated for $C_{32}H_{37}FeNO_2P_2$, $[M+Na]^+$: 608.1547; found: 608.1541.

(2*R*,4*S*,5*R*)-3,4-Dimethyl-2-(α-(*R*$_p$)-phenyl-cyclohexyl-phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (*R*$_p$-108)



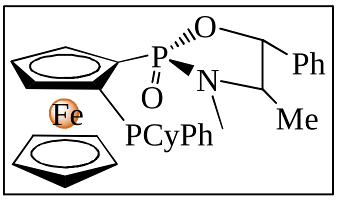
$C_{32}H_{37}FeNO_2P_2$

Mol. Wt.: 585.43

(2*R*,4*S*,5*R*)-3,4-Dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (2.00 g, 5.06 mmol), ^{t}BuLi (1.7 M) (4.0 mL, 6.8 mmol, 1.35 eq.), dichlorophenylphosphine (1.0 mL, 7.6 mmol, 1.50 eq.) and cyclohexylmagnesium bromide in THF [prepared from cyclohexyl bromide (2.5 mL, 20.2 mmol) and magnesium (0.54 g, 22.3 mmol) at 0ºC during addition and then at room temperature during approximately 4h] were used in this reaction. A fraction of the pure product was recovered as an orange solid in 19.8 % yield (0.56 g, 0.96 mmol).

Mp: 83-84ºC. **^{1}H NMR** ($CDCl_3$) δ (ppm): 0.87 (3H, d, *J*=6.64 Hz, CH_3), 1.02-1.66 (11H, m, Cy), 2.80 (3H, d, *J*=10.1 Hz, NMe), 3.24 (1H, ddq, *J*=6.64 Hz, CHMe), 3.83 (5H, s, Cp), 4.38 (1H, m, subst. Cp), 4.52-4.59 (2H, m, subst. Cp), 5.57 (1H, t (dd), *J*= 6.64 Hz, CHPh), 7.12-7.52 (10H, m, Ph). **^{31}P NMR** ($CDCl_3$) δ (ppm): -20.6, 38.9. **$[\alpha]^{20}_D$**= -220º (c=1.0 $CHCl_3$). **HRMS,** calculated for $C_{32}H_{37}FeNO_2P_2$, $[M+Na]^+$: 608.1547; found: 608.1519. **EA** calculated for $C_{32}H_{37}FeNO_2P_2$: C (65.65%), H (6.37%), N (2.39%); found: C (66.83%), H (6.47%), N (2.22%).

Attempting the synthesis of (2*R*,4*S*,5*R*)-3,4-Dimethyl-2-(α-(*R*$_p$)-cyclohexyl-phenyl-phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (*R*$_p$-109)



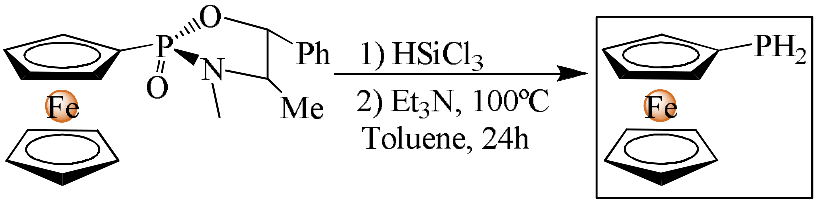
$C_{32}H_{37}FeNO_2P_2$

Mol. Wt.: 585.43

(2*R*,4*S*,5*R*)-3,4-Dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (2.00 g, 5.06 mmol), ^{t}BuLi (1.7 M) (4.0 mL, 6.8 mmol, 1.35 eq.), dichlorocyclohexylphosphine (1.41 g, 1.20 mL, 7.59 mmol, 1.50 eq.) and phenylmagnesium bromide in THF [prepared from bromobenzene (2.13 mL, 20.2 mmol) and magnesium (0.54 g, 22.3 mmol) at 0 ºC during addition and then at room temperature during approximately 3h] were used in this reaction. A crude ^{31}P NMR suggested that among other compounds the product was synthesized, ^{31}P NMR ($CDCl_3$) δ (ppm): -15.4, 38.4. The crude orange solid was purified by flash chromatography using EtOAc as eluent, one fraction being isolated with what is possibly the oxidized product. **^{1}H NMR** ($CDCl_3$) δ (ppm): 0.85 (3H, d, *J*=6.5 Hz, CH_3), 1.02-1.92 (11H, m, Cy), 2.60 (3H, d, *J*=10.4 Hz, NMe), 3.62 (1H, ddq, *J*=6.4 Hz, CHMe), 4.38 (5H, s, Cp), 4.41-4.53 (2H, m, subst. Cp), 4.72 (1H, s, subst. Cp), 5.50 (1H, t (dd), *J*=6.7 Hz, CHPh), 7.19-7.65 (10H, m, Ph). **^{31}P NMR** ($CDCl_3$) δ (ppm): 36.5, 40.9.

Reduction of the oxazaphospholidine oxide moiety

Ferrocenylphosphine (111)



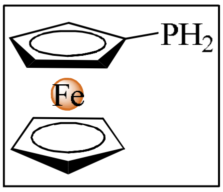
$C_{10}H_{11}FeP$

Mol. Wt.: 218.01

A Schlenk tube, equipped with magnetic stirrer bar and septum, was charged with (2*R*,4*S*,5*R*)-3,4-dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (**82**) (0.70 g, 1.77 mmol). The tube was degassed using vacuum-nitrogen cycles and then toluene was added. Trichlorosilane ($HSiCl_3$) (0.45 mL, 4.43 mmol) was added and the mixture allowed stirring for a few minutes before NEt_3 (0.62 mL, 4.43 mmol) addition. Temperature was raised to 100ºC and the reaction left stirring overnight. The mixture was cooled to R.T., the solvent being evaporated under reduced pressure. Purification was performed by flash chromatography with degassed Et_2O under N_2 to afford a reddish oil.

^{1}H NMR ($CDCl_3$) δ (ppm): 3.75 (2H, d, J_{HP}=203.1 Hz, PH_2), 4.10 (5H, s, Cp), 4.20 (4H, m, subst. Cp); **^{13}C NMR** ($CDCl_3$) δ (ppm): 62.97, 63.02, 66.95, 68.15, 68.46, 68.73, 69.56, 69.60, 74.47. **^{31}P NMR** ($CDCl_3$) δ (ppm): -142.9 (t, J_{PH}=203.1 Hz). **MS** (CI+(NH_3)) m/z 219 $[M+H]^+$.[213,214]

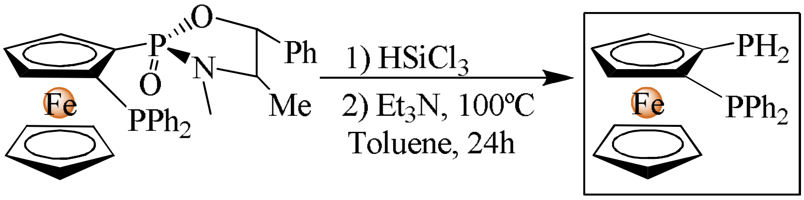
Ferrocenylphosphine (111)



The reaction was repeated with compound (2*S*,4*S*,5*R*)-3,4-dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (**81**) (2.0 g, 5.06 mmol), $HSiCl_3$ (2.02 mL, 20.0 mmol) and NEt_3 (2.8 mL, 20.0 mmol), under the same set of conditions imparting a similar result, (0.30 g, 1.38 mmol, 27%).

^{1}H NMR ($CDCl_3$) δ (ppm): 3.73 (2H, d, J_{HP}=202.9 Hz, PH_2), 4.07 (5H, m, Cp), 4.23 (4H, m, subst. Cp); **^{31}P NMR** ($CDCl_3$) δ (ppm): -141.4 (t, J_{PH}=203.0 Hz).

α-(S_p)-Diphenyl(2-phosphinoferrocenly)phosphine-(S_p-112)



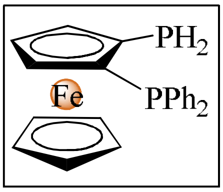
$C_{22}H_{20}FeP_2$

Mol. Wt.: 402.19

A Schlenk tube, equipped with magnetic stirrer bar and septum, was charged with (2*R*,4*S*,5*R*)-3,4-dimethyl-2-(α-(R_p)-diphenyl-phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (**R_p-90**) (0.69 g, 1.20 mmol). The tube was degassed using vacuum-nitrogen cycles and then toluene was added. Trichlorosilane (0.30 mL, 3.0 mmol) was added and the mixture allowed stirring for a few minutes before NEt_3 (0.42 mL, 4.43 mmol) addition which was followed by immediate change of colour into white due to the formation of salts. The temperature was raised to 100°C and the reaction left stirring overnight. The mixture was cooled to R.T., the solvent being evaporated under reduced pressure. The product was extracted with freshly distilled pentane.

^{31}P NMR ($CDCl_3$) δ (ppm): -150.2 (d, J_{PP}=30.9 Hz), -19.9 (proton decoupled NMR).[174]

α-(S_p)-Diphenyl(2-phosphinoferrocenly)phosphine-(S_p-112)



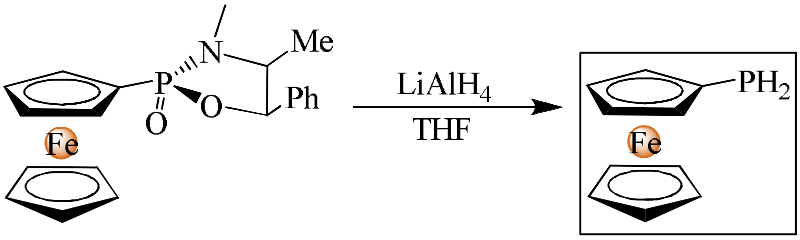
The reaction was repeated according with the following:

A Schlenk tube, equipped with magnetic stirrer bar and septum, was charged with (2*R*,4*S*,5*R*)-3,4-dimethyl-2-(α-(R_p)-diphenyl-phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (R_p-**90**) (1.70 g, 2.93 mmol). The tube was degassed using vacuum-nitrogen cycles and then toluene was added. Trichlorosilane (1.2 mL, 11.7 mmol) was added and the mixture allowed stirring for a few minutes before NEt_3 (1.63 mL, 11.7 mmol) addition which was followed by immediate change of colour into white due to the formation of salts. The temperature was raised to 100ºC and the reaction left stirring overnight. The mixture was cooled to R.T., the solvent being partially evaporated under reduced pressure. The mixture was filtered through a column of alumina (Al_2O_2 - neutral) and eluted with Et_2O. The solvent was evaporated affording an orange solid (0.70 g, 1.74 mmol, 59.3%).

^{31}P NMR ($CDCl_3$) δ (ppm): -150.5 (t (dt), J_{PH}=203.4 Hz, J_{PP}=30.9 Hz), -21.9. **MS** (CI+(NH_3)) m/z 403 $[M+H]^+$.

Using $LiAlH_4$

Ferrocenylphosphine (111)

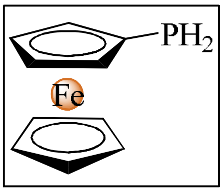


A Schlenk tube, equipped with magnetic stirrer bar and septum, was charged with (2S,4*S*,5*R*)-3,4-dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (**81**) (0.50 g, 1.26 mmol). The tube was degassed using vacuum-nitrogen cycles and then THF was added. The solution was cooled in an ice bath and subsequently lithium aluminium hydride ($LiAlH_4$) (0.48 g, 12.65 mmol) was added. The mixture was allowed stirring for 30 minutes before removal of the ice bath stirring at R.T. overnight. At 0ºC excess $LiAlH_4$ was destroyed with MeOH, followed by aqueous work-up with Et_2O, an aqueous solution of Na_2CO_3 and brine. The reddish oil product was obtained in 14.5% yield. **^{1}H NMR** ($CDCl_3$) δ (ppm): 3.75 (2H, d, J_{HP}=203.1 Hz, PH_2), 4.09 (5H, s, Cp), 4.29 (4H, m, subst. Cp); **^{31}P NMR** ($CDCl_3$) δ (ppm): -142.9 (t, J_{PH}=203.0 Hz).

What we believe to be the corresponding oxide was obtained as well:

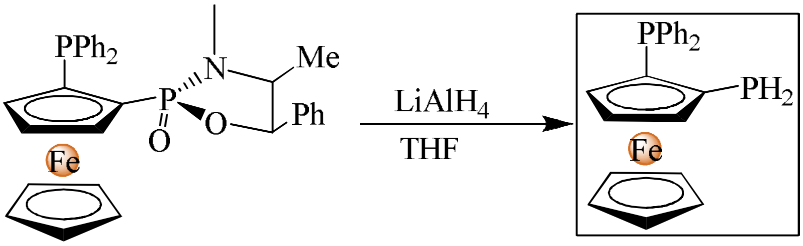
^{1}H NMR ($CDCl_3$) δ (ppm): 4.32 (5H, s, Cp), 4.50 (4H, m, subst. Cp), 7.66 (2H, d, J_{HP}=483.9 Hz, $P(O)H_2$), **^{31}P NMR** ($CDCl_3$) δ (ppm): 0.2 (t, J_{PH}=483.0 Hz).

Ferrocenylphosphine (111)



Repetition of the last reaction would lead to the same results (0.15g, 0.69 mmol, 27.2%). ^{1}**H NMR** ($CDCl_3$) δ (ppm): 3.75 (2H, d, J_{HP}=203.1 Hz, PH_2), 4.09 (5H, s, Cp), 4.26 (4H, m, subst. Cp); ^{13}**C NMR** ($CDCl_3$) δ (ppm): 66.90, 68.14, 68.40, 68.68, 69.56, 69.60, 70.71, 71.50, 74.47, 74.61. ^{31}**P NMR** ($CDCl_3$) δ (ppm): -142.9 (t, J_{PH}=203.0 Hz).

α-(*R*$_p$)-Diphenyl(2-phosphinoferrocenly)phosphine-(*R*$_p$-117)



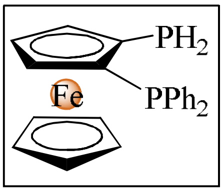
A Schlenk tube, equipped with magnetic stirrer bar and septum, was charged with (2S,4*S*,5*R*)-3,4-dimethyl-2-(α-(S$_p$)-diphenyl-phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (*S*$_p$-87) (0.5 g, 0.86 mmol). The tube was degassed using vacuum-nitrogen cycles and then THF was added. The solution was cooled in an acetone/dry ice bath and subsequently lithium aluminium hydride ($LiAlH_4$) (0.33 g, 8.63 mmol) was added. The mixture was allowed stirring for 30 minutes before removal of the bath stirring at R.T. overnight. At 0ºC excess $LiAlH_4$ was destroyed with MeOH, followed by aqueous work-up with Et_2O, an aqueous solution of Na_2CO_3 and brine. The organic layer was dried with $MgSO_4$, filtrated, and the solvent was evaporated affording a red oil.

^{31}**P NMR** ($CDCl_3$) δ (ppm): -150.2 (t (dt), J_{PH}=204.1 Hz, J_{PP}=31.1 Hz, PH_2), -20.0 (d, J_{PP}=30.9 Hz, PPh_2).

What we believe to be the corresponding oxide was obtained as well:

^{31}**P NMR** ($CDCl_3$) δ (ppm):-3.0 (t (dt), J_{PH}=487.7 Hz, J_{PP}=43.7 Hz, $P(O)H_2$), -22.0 (d, PPh_2).

α-(S_p)-Diphenyl(2-phosphinoferrocenly)phosphine-(S_p-112)

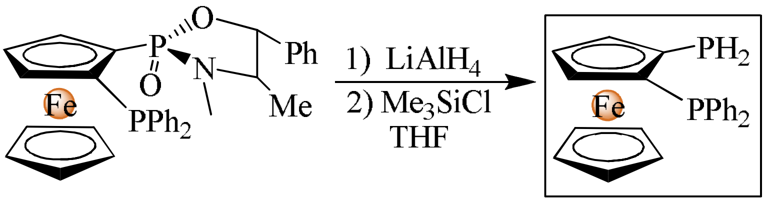


A Schlenk tube, equipped with magnetic stirrer bar and septum, was charged with (2*R*,4*S*,5*R*)-3,4-dimethyl-2-(α-(R_p)-diphenyl-phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (**R_p-90**) (0.5 g, 0.86 mmol). The tube was degassed using vacuum-nitrogen cycles and then THF was added. The solution was cooled in an acetone/dry ice bath and subsequently lithium aluminium hydride ($LiAlH_4$) (0.2 g, 5.3 mmol) was added. The mixture was allowed stirring for 30 minutes before removal of the bath stirring at R.T. overnight. At 0ºC excess $LiAlH_4$ was destroyed with MeOH, followed by aqueous work-up with Et_2O, an aqueous solution of Na_2CO_3 and brine. The organic layers were dried over $MgSO_4$ and the solvent evaporated affording a red oil.

^{31}P NMR ($CDCl_3$) δ (ppm): -151.4 (t (dt), J_{PH}=204.1 Hz, J_{PP}=30.4 Hz), -21.3.

Using $LiAlH_4$ + TMSCl or $HSiCl_3$

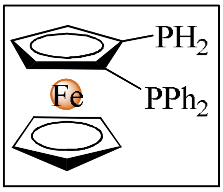
α-(S_p)-Diphenyl(2-phosphinoferrocenly)phosphine-(S_p-112)



To a suspension of LAH (0.12 g, 3.0 mmol) in THF at -78ºC, TMSCl (0.4 ml, 3.0 mmol) was slowly added. The mixture was allowed to stir for one hour and a solution of (2*R*,4*S*,5*R*)-3,4-dimethyl-2-(α-(R_p)-diphenyl-phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (**R_p-90**) (0.5 g, 0.86 mmol) in THF was slowly added. R.T.

was reached and the reaction stirred overnight. Due to little reactivity the temperature was cooled to 0ºC and four more equivalents of LAH were added to the reaction mixture. After refluxing for 3h, a TLC suggested the formation of a new compound and substrate absence. The mixture was cooled to 0ºC, the excess reducing agent was destroyed with MeOH and the solvent was evaporated under reduced pressure. The product was extracted with degassed Et_2O followed by aqueous work up with $NaCO_3$ (aq.), brine and water. The organic layers were dried over $MgSO_4$ and the solvent evaporated affording a red oil. **^{31}P NMR** ($CDCl_3$) δ (ppm): -150.4 (t (dt), J_{PH}=204.2 Hz, J_{PP}=30.6 Hz), -20.0.

α-(*S_p*)-Diphenyl(2-phosphinoferrocenly)phosphine-(*S_p*-112)



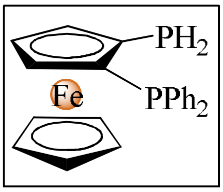
The reaction was repeated, this time using seven equivalents of reducing agent slurry and performing the reaction at reflux temperature.

To a suspension of LAH (0.46 g, 12.1 mmol) in THF at -78ºC, TMSCl (1.5 ml, 12.0 mmol) was slowly added. The mixture was allowed to stir for one hour and a solution of (2*R*,4*S*,5*R*)-3,4-dimethyl-2-(α-(R_p)-diphenyl-phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (R_p-**90**) (1.0 g, 1.72 mmol) in THF was slowly added. The temperature was raised to reflux and the reaction stirred overnight. The mixture was cooled to 0ºC, the excess reducing agent was destroyed with MeOH and the solvent was evaporated under reduced pressure. The product was extracted with degassed Et_2O followed by aqueous work up with $NaCO_3$ (aq.), brine and water. The organic layers were dried over $MgSO_4$ and the solvent evaporated affording a red oil.

^{1}H NMR ($CDCl_3$) δ (ppm): 3.50 (1H, dd, showing further splitting, *J*=3.9 Hz, *J*=12.4 J_{HP}=208.1 Hz, PH_2), 3.71 (1H, s, subst. Cp), 3.87 (1H, dd, with further splitting, *J*=3.3 Hz, *J*=12.4 Hz, J_{HP}=212.2 Hz, PH_2), 4.00 (5H, m, Cp), 4.29 (1H, s, subst. Cp), 4.44 (1H, s, subst. Cp), 7.05-7.50 (10H, m, Ph). **^{31}P NMR** ($CDCl_3$) δ (ppm): -150.2 (t (dt), J_{PH}=204.1 Hz, J_{PP}=30.6 Hz), -20.0 (d, J_{PP}=30.8 Hz).

Due to the compound's sensitivity while performing HRMS analysis the product was oxidized according to the following: **HRMS**, calculated for $C_{22}H_{20}FeOP_2$, $[M+Na]^+$: 441.0237; found: 441.0231; calculated for $C_{22}H_{20}FeO_2P_2$, $[M+Na]^+$: 457.0186; found: 457.0166.

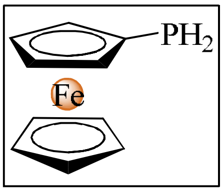
α-(*S$_p$*)-Diphenyl(2-phosphinoferrocenly)phosphine-(*S$_p$*-112)



To a solution of (2*R*,4*S*,5*R*)-3,4-dimethyl-2-(α-(*R$_p$*)-diphenyl-phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (*R$_p$*-**90**) (1.0 g, 1.72 mmol) at -78ºC LAH (0.66 g, 17.3 mmol) was added. After 1h at R.T. $HSiCl_3$ was added (0.1 ml, 1.0 mmol). Stirring was allowed overnight at R.T., before methanol (4 mL) was added at 0ºC and after half an hour the solvent being removed. The product was extracted with hexane and filtered through a small silica pad, (m=0.55g; 1.37 mmol; 79.2%).**^{1}H NMR** ($CDCl_3$) δ (ppm): 3.49 (1H, dd, with further splitting, *J*=3.5 Hz, *J*=12.6 Hz, J_{HP}=204.1 Hz, PH_2), 3.71 (1H, s, subst. Cp), 3.87 (1H, dd, showing further splitting, *J*=3.5 Hz, *J*=12.4 Hz, J_{HP}=213.1 Hz, PH_2), 3.99 (5H, m, Cp), 4.29 (1H, s, subst. Cp), 4.43 (1H, s, subst. Cp), 7.05-7.50 (10H, m, Ph). **^{31}P NMR** ($CDCl_3$) δ (ppm): -150.2 (t (dt), J_{PH}=204.1 Hz, J_{PP}=31.1 Hz), -20.0 (d, J_{PP}=30.6 Hz).

Due to the compound's sensitivity while performing HRMS analysis the product was oxidized according to the following: **HRMS**, calculated for $C_{22}H_{20}FeOP_2$, $[M+Na]^+$: 441.0237; found: 441.0219; calculated. for $C_{22}H_{20}FeO_2P_2$, $[M+Na]^+$: 457.0186; found: 457.0170.

Ferrocenylphosphine (111)



To a solution of (2S,4*S*,5*R*)-3,4-dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (**81**) (0.5 g, 1.27 mmol) at 0ºC LAH (0.48 g, 12.7 mmol) was added. After stirring overnight at R.T. $HSiCl_3$ was added (0.15 ml, 1.3 mmol). Stirring was allowed at R.T. for 2 h, before methanol (4 mL) was added at 0ºC and after half an hour the solvent being removed. The product was purified via flash chromatography with Et_2O under nitrogen.

^{1}H NMR ($CDCl_3$) δ (ppm): 3.73 (2H, d, J_{HP}=203.3 Hz, PH_2), 4.09 (5H, s, Cp), 4.19 (4H, m, subst. Cp), **^{31}P NMR** ($CDCl_3$) δ (ppm): -142.9 (t, J_{PH}=203.3 Hz).

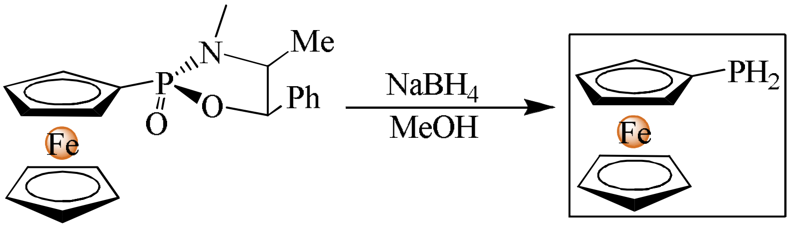
What we believe to be the corresponding oxide was obtained as well:

^{1}H NMR ($CDCl_3$) δ (ppm): 4.28 (5H, s, Cp), 4.50 (4H, m, subst. Cp), 7.60 (2H, d, J_{HP}=483.9 Hz, $P(O)H_2$), **^{31}P NMR** ($CDCl_3$) δ (ppm): -0.01 (t, J_{PH}= 482.5 Hz).

In addition to these reducing systems we also attempted reduction with sodium borohydride in reflux methanol though with no reaction taking place.

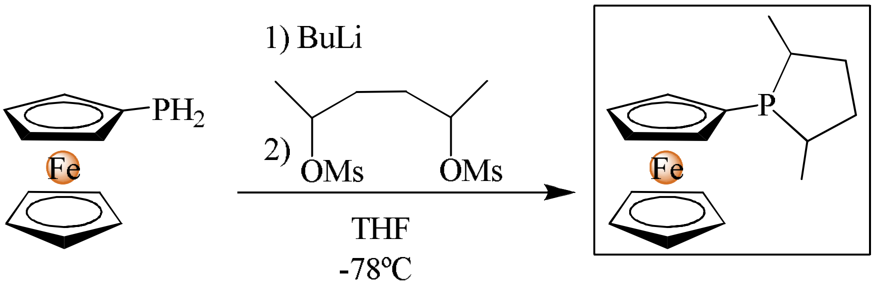
Using $NaBH_4$

Ferrocenylphosphine (111)



To a solution of (2S,4*S*,5*R*)-3,4-dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (**81**) (0.5 g, 1.27 mmol) in methanol at R.T., $NaBH_4$ (0.48 g, 12.7 mmol) was added and the temperature raised to 67ºC. After stirring overnight no reaction had taken placed even with prolonged reaction time. The starting material was recovered pure.

2,5-Dimethyl-1-ferrocenylphospholane (118)



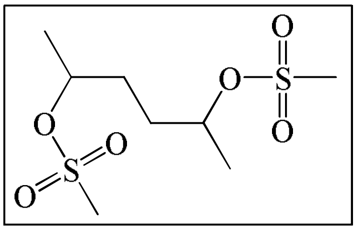
$C_{16}H_{21}FeP$

Mol. Wt.: 300.16

To a solution of ferrocenyl phosphine (0.55 g, 2.52 mmol) in THF at -78ºC a solution of ^{n}BuLi (1.0 mL, 2.52 mmol) in hexane was added. After the addition of about 0.5 mL the mixture turned from orange into red. A THF solution of hexane-2,5-diyldimethanesulfonate was added after total addition of ^{n}BuLi and allowed to slowly reach R.T. At the end of 3h30 the mixture was orange again, turning back to red upon addition of more ^{n}BuLi (1.0 mL, 2.52 mmol) at -78°C. The temperature rose slowly to R.T. and was stirred overnight. The solvent was evaporated, hexane was added and the solution filtered. An orange oil was obtained upon solvent evaporation.

^{1}H NMR ($CDCl_3$) δ (ppm): 0.65 (6H, m, CH_3), 1.20 (4H, m, CH_2), 1.85 (2H, m, CH), 4.09 (5H, s, Cp), 4.26 (4H, m, subst. Cp); **^{31}P NMR** ($CDCl_3$) δ (ppm): 1.40 ppm. **MS** (CI+(NH_3)) m/z 301 $[M+H]^+$ (100%). Due to the compound's sensitivity while performing HRMS analysis the product was oxidized in the methanol solution according to the following: **HRMS**, calculated for $C_{16}H_{21}FeOP$, $[M+Na]^+$: 339.0577; found: 339.0581.

2,5-Hexanediol bis(methanesulfonate)



$C_8H_{18}O_6S_2$

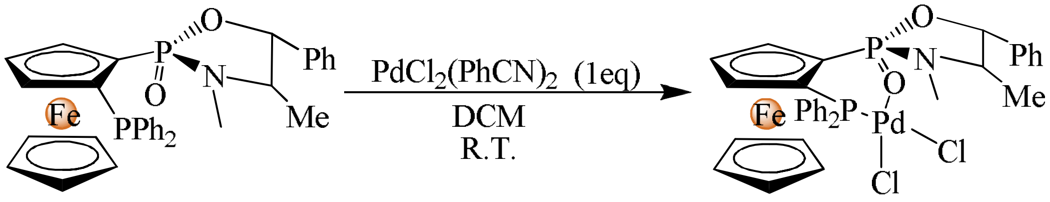
M.W.: 274.35

To a solution of 2,5-hexanediol (2.5 mL, 20.3 mmol) in DCM at R.T. methanosulfonyl chloride (3.6 ml, 45.5 mmol) and triethyl amine (7.0 ml, 50.2 mmol) were added. Formation of a white precipitate and temperature rising were observed. After remaining stirring overnight at R.T. the reaction was neutralized with HCl (aq.) and washed with brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to afford a yellowish solid (m=3.05 g, 0.011 mmol, 54.7%). **^{1}H NMR** ($CDCl_3$) δ (ppm): 1.45 (6H, d, J_{HH}=6.3 Hz, CH_3), 1.79 (4H, m, CH_2), 3.03 (6H, s, CH_3), 4.83 (2H, m, CH). **^{13}C NMR** ($CDCl_3$) δ (ppm): 22.00, 31.98, 32.04, 36.07, 38.81, 14, 68.40; 68.68; 69.56; 69.60; 79.69; 79.83. MS (CI+(NH_3)) m/z 275 $[M+H]^+$.[375]

5.3 EXPERIMENTAL PROCEDURE FOR CHAPTER 3

Complexation of ferrocenyl oxazaphospholidine oxide ligands with Pd metal

Dichloro[(2*R*,4*S*,5*R*)-3,4-dimethyl-2-(α-(*R*$_p$)-diphenyl-phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide] palladium II (Pd-90)

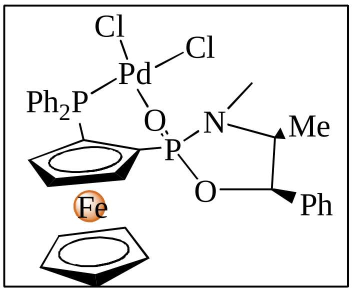


To a (1:1) solid mixture of (2*R*,4*S*,5*R*)-3,4-dimethyl-2-(α-(*R*$_p$)-diphenyl-phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (*R*$_p$-**90**) (0.05 g, 0.086 mmol) and bis(benzonitrile)dichloropalladium(II), (0.0331g, 0.086 mmol) in a degassed Schlenck flask, dry DCM was added. The mixture was allowed to stir for around 30 min. at room temperature. The complex crystallized by standing overnight. The crystals were analysed by X-ray diffraction (for more structural details see the appendix), (m=0.066 g; $2(C_{32}H_{31}Cl_2FeNO_2P_2Pd)$, C_7H_5N, $CHCl_3$, M=1701.38, 0.039 mmol; 91%).

^{1}H NMR ($CDCl_3$) δ (ppm): 0.78 (3H, s, CH_3), 2.00 (3H, d, *J*=11.2 Hz, NMe), 3.69 (1H, m, CHMe), 4.15 (1H, m, subst. Cp), 4.75 (5H, s, Cp), 4.80 (1H, m, subst. Cp), 4.83 (1H, m, subst. Cp), 5.70 (1H, m, CHPh), 7.30-7.90 (15H, m, Ph). **^{31}P NMR** ($CDCl_3$) δ (ppm): 16.4 (s, PPh_2), 46.6 (s, P(O)Eph). **MS** (ESI^+): calculated for $C_{32}H_{31}Cl_2FeNO_2P_2Pd$: 719.9920; observed 719.9918 (M^+Cl^-).[198]

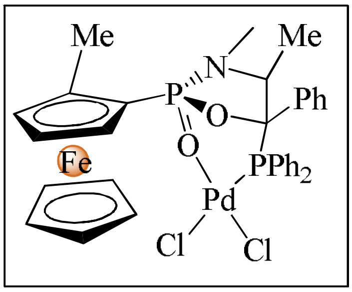
Following the procedure above other complexes were prepared:

Dichloro[(2*S*,4*S*,5*R*)-3,4-dimethyl-2-(α-(S_p)-diphenyl-phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide] palladium II (Pd-85)



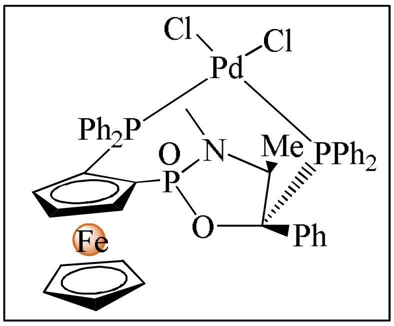
^{31}**P NMR** (CDCl$_3$) δ (ppm): 18.3 (s, PPh$_2$), 42.8 (s, P(O)Eph).

Dichloro[(2*S*,4*S*,5*S*)-3,4-dimethyl-2-(α-(S_p)-methyl-ferrocenyl)-5-phenyl-5-diphenyl-phosphanyl-[1,3,2]-oxazaphospholidine 2-oxide]palladium II (Pd-99)



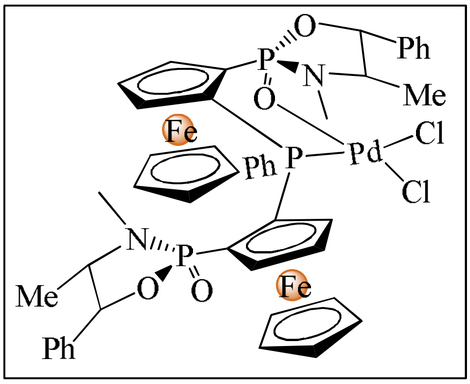
^{31}**P NMR** (CDCl$_3$) δ (ppm): 58.7 (d, J_{PP}=48.4 Hz; P(O)Eph), 66.8 (d, J_{PP}=47.5 Hz; PPh$_2$).

Dichloro[(*2S,4S,5S*)-3,4-dimethyl-2-(*α*-(*S*$_p$)-diphenyl-phosphanyl-ferrocenyl)-5-phenyl-5-diphenyl-phosphanyl-[1,3,2]-oxazaphospholidine 2-oxide]palladium II (Pd-100)



^{31}P NMR (CDCl$_3$) δ (ppm): 18.3 (s, PPh$_2$), 22.5 (s, P(O)Eph), 69.3 (s, PPh$_2$CPh).

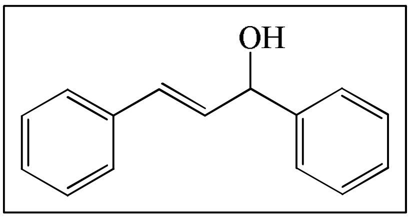
Dichloro[(*2R,2R',4S,4'S,5R,5'R*)-(2-(***R***$_p$),2'-(***R***$_p$)-(phenylphosphinediyl)bis(ferrocen-2,1-diyl))bis(3,4-dimethyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide)]palladium II (Pd-95)



^{31}P NMR (CDCl$_3$) δ (ppm): 18.6 (s, PPh), 38.0 (s, P(O)Eph), 46.8 (s, P((O)Eph)Pd).

Asymmetric allylic alkylation reactions

(rac)-(E)-1,3-Diphenyl Allyl Alcohol

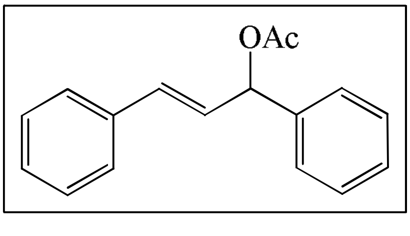


$C_{15}H_{14}O$

Mol. Wt.: 210.27

A Schlenk flask equipped with magnetic stirrer bar and septum was charged with chalcone (10.5 g, 50.6 mmol) and MeOH (150 mL). The mixture was cooled to 0 °C and $NaBH_4$ (1.9 g, 50.6 mmol) was slowly added over 1 hour period. The crude reaction was diluted with brine and the aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organic layers were washed with brine (1 x 100 mL), dried over $MgSO_4$, concentrated and the solid product was recrystallized from pentane to yield *(rac)-(E)*-1,3-diphenyl allyl alcohol as white needles in 95.0 % (10.1 g, 48.1 mmol). Mp: 56-57 °C, lit. 58-59 °C). **^{1}H NMR** ($CDCl_3$) δ (ppm): 2.02 (s, 1H), 5.39 (dd, *J*=6.1 Hz, 3.4 Hz, 1H), 6.39 (dd, *J*=15.8 Hz, 6.4 Hz, 1H), 6.69 (d, *J*=15.8 Hz, 1H), 7.21-7.45 (m, 10H), **^{13}C NMR** ($CDCl_3$) δ (ppm): 75.4, 126.6, 126.8, 128.0, 128.2, 128.8, 128.9, 130.8, 131.7, 136.7,143.0. **MS** (EI) *m*/*z* 210 [M^+].[266]

(rac)-(E)-1,3-Diphenyl Allyl Acetate

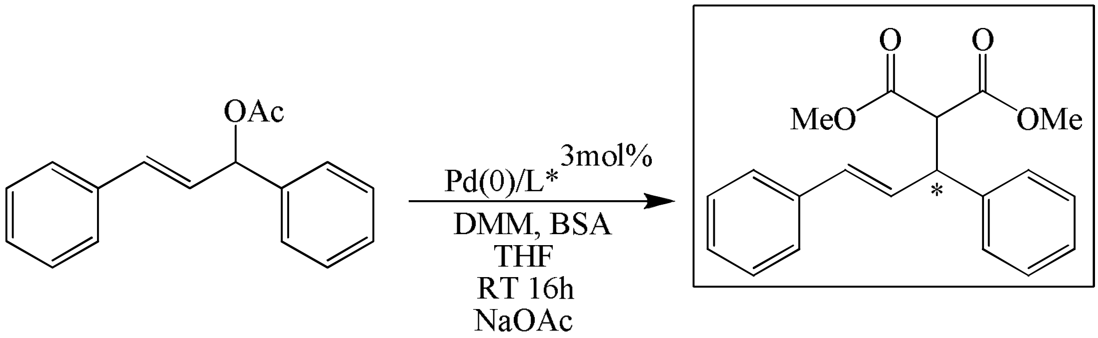


$C_{17}H_{16}O_2$

Mol. Wt.: 252.31

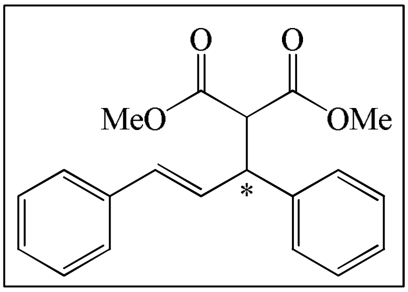
In an oven-dried, one neck, 250 mL round bottom flask equipped with magnetic stir bar and septum, was placed *(rac)-(E)*-1,3-diphenyl allyl alcohol (10 g, 47.6 mmol) followed by dichloromethane (100 mL) and triethylamine (13.3 mL, 95.2 mmol) via syringe, under nitrogen. The flask was placed into an ice-water bath and acetic anhydride (9.0 mL, 95.2 mmol) was slowly added via syringe. The reaction was allowed to stir overnight at room temperature, when TLC showed no remaining alcohol. The organic layer was extracted with saturated $NaHCO_3$ (1 x 100 mL), water (1 x 100 mL), brine (1 x 100 mL), dried (Na_2SO_4) and concentrated to yield a dark yellow oil that was purified by flash chromatography on silica gel using hexane/ethyl acetate (9:1) to yield *(rac)-(E)*-1,3-diphenyl allyl acetate as a clear oil in 90% (10.8 g, 42.8 mmol). **^{1}H NMR** ($CDCl_3$) δ (ppm): 2.14 (s, 3H), 6.35 (dd, *J*=6.9 Hz, 15.7 Hz, 2H), 6.44 (d, *J*=7.2 Hz, 1H), 6.64 (d, *J*=15.5 Hz, 1H), 7.24-7.41 (m, 10H); **^{13}C NMR** ($CDCl_3$) δ (ppm): 21.4, 76.3, 126.8, 127.2, 127.6, 128.2, 128.3, 128.7, 128.8, 132.7, 136.3, 139.4, 170.2. **MS** (EI) *m*/*z* 252 [M^+].[376]

General procedure for the allylic alkylation of rac-1,3-diphenyl-3-acetoxyprop-1-ene



A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (5.45 mg, 0.015 mmol) and the ligand (0.015 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene (126 mg, 0.5 mmol) in the stated solvent (1.5 mL), dimethyl malonate (115 μL, 1.0 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (250 μL, 1.0 mmol), and a pinch of NaOAc were added. The reaction mixture was stirred at room temperature. After 5 min the reaction mixture was diluted with Et_2O (5 mL) and saturated NH_4Cl (aq.) (25 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the extract dried over $MgSO_4$. Solvent was removed and conversion was measured by ^{1}H NMR. To determine the ee by HPLC (Chiralcel-OB, 5% 2-propanol/hexane, flow 0.5 mL/min), a sample was purified by flash-chromatography on silica-gel using hexane/ethyl acetate (9:1) as the eluent.

(*E*)-dimethyl 2-(1,3-diphenylallyl)malonate

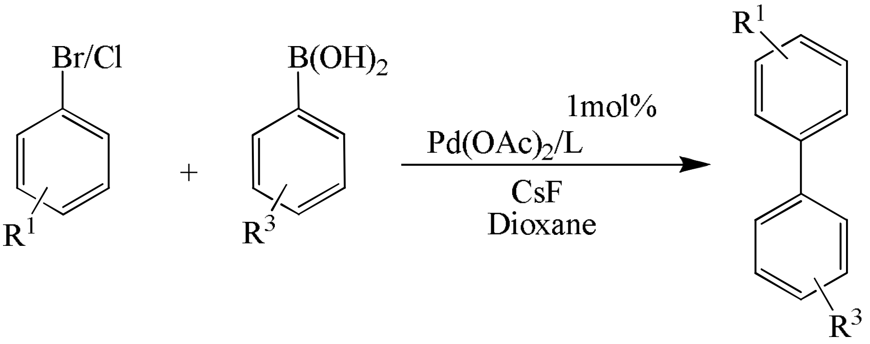


$C_{20}H_{20}O_4$

Mol. Wt.: 324,37

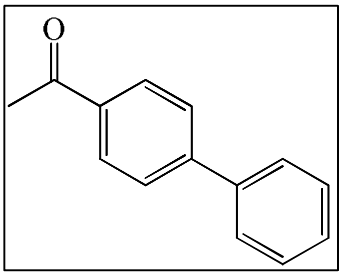
^{1}H NMR ($CDCl_3$) δ (ppm): 3.53 (3H, s, CO_2CH_3), 3.70 (3H, s, CO_2CH_3), 3.95 (1H, d, *J*=11 Hz, $CH(CO_2Me)_2$), 4.27 (1H, dd, *J*=11 Hz, *J*=8.0 Hz: CH-C$\underline{H}$-Ph), 6.32 (1H, dd, *J*=15 Hz, *J*=8.0 Hz, $\underline{H}$C=CH-Ph), 6.48 (1H, d, *J*=15 Hz, C=CH-Ph), 7.44-7.15 (10H, m, Ph). **^{13}C NMR** ($CDCl_3$) δ (ppm): 49.2, 52.4, 52.6, 57.6, 126.4, 127.2, 127.6, 127.9, 128.5, 128.7, 129.1, 131.8, 136.8, 140.2, 167.8, 168.2. **MS** (EI) *m*/*z* 324 [M^+].[173,174]

Suzuki-Miyaura Couplings - General procedure for Suzuki-Miyaura coupling reactions



An oven-dried Schlenck tube was charged with boronic acid (0.75 mmol), base (1.5 mmol), the ligand, and Pd(OAc)$_2$ (as stated). The aryl halide (0.5 mmol) was introduced at this stage in case of a solid or after degassing by injection through a rubber septum in case of a liquid. The reaction vessel was evacuated and backfilled with N$_2$. This process was repeated five times. Solvent was added to ensure that 3 mL of solution was used in each reaction. The reactions were heated at the 105°C for the stated time. Conversions were calculated from crude ^{1}H NMR.

4-Acetylbiphenyl

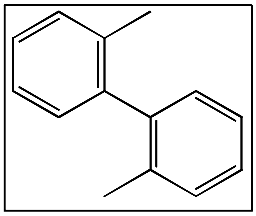


$C_{14}H_{12}O$

Mol. Wt.: 196.24

^{1}H NMR ($CDCl_3$) δ (ppm): 2.60 (s, 3H), 7.35-7.46 (m, 3H), 7.58-7.66 (m, 4H), 8.00 (d, 2H, *J*=8.6 Hz); **^{13}C NMR** ($CDCl_3$) δ (ppm): 26.5, 127.1, 127.1, 128.1, 128.8, 128.8, 135.7, 139.7, 145.6, 198.2. **MS** (EI) *m/z* 196 [M^+]. **EA** calculated for $C_{14}H_{12}O$: C (85.68%), H (6.16%); found: C (85.33%), H (6.22%).

2,2'-Dimethyl-biphenyl

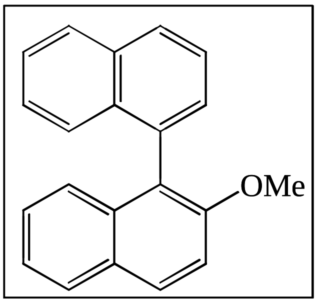


$C_{14}H_{14}$

Mol. Wt.: 182.26

^{1}H NMR ($CDCl_3$) δ (ppm): 2.04 (s, 6H), 7.09 (d, *J*=7.6 Hz, 2H), 7.20-7.25 (m, 6H); **^{13}C NMR** ($CDCl_3$) δ (ppm): 20.3, 125.5, 127.1, 129.3, 129.8, 135.8, 142.1. **MS** (EI) m/z 182 [M^+].

2-Methoxy-1,1'-binaphthyl

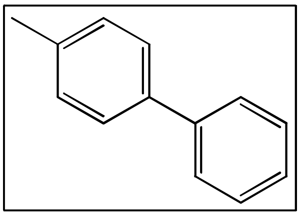


$C_{21}H_{16}O$

Mol. Wt.: 284.35

^{1}**H NMR** ($CDCl_3$) δ (ppm): 3.75 (s, 3H), 7.14 (d, 1H, *J*=8.8 Hz), 7.21 (dd, 1H, *J*=1.1, 5.5 Hz), 7.27 (dd, 1H, *J*=1.1, 5.5 Hz), 7.30-7.33 (m, 2H), 7.42-7.47 (m, 3H), 7.61 (t, 1H, *J*=7.7 Hz), 7.86 (d, 1H, *J*=8.0 Hz), 7.93 (d, 1H, *J*=8.0 Hz), 7.94 (d, 1H, *J*=8.0 Hz), 7.97 (d, 1H, *J*=8.8 Hz); ^{13}**C NMR** ($CDCl_3$) δ (ppm): 56.77, 113.84, 123.24, 123.55, 125.49, 125.55, 125.66, 125.83, 126.16, 126.36, 127.72, 127.78, 128.21, 128.42, 129.01, 129.45, 132.93, 133.68, 134.25, 134.52, 154.60. **MS** (EI) *m/z* 284 [M^+]. **EA** calculated for $C_{21}H_{16}O$: C (88.70%), H (5.67%), found: C (88.30%), H (5.63%).

4-Methylbyphenyl

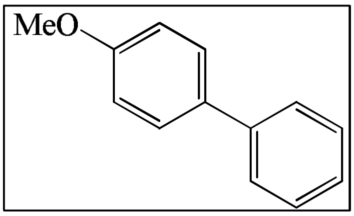


$C_{13}H_{12}$

Mol. Wt.: 168.23

^{1}**H NMR** ($CDCl_3$) δ (ppm): 2.42 (s, 3H), 7.26-7.62 (m, 9H); ^{13}**C NMR** ($CDCl_3$) δ (ppm): 21.5, 127.4, 127.6, 127.7, 137.4, 138.8, 141.7. **MS** (EI) m/z 168 [M^+]. **EA** calculated for $C_{13}H_{12}$: C (92.81%), H (7.19%), found: C (92.59%), H (7.22%).

4-Methoxylbyphenyl

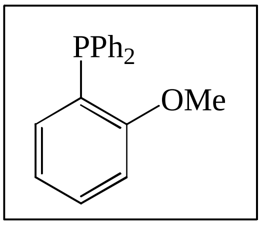


$C_{13}H_{12}O$

Mol. Wt.: 196.24

^{1}H NMR ($CDCl_3$) δ (ppm): 3.86 (s, 3H), 6.98-7.01 (m, 2H), 7.26-7.34 (m, 2H), 7.40-7.45 (m, 2H), 7.53-7.58 (m, 3H); **^{13}C NMR** ($CDCl_3$) δ (ppm): 55.8, 114.6, 127.1, 127.2, 128.6, 129.1, 134.2, 141.2, 159.5. **MS** (EI) *m/z* 184 [M^+]. **EA** calculated for $C_{14}H_{12}O$: C (84.75%), H (6.57%); found: C (84.82%), H (6.59%).

(2-methoxyphenyl)diphenylphosphine



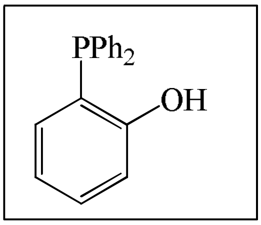
$C_{19}H_{17}OP$

Mol. Wt.: 292.31

A THF solution of 2-methoxyphenylmagnesiumbromide (16.7 mmol) was prepared from magnesium turnings (0.41 g, 16.9 mmol), iodide (a small crystal) and bromoanisol (2.1 mL, 16.7 mmol) initially at 0ºC and then at reflux temperature for 2 hours. The solution was cooled down to 0ºC and chlorodiphenylphosphine (2.0 mL, 11.1 mmol) was added. The mixture was refluxed for 3 h followed by aqueous work-up with NH_4Cl and water using toluene to extract the product. The solution was dried with $MgSO_4$ filtrated and the solvent evaporated. A white solid was obtained (3.0 g, 10.3 mmol, 92.1%).

Mp: 119-121ºC. **^{1}H NMR** ($CDCl_3$) δ (ppm): 3.74 (3H, s, OCH_3); 6.71-6.67 (1H, m, Ar), 6.91-6.84 (3H, m, Ar), 7.35-7.25 (10H, m, Ph). **^{31}P NMR** ($CDCl_3$) δ (ppm): 56.1; 110.6; 121.4; 128.6; 128.7; 128.8; 130.1; 134.0; 134.2; 134.4; 136.0, 162.0. **^{31}P NMR** ($CDCl_3$) δ (ppm): -15.6 ppm. **MS** (CI+(NH_3)) m/z 293 $[M+H]^+$ (100%). **EA** calculated for $C_{19}H_{17}OP$: C (78.07%), H (5.86%). Found: C (77.91%), H (5.90%).[377]

(2-Hydroxyphenyl)diphenylphosphine



$C_{18}H_{15}OP$

Mol. Wt.: 278.28

To a DCM solution of (2-methoxyphenyl)diphenylphosphine (3.0 g, 10.26 mmol) at -10ºC boron tribromide (BBr_3, 1M) (23.0 mL, 23.0 mmol) was added. After 20 h of reaction at R.T., the solvent was evaporated and MeOH was added. The solvent was again evaporated and finally water was added following aqueous work up with NH_4Cl and water, using EtOAc to extract the product. The organic layer was dried with $MgSO_4$ filtrated and the solvent evaporated. A white solid was obtained (2.67 g, 9.59 mmol, 93.5%).

Mp: 144-146ºC. **^{1}H NMR** ($CDCl_3$) δ (ppm): 6.12 (1H, s, OH); 6.78-6.92 (3H, m, Ar), 7.20-7.28 (11H, m, Ar). **^{13}C NMR** ($CDCl_3$) δ (ppm): 114.6; 120.0; 120.1; 127.6; 127.7; 128.0; 130.5; 132.3; 132.5; 133.7, 134.0, 158.0, 158.2. **^{31}P NMR** ($CDCl_3$) δ (ppm): -27.4 ppm. **MS** (CI+(NH_3)) m/z 279 $[M+H]^+$ (100%). **EA** calculated for $C_{18}H_{15}OP$: C (77.69%), H (5.43%); found: C (77.46%), H (5.46%).[378]

Interestingly we have noticed that while synthesizing this last ligand, if using an HCl solution during the work up the ligand would be protected with HCl and deprotected using aqueous solution of NaOH.

Mp: 201-203ºC. **^{1}H NMR** ($CDCl_3$) δ (ppm): 6.92 (1H, m, Ar), 7.41-7.85 (13H, m, Ar), 10.34 (1H, m, OH); **^{13}C NMR** ($CDCl_3$) δ (ppm): 118.2, 121.2, 128.6, 129.4, 130.2, 130.4, 134.3, 134.4, 134.7, 134.9, 135.0, 137.6, 162.0. ^{31}**P NMR** ($CDCl_3$) δ (ppm): -4.7 (br).

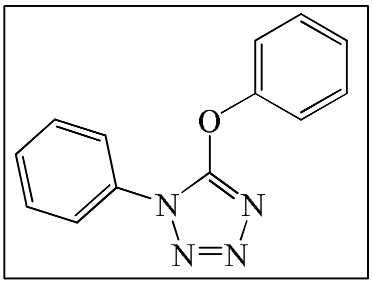
The free ligand could form a stable yellow (2:1) complex with palladium acetate in THF at R.T.

^{1}**H NMR** ($CDCl_3$) δ (ppm): 6.38 (1H, m, Ar), 6.71 (1H, m, Ar), 7.28-6.91 (12H, m, Ar). ^{31}**P NMR** ($CDCl_3$) δ (ppm): 45.2 ppm.

5.4 EXPERIMENTAL PROCEDURE FOR CHAPTER 4

Typical procedure (A) for the preparation of tetrazolyl ethers

5-Phenoxy-1-phenyl-1*H*-tetrazole



$C_{13}H_{10}N_4O$

Mol. Wt.: 238.24

A solution of phenol (1.26 g, 13.29 mmol) in dry THF (10 mL) was added to slurry of sodium hydride (0.75 g, 17.29 mmol) in dry THF (10 mL) under anhydrous conditions. When effervescence had ceased (30 min) a solution of 5-chloro-1-phenyl-1*H*-tetrazole (1.97 g, 11.07 mmol) in THF (10 mL) was added. The mixture was allowed to stir at room temperature overnight and then ice-water was added (40 ml). The organic product was extracted with DCM (2×50 ml) and washed with a saturated solution of $NaHCO_3$ (2 × 50 mL), brine (2 × 50 mL), and water (2 × 50 mL). The organic layer was dried over anhydrous sodium sulphate, filtered, and the filtrate evaporated to dryness to give a white solid which was recrystallized from toluene/DCM to give 5-phenoxy-1-phenyl-1*H*-tetrazole as colourless needles in (1.81 g, 68.4% yield; m.p. 127.0-129.4ºC, lit. 132-133ºC). IR: 1597 (C=N), 1537, 1296, 1074 (=C-O-C), 1180, 804, 768 cm^{-1}. **^{1}H NMR** ($CDCl_3$) δ (ppm): 7.28-7.33 (m, 2H), 7.38-7.62 (m, 6H), 7.78-7.83 (m, 2H). **^{13}C NMR** ($CDCl_3$) δ (ppm): 119.81, 122.61, 123.02, 123.56, 126.12, 126.96, 129.89, 130.17, 130.45, 133.53, 145.34, 153.89, 159.82. **MS** (CI, *m/z*) 239 (100%) $[M+H]^+$, 256 (23%) $[M+NH_4]^+$; **EA** calculated for $C_{13}H_{10}N_4O$: C (65.54%), H (4.23%), N (23.52%); found: C (65.60%), H (4.22%), N (23.60%).[350,359,360]

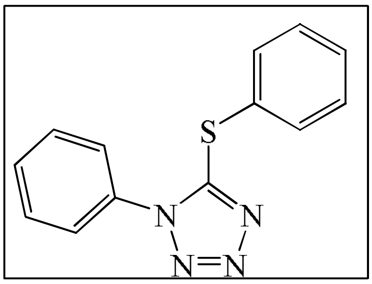
The synthesis of 5-phenoxy-1-phenyltetrazole was repeated, this time, using different reaction conditions, namely, solvent and base.

Typical procedure (B) for the preparation of tetrazolyl ethers

5-Phenoxy-1-phenyl-1*H*-tetrazole

In a typical reaction, potassium *tert*-butoxide (2.41 g, 20.44 mmol) was added to a stirred solution of phenol (1.89 g, 19.20 mmol) in dry dimethylformamide (25 mL). After the butoxide had dissolved (30 min.), 5-chloro-1-phenyl-1*H*-tetrazole (3.00 g, 16.61 mmol) was added and stirring was continued at R.T. for 2 h. The mixture was poured into an excess of ice-water (40 ml). The organic product was extracted with DCM (2×50 ml) and washed with a saturated solution of $NaHCO_3$ (2 × 50 mL), brine (2 × 50 mL), and water (2 × 50 mL). The organic layer was dried over anhydrous sodium sulphate, filtered, and the filtrate evaporated to dryness to give a white solid which was recrystallized from toluene/DCM to give 5-phenoxy-1-phenyl-1*H*-tetrazole as colourless needles (3.65 g, 92.3% yield). **^{1}H NMR** ($CDCl_3$) δ (ppm): 7.38-7.60 (8H, m, Ar), 7.80-7.82 (2H, d, Ar). **MS** (CI+(NH_3)) m/z 238 $[M+H]^+$.

1-Phenyl-5-phenylsulphanyl-1*H*-tetrazole

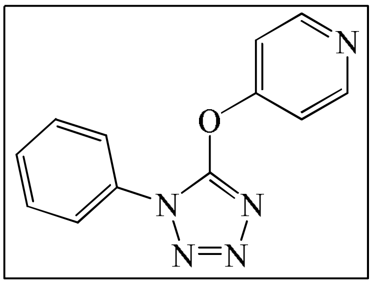


$C_{13}H_9N_4S$

Mol. Wt.: 254.31

Procedure A was used in this reaction. Sodium hydride (0.88 g, 20.13 mmol), thiophenol (1.62 g, 14.68 mmol) and 5-chloro-1-phenyl-1*H*-tetrazole (2.52 g, 13.98 mmol) were used to afford a white solid of 1-phenyl-5-phenylsulphanyl-1*H*-tetrazole (0.90 g, 25.3%; m.p. 58.1-62.4ºC). **IR**: 1574, 1475, 1437, 1072, 736, 687 cm^{-1}. **^{1}H NMR** ($CDCl_3$) δ (ppm): 7.21-7.31 (m, 8H), 7.48-7.51 (m, 2H). **^{13}C NMR** ($CDCl_3$) δ (ppm): 127.56, 127.99, 129.44, 137.48. **MS** (CI+(NH_3)) m/z 255 $[M+H]^+$.

4-(1-Phenyl-1*H*-tetrazole-5-yloxy)-pyridine

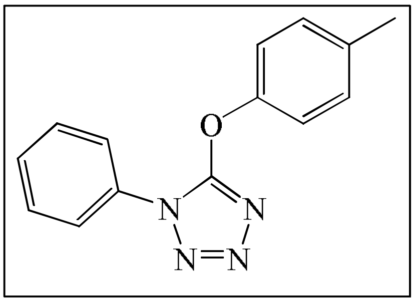


$C_{12}H_9N_5O$

Mol. Wt.: 239.23

Procedure B was used in this reaction. Potassium *tert*-butoxide (0.96 g, 8.0 mmol), 4-hidroxypyridine (0.66 g, 6.58 mmol) and 5-chloro-1-phenyl-1*H*-tetrazole (1.00 g, 5.48 mmol) were used to afford light pink crystals of 4-(1-phenyl-1*H*-tetrazole-5-yloxy)-pyridine (1.02 g, 77.5% yield; m.p. 219.8-222.6ºC). IR: 1659, 1531, 1298, 1053, 1186, 847, 768 cm^{-1}. **^{1}H NMR** ($CDCl_3$) δ (ppm): 6.40 (d, *J*=8.7 Hz, 2H), 7.43-7.53 (m, 5H), 7.61-7.70 (m, 2H). **^{13}C NMR** ($CDCl_3$) δ (ppm): 110.10, 121.11, 125.32, 125.56, 128.10, 132.00, 132.85, 133.40, 138.06, 155.20, 155.24, 178. **MS** (CI+(NH_3)) m/z 240 $[M+H]^+$. **EA** calculated for $C_{12}H_9N_5O$: C (60.25%), H (3.79%), N (29.27%) found: C (60.33%), H (3.77%), N (29.34%)

1-Phenyl-5-(4-tolyloxy)-1*H*-tetrazole

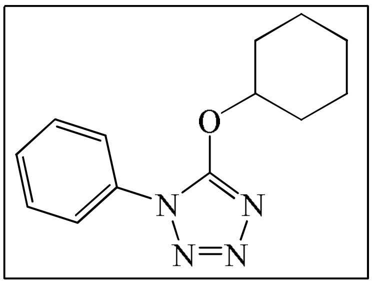


$C_{14}H_{12}N_4O$

Mol. Wt.: 252.27

Procedure B was used in this reaction. Potassium *tert*-butoxide (2.04 g, 17.27 mmol), 4-cresol (1.47 g, 13.29 mmol) and 5-chloro-1-phenyl-1*H*-tetrazole (2.00 g, 11.07 mmol) were used to afford light brown crystals of 1-phenyl-5-(4-tolyloxy)-1*H*-tetrazole (2.55 g, 84.2% yield; m.p. 86.0-89.8ºC, lit. 91-92ºC). **IR:** 1595, 1547, 1504, 1301, 1072, 1197, 816, 764 cm^{-1}. **^{1}H NMR** ($CDCl_3$) δ (ppm): 2.36 (3H, s, CH_3) 7.20-7.35 (5H, m, Ar), 7.45-7.81 (4H, m, Ar). **^{13}C NMR** ($CDCl_3$) δ (ppm): 21.39, 116.26, 120.36, 123.32, 126.06, 130.64, 130.95, 131.17, 131.71, 134.37, 137.73, 152.74, 154.90, 161.09. **MS** (CI+(NH_3)) m/z 253 $[M+H]^+$ (100%); **EA** calculated for $C_{14}H_{12}N_4O$: C (66.65%), H (4.79%), N (22.21%); found: C (66.74%), H (4.77%), N (22.38%).[351,359]

5-(Cyclohexyloxy)-1-phenyl-1*H*-tetrazole

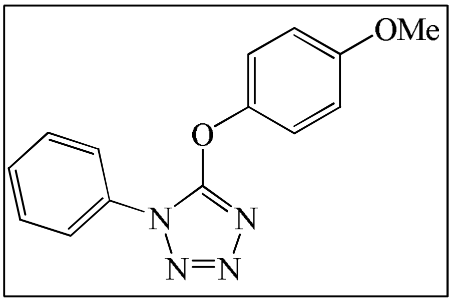


$C_{13}H_{16}N_4O$

Mol. Wt.: 244.29

Procedure B was used in this reaction, nevertheless after addition of 5-chloro-1-phenyl-1*H*-tetrazole the temperature was raised to 80ºC for 5 hours. Potassium *tert*-butoxide (1.30 g, 10.98 mmol), cyclohexanol (0.97 g, 9.55 mmol) and 5-cloro-1-phenyltetrazole (1.50 g, 8.31 mmol) were used to afford crystals of 5-(cyclohexyloxy)-1-phenyl-1*H*-tetrazole (1.34 g, 66.3 yield; m.p. 73.5-75.4ºC). **IR:** 1595, 1552, 1290, 1072, 1182, 758 cm^{-1}. **MS** (CI+(NH_3)) m/z 245 $[M+H]^+$. **^{1}H NMR** (MeOD) δ (ppm): 1.40-2.15 (10H, m, Cy), 5.00-5.10 (1H, m, O-C-H), 7.50-7.80 (5H, m, Ar). **^{13}C NMR** (MeOD) δ (ppm): 24.68, 26.59, 31.06, 32.64, 85.24, 123.62, 130.70, 131.14, 135.17, 161.43.

5-(4-Methoxy-phenoxy)-1-phenyl-1*H*-tetrazole

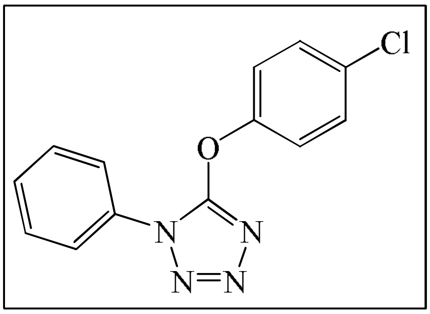


$C_{14}H_{12}N_4O_2$

Mol. Wt.: 268.27

Procedure B was used in this reaction. Potassium *tert*-butoxide (1.88 g, 15.95 mmol), 4-methoxyphenol (1.65 g, 13.29 mmol) and 5-chloro-1-phenyl-1*H*-tetrazole (2.00 g, 11.07 mmol) were used to afford small white crystals of 5-(4-methoxy-phenoxy)-1-phenyl-1*H*-tetrazole (2.54 g, 85.7% yield; m.p. 77.4-80.2°C, lit. 79-80°C). **IR:** 1597, 1550, 1502, 1450, 1250, 1192, 1030, 829, 762 cm^{-1}. **^{1}H NMR** ($CDCl_3$) δ (ppm): 3.82 (s, 3H), 6.94 (m, 2H), 7.32 (m, 2H), 7.42-7.61 (m, 5H). **^{13}C NMR** ($CDCl_3$) δ (ppm): 21.39, 116.26, 120.36, 123.32, 126.06, 130.64, 130.95, 131.17, 131.71, 134.37, 137.73, 152.74, 154.90, 161.09. **MS** (CI, *m/z*) 269 (100%) $[M+H]^+$; **EA** calculated for $C_{14}H_{12}N_4O_2$: C (62.68%), H (4.51%), N (20.88%); found: C (63.21%), H (4.99%), N (20.01%).[350,359,360]

5-(4-Chlorophenoxy)-1-phenyl-1*H*-tetrazole

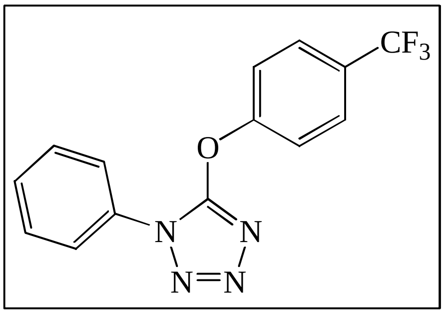


$C_{13}H_9ClN_4O$

Mol. Wt.: 272.69

Procedure A was used in this reaction, nevertheless the reaction was allowed to reflux for two hours after the addition of 5-chloro-1-phenyl-1*H*-tetrazole. Sodium hydride (0.88 g, 20.00 mmol), 4-chlorophenol (1.73 g, 13.29 mmol) and 5-chloro-1-phenyl-1*H*-tetrazole (2.08 g, 11.07 mmol) were used to afford transparent colourless needles of 5-(4-chlorophenoxy)-1-phenyl-1*H*-tetrazole (2.32 g, 73.7%; m.p. 99.0-101.9°C). IR: 1595, 1552, 1485, 1298, 1097, 1194, 829, 768 cm^{-1}. **^{1}H NMR** ($CDCl_3$) δ (ppm): 6.80 (m, 2H), 7.12-7.18 (m, 2H), 733-7.43 (m, 1H), 7.50-7.62 (m, 2H), 7.76-7.80 (m, 2H). **^{13}C NMR** ($CDCl_3$) δ (ppm): 117.90, 122.03, 123.41, 123.44, 129.44, 130.25, 130.97, 131.06, 133.37, 134.05, 152.17, 154.94, 160.62. **MS** (CI+(NH_3)) m/z 273 $[M+H]^+$ (100%), 290 $[M+NH_4]^+$. **EA** calculated for $C_{13}H_9ClN_4O$: C (57.26%), H (3.33%), N (20.55%); found: C (57.54%), H (3.56%), N (22.38%).

5-(4-(α,α,α-Trifluoromethyl)phenoxy)-1-phenyl-1*H*-tetrazole

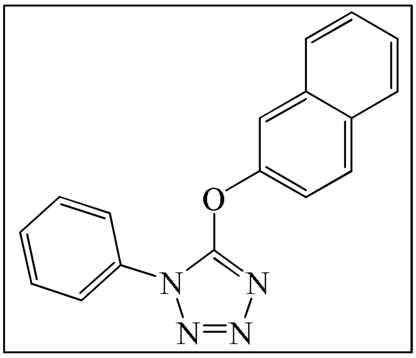


$C_{14}H_9F_3N_4O$

Mol. Wt.: 306.24

Procedure B was used in this reaction, nevertheless after addition of 5-cloro-1-phenyltetrazole the temperature was raised to 70°C for one and an half hours. Potassium *tert*-butoxide (2.38 g, 20.76 mmol), 4-(α,α,α-trifluoromethyl) phenol (2.70 g, 16.6 mmol) and 5-cloro-1*H*-phenyltetrazole (3.03 g, 16.61 mmol) were used to afford colourless crystals of 5-(4-(α,α,α-trifluoromethyl)phenoxy)-1-phenyl-1*H*-tetrazole (4.08 g, 80.2% yield; m.p. 68.0-71.2°C, lit. 70-71°C). **IR:** 1597, 1547, 1510, 1288, 1117, 1065, 845, 762 cm^{-1}. **^{1}H NMR** ($CDCl_3$) δ (ppm): 7.52-7.64 (5H, m, Ar); 7.73-7.75 (m, 2H, Ar), 7.76-7.81 (m, 2H, Ar). **^{13}C NMR** ($CDCl_3$) δ (ppm): 115.90, 120.15, 122.77, 125.52, 127.96, 130.19, 130.27, 131.46, 132.15, 133.23, 143.17, 155.90, 159.13, 161.97. **MS** (CI+(NH_3)) m/z 307 $[M+H]^+$ (100%), 324 $[M+NH_4]^+$ (78%); **EA** calculated for $C_{14}H_9F_3N_4O$: C (54.91%), H (2.96%), N (18.29%); found: C (54.91%), H (3.03%), N (18.35%).[359]

5-(2-Naphtoxy)-1-phenyl-1*H*-tetrazole

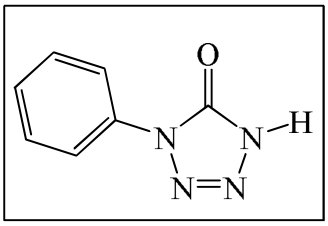


$C_{17}H_{12}N_4O$

Mol. Wt.: 288.30

Procedure B was used in this reaction. Potassium *tert*-butoxide (0.94 g, 7.97 mmol), 2-napthol (0.96 g, 6.65 mmol) and 5-chloro-1-phenyl-1*H*-tetrazole (1.00 g, 5.54 mmol) were used to afford pink plates of 5-(2-Naphtoxy)-1-phenyl-1*H*-tetrazole (1.63 g, 91.9% yield; m.p. 138.2.0-142.4ºC, lit. 136-137ºC). **IR:** 1593, 1554, 1113, 1095, 1018, 768 cm^{-1}. **^{1}H NMR** ($CDCl_3$) δ (ppm): 7.49-7.65 (m, 5H), 7.83-7.99 (m, 7H). **^{13}C NMR** ($CDCl_3$) δ (ppm): 117.30, 119.84, 120.08, 122.91, 123.43, 125.48, 127.44, 128.13, 129.05, 129.95, 130.74, 131.10, 132.02, 133.55, 134.09, 151.44, 159.86. **MS** (CI+(NH_3)) m/z 289 $[M+H]^+$, (100%). **EA** calculated for $C_{17}H_{12}N_4O$: C (70.82%), H (4.20%), N (19.43%); found: C (70.62%), H (4.25%), N (19.32%).[350,359,360]

1-phenyl-1H-tetrazol-5(4H)-one

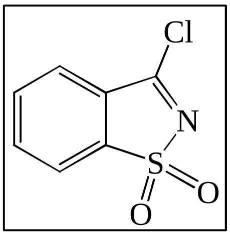


$C_7H_6N_4O$

Mol. Wt.: 162.15

5-Chloro-1-phenyl-1*H*-tetrazole (1.0 g, 5.54 mmol) was added to a mixture (3:1 v/v, 20 ml) of aqueous sodium hydroxide (1.75 g, 31.2 mmol) and ethanol and warmed to 70ºC with stirring overnight. The resulting clear solution was cooled neutralized with HCl. A white precipitate was filtrated, washed with water and dried at R.T. (0.76 g, 4.69 mmol, 84.6%). **^{1}H NMR** ($CDCl_3$) δ (ppm): 7.40-7.50 (1H, m, Ar). 7.50-7.60 (2H, m, Ar), 7.80-7.90 (2H, m, Ar). **MS** (CI+(NH_3)) m/z 162 $[M+H]^+$. **EA** calculated for $C_7H_6N_4O$: C (51.85%), H (3.73%), N (34.55%); found: C (52.12%), H (3.76%), N (34.38%).[379,380]

3-Chloro-1,2-benzisothiazole 1,1-dioxide



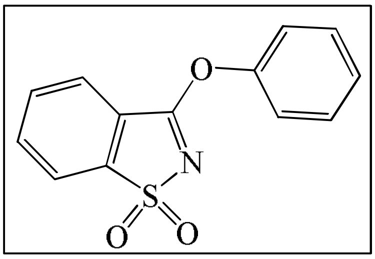
$C_7H_4ClNO_2S$

Mol. Wt.: 201.63

In a 100 mL round bottom flask equipped with a magnetic stirring bar a solid mixture of phosphorus pentachloride (34 g; 164 mmol) and saccharine (20 g; 109 mmol) was stirred and warmed until melting was reached. Following the mixture was allowed to reflux, at approximately 180ºC, during 3 h, until no more gas (HCl) would be released. Phosphorus oxychloride ($POCl_3$) was distilled under reduced pressure resulting in a mixture that crystallized upon cooling. The product was recrystallized in toluene affording white needles (10.38 g, 51.5 mmol, 47.2%), m.p.143.1-145.2ºC, lit. 144-145ºC. **IR:** 1533, 1344 (SO_2), 1236, 1178, 993, 775 e 623 cm^{-1}. **^{1}H NMR** ($CDCl_3$) δ (ppm):7.81-8.02 (m, 4H).[381-383]

Typical procedure for the preparation of pseudosaccharyl ethers

3-Phenoxy-1,2-benzisothiazol 1,1-dioxide

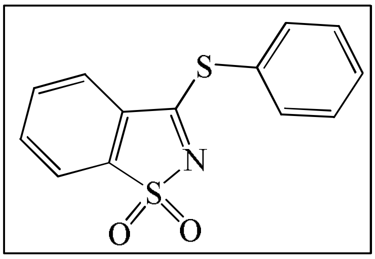


$C_{13}H_9NO_3S$

Mol. Wt.: 259.28

A mixture of 3-chloro-1,2-benziothiazole 1,1-dioxide (0.81 g, 4.00 mmol), phenol (0.43 g, 4.48 mmol) and triethylamine (6 mL, 4.30 mmol) in toluene (20 ml) was stirred at room temperature until TLC analysis (DCM as eluent) indicated the absence of starting material (3,5 h). Water (30 mL) was then added to the reaction and the product was extracted with dichloromethane (2X50 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (2 × 50 mL), NH_4Cl (2 × 50 mL), brine (100 ml) and with water (100 mL). Finally the organic phase was dried over sodium sulphate. The filtrate was evaporated to dryness at room temperature. Recrystallization from toluene/DCM gave 3-phenoxy-1,2-benzisothiazol 1,1-dioxide as white needles (0.90 g, 87.2% yield; m.p. 183.0-184.2°C, lit. 180-182°C). **IR:** 1620, 1549 (ROC=N-), 1161 (C-O), 775 cm^{-1}. **^{1}H NMR** ($CDCl_3$) δ (ppm): 7.34-7.49 (m, 2H), 7.45-7.62 (m, 2H), 7.77-7.86 (m, 3H), 7.91-7.98 (m, 2H). **^{13}C NMR** ($CDCl_3$) δ (ppm): 99.99, 121.16, 121.54, 124.04, 127.20, 127.69, 130.31, 134.04, 134.84, 137.71, 144.06, 152.28, 169.14. **MS** (CI+(NH_3)) m/z 260 $[M+H]^+$ (23%), 277 $[M+NH_4]^+$ (100%). **EA** calculated for $C_{13}H_9NO_3S$: C (60.22%), H (3.50%), N (5.40%); found: C (60.25%), H (3.49%), N (5.38%).[355,360]

3-Phenylsulfanyl-1,2-benzisothiazol 1,1-dioxide

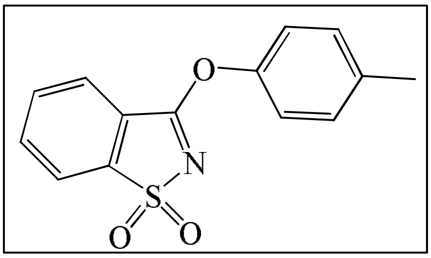


$C_{13}H_9NO_2S_2$

Mol. Wt.: 275.35

From 3-chloro-1,2-benziothiazole 1,1-dioxide (1.88 g, 9.32 mmol), thiophenol (1mL, 9.78 mmol) and triethylamine (13 mL) 3-(phenylsulphanyl)-1,2-benziothiazole 1,1-dioxide was afforded as yellow needles (2.26 g, 90.7% yield; m.p. 224.8-228.0°C). **IR:** 1595, 1510, 1327, 1171, 760 cm^{-1}. **^{1}H NMR** ($CDCl_3$) δ (ppm): 7.46-7.55 (m, 2H), 7.64-7.68 (m, 3H), 7.71-7.81 (m, 2H), 7.88-7.91 (m, 2H). **^{13}C NMR** ($CDCl_3$) δ (ppm): 99.99, 123.46, 122.53, 124.30, 127.12, 130.22, 131.31, 132.21, 134.11, 134.43, 135.18, 139.62, 176.21. **MS** (CI+(NH_3)) 276 $[M+H]^+$ (88%), 293 $[M+NH_4]^+$ (100%). **EA** calculated for $C_{13}H_9NO_2S_2$: C (56.71%), H (3.29%), N (5.09%); found: C (56.60%), H (3.27%), N (5.06%).

3-(4-Tolyloxy)-1,2-benzisothiazol 1,1-dioxide

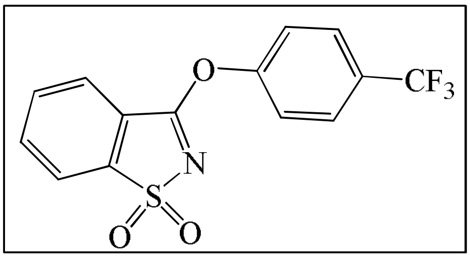


$C_{14}H_{11}NO_3S$

Mol. Wt.: 273.31

From 3-chloro-1,2-benziothiazole 1,1-dioxide (2.00 g, 9.92 mmol), 4-cresol (1.01 g, 8.87 mmol) and triethylamine (7 mL), 3-(4-tolyloxy)-1,2-benzisothiazol 1,1-dioxide was afforded as yellow crystals (2.39 g, 95.9% yield; m.p. 173.4-175.5°C). **IR:** 1614, 1550, 1502, 1377, 1171, 769 cm^{-1}. **^{1}H NMR** ($CDCl_3$) δ (ppm): 2.40 (s, 3H), 7.10-7.40 (m, 4H), 7.70-7.95 (m, 4H). **^{13}C NMR** ($CDCl_3$) δ (ppm): 21.37, 99.99, 115.12, 120.81, 122.44, 124.12, 127.17, 130.77, 134.14, 134.89, 137.55, 143.97, 150.20, 169.38. **MS** (CI+(NH_3)) m/z 274 (41%) $[M+H]^+$, 291 (100%) $[M+NH_4]^+$. **EA** calculated for $C_{14}H_{11}NO_3S$: C (61.52%), H (4.06%), N (5.12%), found: C (61.46%), H (4.09%), N (5.10%).

3-(4-(Trifluoromethyl)phenoxy)-1,2-benzisothiazol 1,1-dioxide

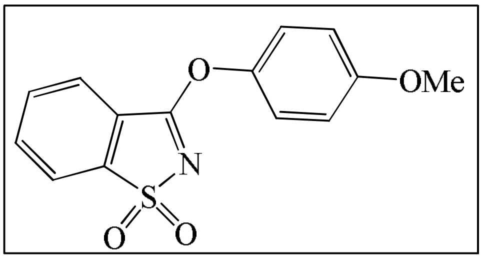


$C_{14}H_8F_3NO_3S$

Mol. Wt.: 327.28

From 3-chloro-1,2-benziothiazole 1,1-dioxide (1.50 g, 7.44 mmol), 4-(α,α,α-trifluoromethyl) phenol (1.22 g, 7.53 mmol) and triethylamine (10 mL), 3-(4-(trifluoromethyl)phenoxy)-1,2-benzisothiazol 1,1-dioxide was afforded as light yellow crystals (1.78 g, 73.0% yield; m.p. 140.0-142.7°C). **IR:** 1621, 1562, 1383, 1173, 771 cm^{-1}. **^{1}H NMR** ($CDCl_3$) δ (ppm): 7.43 (m, 2H), 7.68 (m, 2H), 7.72-7.80 (m, 2H), 7.85-7.91 (m, 2H). **^{13}C NMR** ($CDCl_3$) δ (ppm): 114.48, 120.52, 121.48, 121.71, 125.25, 122.69, 126.35, 132.84, 133.77, 142.48, 152.96, 154.23, 167.42,176.26. **MS** (CI+(NH_3)) m/z 345 $[M+NH_4]^+$ (100%). **EA** calculated for $C_{14}H_8F_3NO_3S$: C (51.38%), H (2.46%), N (4.28%); found: C (51.50%), H (2.62%), N (4.18%).

3-(4-Methoxy-phenoxy)-1,2-benzisothiazol 1,1-dioxide

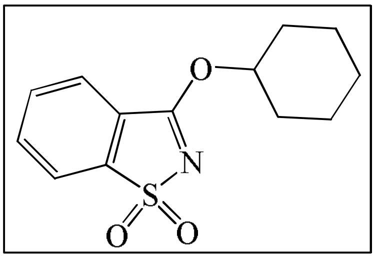


$C_{14}H_{11}NO_4S$

Mol. Wt.: 289.31

From 3-chloro-1,2-benziothiazole 1,1-dioxide (2.00 g, 9.92 mmol), 4-methoxyphenol (1.13 g, 9.00 mmol) and triethylamine (7 mL), 3-(4-methoxy-phenoxy)-1,2-benzisothiazol 1,1-dioxide was afforded as light yellow crystals (2.26 g, 86.9% yield; m.p. 167.4-169.1°C, lit. 185-186°C). **IR:** 1620, 1562, 1502, 1331, 1178, 769 cm^{-1}. **^{1}H NMR** ($CDCl_3$) δ (ppm): 3.84 (s, 3H), 6.96 (d, *J*=9.2 Hz, 2H), 7.29 (d, *J*=9.12 Hz, 2H), 7.76-7.85 (m, 5H), 7.91-7.96 (m, 2H). **^{13}C NMR** ($CDCl_3$) δ (ppm): 56.10, 99.99, 115.17, 122.00, 122.50, 124.03, 127.21, 131.15, 134.02, 134.80, 144.07, 145.84, 158.61, 169.50. **MS** (CI+(NH_3)) m/z 290 $[M+H]^+$ (28%), 307 $[M+NH_4]^+$ (100%). **EA** calculated for $C_{14}H_{11}NO_4S$: C (58.12%), H (3.83%), N (4.84%); found: C (58.10%), H (3.79%), N (4.79%).[360]

3-(Cyclohexyloxy)-1,2-benzisothiazol 1,1-dioxide

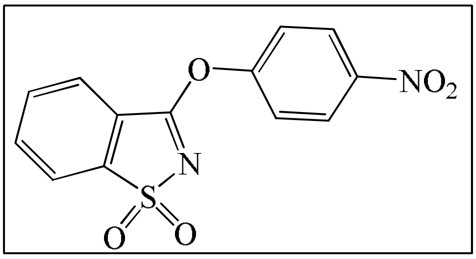


$C_{13}H_{15}NO_3S$

Mol. Wt.: 265.33

From 3-chloro-1,2-benziothiazole 1,1-dioxide (1.51 g, 7.44 mmol), cyclohexanol (0.87 g, 8.56 mmol) and triethylamine (8 mL), 3-(cyclohexyloxy)-1,2-benzisothiazol 1,1-dioxide was afforded as dark yellow crystals (1.33 g, 67.2% yield; m.p. 105.9-110.8ºC). **IR:** 1612, 1552, 1402, 1342, 1174, 768 cm^{-1}. **^{1}H NMR** ($CDCl_3$) δ (ppm): 1.20-1.55 (3H, m, Cy), 1.61-1.75 (3H, m, Cy), 1.80-1.93 (2H, m, Cy), 2.00-2.15 (2H, m, Cy), 5.10-5.20 (1H, m, O-C-H), 7.65-7.90 (4H, m, Ar). **^{13}C NMR** ($CDCl_3$) δ (ppm): 23.87, 25.48, 31.52, 81.92, 122.13, 122.91, 123,08, 123.71, 125.64, 128.02, 132.55, 132.97, 133.06, 133.79, 134.30, 143.87, 168.73. **MS** (CI+(NH_3)) m/z 266 $[M+H]^+$ (100%), 283 $[M+NH_4]^+$ (45%). **EA** calculated for $C_{13}H_{15}NO_3S$: C (58.85%), H (5.70%), N (5.28%); found: C (58.63%), H (5.74%), N (5.42%).

3-(4-Nitrophenoxy)-1,2-benzisothiazol 1,1-dioxide

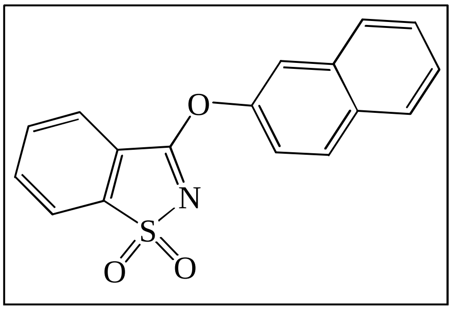


$C_{13}H_8N_2O_5S$

Mol. Wt.: 304.28

Although the same procedure was used, in this reaction, after addition of all the reagents the mixture was refluxed 4h30 min. From 3-chloro-1,2-benziothiazole 1,1-dioxide (3.00 g, 14.87 mmol), 4-nitrophenol (2.53 g, 18.12 mmol) and triethylamine (7 mL), 3-(4-nitrophenoxy)-1,2-benzisothiazol 1,1-dioxide was afforded as transparent yellow crystals in losange-shape. (3.08 g, 71.4% yield; m.p. 250.1-252.4ºC, lit. 246-247ºC). **IR:** 1620, 1550, 1531, 1352, 1173, 771 cm^{-1}. **^{1}H NMR** ($CDCl_3$):δ 7.49-7.54 (2H, d), 7.20-7.86 (4H, m), 8.29-8.39 (2H, d), **MS** (EI) *m/z* 304 [M^+].[355,360]

3-(2-Naphthoxy)-1,2-benzisothiazol 1,1-dioxide

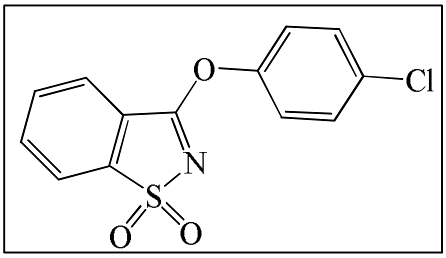


$C_{17}H_{11}NO_3S$

Mol. Wt.: 309.34

Although the same procedure was used, in this reaction, after addition of all the reagents the temperature was increased to 70ºC and maintained for 2h15 min. From 3-chloro-1,2-benziothiazole 1,1-dioxide (1.70 g, 8.43 mmol), 2-napthol (1.46 g, 10.10 mmol) and triethylamine (5 mL), 3-(2-naphthoxy)-1,2-benzisothiazol 1,1-dioxide was afforded as brown crystals. (2.22 g, 85.2% yield; m.p. 257.0-259.3ºC, lit. 260-261 ºC). **IR:** 1614, 1552, 1380, 1323, 1171, 771 cm^{-1}. **^{1}H NMR** ($CDCl_3$) δ (ppm): 7.45-7.49 (m, 2H) 7.80-7.92 (m, 4H), 7.94-8.04 (m, 5H). **^{13}C NMR** ($CDCl_3$) δ (ppm): 99.99, 118.60, 120.02, 122.61, 124.08, 126.99, 127.22, 127.57, 128.34, 128.41, 130.53, 133.90, 134.09, 149.82, 153.20, 163.80. **MS** (CI+(NH_3)) 310 $[M+H]^+$ (26%), 327 $[M+NH_4]^+$ (100%). EA calculated for $C_{17}H_{11}NO_3S$: C (66.01%), H (3.58%), N (4.53%); found: C (66.23%), H (3.57%), N (4.53%).[355,360]

3-(4-Chlorophenoxy)-1,2-benzisothiazol 1,1-dioxide

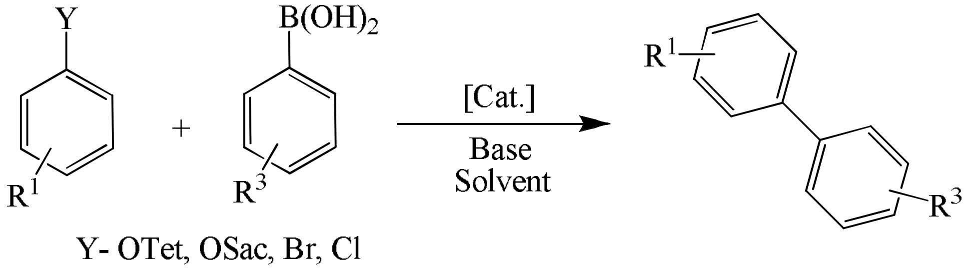


$C_{13}H_8ClNO_3S$

Mol. Wt.: 293.73

Although the same procedure was used, in this reaction, after addition of all the reagents the temperature was increased to 70ºC and maintained for 2h15 min. From 3-chloro-1,2-benziothiazole 1,1-dioxide (2.01 g, 9.92 mmol), 4-chlorophenol (1.57 g, 12.15 mmol) and triethylamine (7 mL), 3-(4-chlorophenoxy)-1,2-benzisothiazol 1,1-dioxide was afforded as yellow crystals. (2.43 g, 83.0% yield; m.p. 172.5-174.0ºC). **IR:** 1614, 1552, 1380, 1323, 1171, 771 cm^{-1}. **^{1}H NMR** ($CDCl_3$) δ (ppm): 7.32 (m, 2H), 7.44 (m, 2H), 7.75-7.88 (m, 3H), 7.90-7.98 (m, 1H). **^{13}C NMR** ($CDCl_3$) δ (ppm): 99.95, 122.53, 123.35, 123.40, 124.84, 127.60, 131.17, 134.03, 135.01, 135.88, 144.84, 155.14, 166.87. **MS** (CI+(NH_3)) m/z 294 $[M+H]^+$ (69%), 311 $[M+NH_4]^+$ (100%). **EA** calculated for $C_{13}H_8ClNO_3S$: C (53.16%), H (2.75%), N (4.77%); found: C (55.08%), H (2.74%), N (4.74%).

Typical procedure for Suzuki coupling involving tetrazolyl and pseudosacharyl ethers.



To a round bottom flask equipped with a stirring bar, the stated quantities of metal catalyst, or pre-catalyst and ligand, were added. The flask was saturated with argon or nitrogen and sealed. The solvent was added and any additives to activate the ligand were added at this point. The mixture was stirred for a few minutes before another one containing the base, electrophile, boron nucleophile and the internal standard, was added. The system was set to warm to the stated temperature and the reaction stirred for the stated time. Samples of the reaction mixture were analysed by GC and GC-MS, allowing identification of the products and to calculate conversions based on the amount of internal standard. In some cases conversions were based on ^{1}H NMR.

Synthesis of organometallic compounds

Dibromo-1,3-bis(diphenylphosphine)-propane nickel II (NiBr$_2$dppp)

To a warm dry butanol (30 mL) solution of nickel (II) bromide (1.07 g, 4.90 mmol) another warm dry butanol (35 mL) solution of 1,3-bis(diphenylphosphine)-propane (2.06 g, 5.00 mmol) was added. The solution was stirred at 100ºC undergoing colour change from brown into purple. After 2 hours the solution was cooled resulting in the formation of small purple crystals which were filtered and washed with cold butanol and cold ethyl ether (2.49 g, 79.7%, m.p. 218ºC; **I.R:** 1433, 1097, 742, 694, 511 cm^{-1}).

Dichlorobis(triethylphosphine) nickel II ($NiCl_2(PEt_3)_2$)

To a warm dry butanol (25 mL) solution of nickel (II) chloride (0.42 g, 3.22 mmol) another warm dry butanol (25 mL) solution of triethylphosphine (1 mL, 6.45 mmol) was added. The solution was stirred at 80ºC undergoing colour change from yellow into bordeaux. After 1 hour the solution was cooled resulting in the formation of small bordeaux crystals which were filtered and washed with cold butanol and cold ethyl ether (0.79 g, 99.0%, m.p. 112-113ºC; **I.R:** 1450, 1412, 1036, 764 cm^{-1}).

Dichloro-1,3-bis(diphenylphosphine)-propane nickel II ($NiCl_2$dppp)

To a warm dry butanol (15 mL) solution of nickel (II) chloride (0.39 g, 3.00 mmol) another warm dry butanol (20 mL) solution of 1,3-bis(diphenylphosphine)-propane (1.24 g, 3.00 mmol) was added. The solution was stirred at 80ºC undergoing colour change from yellow into violet. After little more than 1 hour the solution was cooled resulting in a violet precipitate which was filtered and washed with cold ethyl ether (1.43 g, 90.3%, m.p. 232-234ºC; **I.R:** 1435, 1099, 742, 694, 513 cm^{-1}).[384]

Dichloro-1,1'-bis(diphenylphosphine)-ferrocene nickel II ($NiCl_2$dppf)

To a warm dry butanol (10 mL) solution of nickel (II) chloride (0.13 g, 1.00 mmol) another warm dry butanol (25 mL) solution of 1,1'-bis(diphenylphosphine)-ferrocene (0.55 g, 1.00 mmol) was added. The solution was stirred at 90ºC undergoing colour change from yellow into green. After 20 min. the solution was cooled resulting in green crystals which were filtered and washed with cold butanol and ethyl ether (0.50 g, 73.6%, m.p. 280-281ºC ; **I.R:** 1435, 1095, 1028, 752, 698 cm^{-1}).[385]

Tetrakis(triphenylphosphine) nickel (Ni(PPh$_3$)$_4$)

To a solid mixture of nickel (II) chloride (2.61 g, 19.71 mmol) and triphenylphosphine (21.00 g, 78.46 mmol) acetonitrile (300 mL) was added via syringe. A green mixture started to form and to get darker as the system was heated at reflux temperature. After 1h20 min. the solution was cooled to R.T. and zinc powder (2.00 g, 30.59 mmol) was added. The mixture became gradually lighter with the formation of a brown precipitate being stirred overnight. An orange solid was filtered and dissolved in toluene in order to separate the product from the salts. Petroleum ether was added to cause product precipitation, a yellow solid (4.77 g, 24.3%, m.p. 130ºC; **I.R:** 1435, 1190, 1119, 750, 696, 538 cm^{-1}).

Dichloro-1,1'-bis(diphenylphosphine)-ferrocene palladium II (PdCl$_2$dppf)

To a warm dry buthanol (10 mL) solution of palladium (II) chloride (0.21 g, 1.18 mmol) another warm dry buthanol (25 mL) solution of 1,1'-bis(diphenylphosphine)-ferrocene (0.67 g, 1.20 mmol) was added. The solution was stirred at 100ºC undergoing colour change from brown into purple. After 2h the solution was cooled resulting in purple crystals which were filtered and washed with cold buthanol and ethyl ether (0.62 g, 72.0%, the compound is decomposed when trying to determine its melting point; **I.R:** 1435, 1163, 1026, 744, 698 cm^{-1}).[386]

Dichlorobisacetonitrile palladium II (PdCl$_2$(CH$_3$CN)$_2$

A solution of palladium (II) chloride (brown) (1.03 g, 5.81 mmol) was prepared in dry acetonitrile being left stirring at R.T. overnight leading to the formation of a yellow precipitate. The solvent was evaporated and the product was dried on vacuum

(1.45 g, 96.1%, the compound becomes darker when trying to determine its melting point, not melting even at 290ºC, **I.R:** 2922, 2333, 1412, 1354, 1022 cm^{-1}).

Dichlorobis(triethylphosphine) palladium II ($PdCl_2(PEt_3)_2$)

To a suspension of dichlorobisacetonitrile palladium II (0.34 g, 1.29 mmol) in dry ethyl ether triethylphosphine (0.4 mL, 2.58 mmol) was added via syringe and the mixture stirred overnight at R.T. leading to the formation of a yellow precipitate. The initial suspension gave place to a transparent yellow solution which being cooled led to the formation of yellow crystals. Upon filtration and washing with cold petroleum ether the product was dried under reduced pressure (0.53 g, 99.5%, m.p. 121-127ºC; **I.R:** 2962, 2873, 1450, 1030, 764, 729 cm^{-1}).

Final Remarks

In a few words the context of this work and some of the main results and conlutions will be reminded. Some last considerations on the work will be added.

Final Remarks

The growing demand for pure enantiomeric compounds has driven scientists into the research of new and improved synthetic methods. Asymmetric catalysis is normally involved in the development of such methods, highlighting the need for appropriate catalysts. Consequently, though challenging, ligand design is imperative. Often families of modular ligands are built as a means to better suite the specific requirements of a needed catalytic process. Such is the background that took us to carry on work with ferrocenyl oxazaphospholidine oxides, aiming to positively contribute to this area of research.

Summarizing, the CDG oxazaphospholidine oxide was further investigated. Different studies on the lithiation of ferrocenyl oxazaphospholidine oxides as well as on their reduction were performed. As a result the synthesis of several new varied ferrocenes and ligands with different planar and central chiralities was achieved in a somewhat modular way. Also more insight into the oxazaphospholidine oxide potential and drawbacks in the synthesis of ferrocenyl ligands was obtained. The new ligands were tested on catalytic asymmetric allylic alkylations and on the Suzuki Miyaura reaction disclosing high activity in both reactions and also moderate enantioselectivity, in the first one.

Another important trend of research is to improve known methodologies in order to make them more economical, greener, or to expand their scope. Accordingly the Suzuki-Miyaura coupling with tetrazolyl and benzisothiazolyl phenolic ethers was also studied, including the use of a ferrocenyl oxazaphospholidine oxide ligand. The reaction proved to be challenging but possible.

Having in mind the work performed in this thesis we can portray the oxazaphospholidine oxide CDG as being useful in the synthesis of an interesting family of ferrocenes and chiral ligands. High diastereoselectivity is involved in its *ortho*-lithiation/functionalization to form planar chiral 1,2-dissubstituted ferrocenes of both planar chiral configurations. Diferrocenyl ligands and P-chiral ligands were also formed using this methodology. Pertaining to some of our goals we find some drawbacks using this moiety. Namely a second lithiation at the other *ortho* cyclopentadienyl proton was not successful. In fact proton abstraction was involved at the CDG with the configuration at the oxazaphospholidine phosphorus impacting selectivity. Although (S,S_p) derivatives are more susceptible to undergo abstraction at the acidic CHPh oxazaphospholidine proton they lead to the formation of interesting new ligands. Another drawback is the fact that 1,2-ferrocenyl oxazaphospholidine oxides are not prompted to undergo ring opening via nucleophilic displacement. Although alternatively their reduction, with abstraction of the ephedrine fragment, was proved possible the reaction still requires to be improved.

Regarding the use of ferrocenyl oxazaphospholidine oxides in catalysis besides being able to act as hemilabile ligands it was demonstrated that they indeed have potential activity and ability to induce enantioselectivity, with both types of chirality playing a role. The oxazaphospholidine oxide moiety affects the catalytic process, depending on the Pd/ligand ratio it may chelate with palladium via phosphoryl oxygen coordination. Once again the structural effect of the oxazaphospholidine oxide varies according with its configuration.

Concerning coupling of tetrazolyl and benzisothiazolyl phenolic ethers with boron derivatives undesired homocoupling of boronic acid was observed as well as hydrolysis of the ethers. These and other setbacks were partially minimized by the use of bulky electron-rich ligands however this solution needs to be further explored.

In sum selectivity is a key word that motivated this work and that is related to the obstacles we found. Future solutions to take our work a step forward involve pushing for better selectivities both in ligand synthesis as in catalysis. One of the solutions may involve structural modification upon the oxazaphospholidine oxide moiety. Also with respect to lithiation/functionalization reactions the optimization of conditions, such as the choice of other lithiation agents and/or additives, may allow the formation of (S,R_p) and (R,S_p) 1,2-ferrocenyl oxazaphospholidines and increase the selectivity during the formation of P-chiral derivatives. As well important is to control selectivity on the reduction of the oxazaphospholidine oxide in order to allow ring opening and nucleophilic displacement of the free phosphine and alternatively to form phosphetanes from the primary phosphines obtained.

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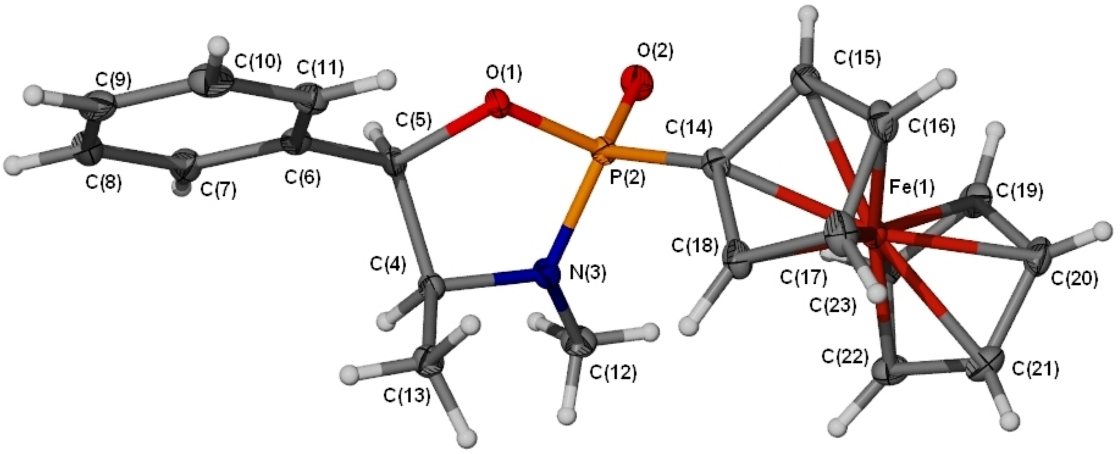
Appendix

X-Ray data of four ferrocenyl oxazaphospholidine oxide compounds prepared in this work will be presented in this section. The structures were resolved by John Bacsa at The University of Liverpool - Chemistry Department.

Appendix

X-Ray Structure report for (2*S*,4*S*,5*R*)-3,4-dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (81)



Crystal data for 81: Identification code cmn82f, $C_{20}H_{22}FeNO_2P$, M = 395.21, orange prism, 0.60 × 0.50 × 0.40 mm^3, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 10.1623(9), b = 12.0052(10), c = 14.5445(13) Å, V = 1774.4(3) Å^3, Z = 4, D_c = 1.479 g/cm^3, F_{000} = 824, Bruker D8 diffractometer with APEX detector, MoKα radiation, λ = 0.71073 Å, T = 110(2)K, $2\theta_{max}$ = 56.7º, 15283 reflections collected, 4163 unique (R_{int} = 0.0217). Final *GooF* = 1.036, *R1* = 0.0232, *wR2* = 0.0568, *R* indices based on 4031 reflections with I >2sigma(I) (refinement on F^2), 314 parameters, 64 restraints. Lp and absorption corrections applied, μ = 0.953 mm^{-1}. Absolute structure parameter = 0.013(9) (Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876-881).

Table 1.1 - Crystal data and structure refinement for **81**.

	D_x = 1.479 Mg m^{-3}
M_r = 395.21	Mo $K\alpha$ radiation
Orthorhombic, $P2_12_12_1$	λ = 0.71073 Å
	Cell parameters from 4783 reflections
a = 10.1623 (9) Å	θ = 2.5-25.8°
b = 12.0052 (10) Å	μ = 0.95 mm^{-1}
c = 14.5445 (13) Å	T = 110 (2) K
V = 1774.4 (3) Å^3	
Z = 4	Prism, orange
F_{000} = 824	0.60 × 0.50 × 0.40 mm
Data collection	
Bruker D8 diffractometer with APEX detector	4163 independent reflections
Radiation source: fine-focus sealed	4031 reflections with $I > 2\sigma(I)$

tube	
Monochromator: graphite	$R_{\mathrm{int}} = 0.022$
$T = 110(2)$ K	$\theta_{\max} = 28.3°$
	$\theta_{\min} = 2.2°$
ω scans with a narrow frame width	$h = -13$ 13
Absorption correction: multi-scan SADABS V2007-2 (Bruker, 2007)	$k = -14$ 15
$T_{\min} = 0.599$, $T_{\max} = 0.702$	$l = -18$ 19
15283 measured reflections	

Refinement on F^2	Primary atom site location: structure-invariant direct methods
Least-squares matrix: full	Secondary atom site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.023$	$w = 1/[\sigma^2(F_o^2) + (0.0364P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.057$	$(\Delta/\sigma)_{\max} < 0.001$
$S = 1.04$	$\Delta\rho_{\max} = 0.34$ e Å^{-3}
4163 reflections	$\Delta\rho_{\min} = -0.25$ e Å^{-3}
314 parameters	Extinction correction: none
64 restraints	Absolute structure: Flack H D (1983), Acta Cryst. A39, 876-881
	Flack parameter: 0.013 (9)

Table 1.2 - Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters for **81** (Å^2).

	x	y	z	$U_{\mathrm{iso}}*/U_{\mathrm{eq}}$
Fe	0.83098 (2)	0.390446 (17)	0.209601 (14)	0.01445 (6)
P2	0.57660 (4)	0.36568 (3)	0.05761 (3)	0.01360 (9)
O1	0.49069 (10)	0.45661 (9)	0.00290 (7)	0.0159 (2)
C18	0.68089 (15)	0.50329 (13)	0.20178 (11)	0.0185 (3)
C4	0.33266 (15)	0.38820 (12)	0.10989 (9)	0.0145 (3)
C19	0.95433 (17)	0.25591 (14)	0.19969 (12)	0.0218 (3)
C15	0.82847 (17)	0.46630 (13)	0.08433 (10)	0.0184 (3)
O2	0.63719 (11)	0.27741 (9)	0.00114 (8)	0.0205 (2)
C14	0.69600 (15)	0.44577 (13)	0.11607 (10)	0.0153 (3)
C6	0.26719 (16)	0.52355 (14)	−0.02063 (10)	0.0156 (3)
C17	0.80100 (16)	0.55861 (14)	0.22191 (12)	0.0221 (3)
C23	0.82411 (17)	0.22036 (13)	0.22057 (11)	0.0199 (3)
C7	0.13517 (16)	0.50337 (14)	−0.04123 (11)	0.0192 (3)
C5	0.35047 (14)	0.42753 (13)	0.00933 (10)	0.0149 (3)
C13	0.30928 (16)	0.48096 (14)	0.17851 (11)	0.0186 (3)
N3	0.45694 (12)	0.32860 (11)	0.12802 (9)	0.0154 (3)
C10	0.23316 (18)	0.71801 (14)	−0.05463 (12)	0.0233 (4)
C16	0.89150 (16)	0.53591 (14)	0.14955 (13)	0.0216 (4)
C11	0.31530 (16)	0.63143 (14)	−0.02742 (10)	0.0184 (3)
C20	0.99571 (16)	0.32739 (15)	0.27145 (12)	0.0230 (4)
C8	0.05351 (16)	0.58979 (16)	−0.06850 (11)	0.0234 (4)
C21	0.89101 (18)	0.33704 (15)	0.33634 (11)	0.0239 (4)
C12	0.45159 (18)	0.22386 (15)	0.17669 (12)	0.0219 (4)
C22	0.78546 (17)	0.27079 (14)	0.30453 (11)	0.0214 (3)
C9	0.10246 (18)	0.69742 (15)	−0.07497 (11)	0.0233 (4)

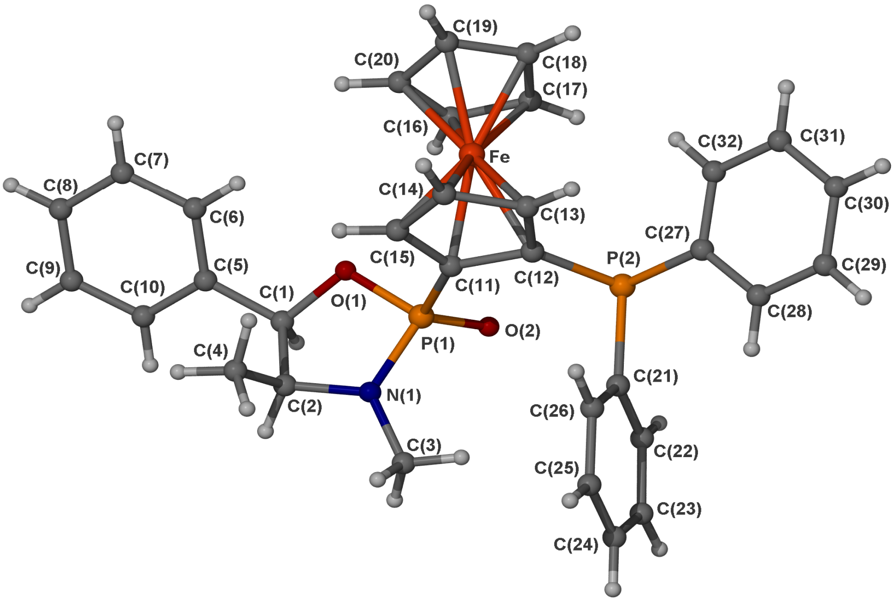
Table 1.3 - Geometric parameters for **81**(Å,°)

Fe—C15	2.0371 (15)	C6—C7	1.396 (2)
Fe—C14	2.0429 (15)	C6—C5	1.495 (2)
Fe—C18	2.0432 (16)	C17—C16	1.424 (2)
Fe—C21	2.0448 (17)	C17—H17	0.938 (9)
Fe—C22	2.0454 (16)	C23—C22	1.418 (2)
Fe—C20	2.0457 (16)	C23—H23	0.923 (10)
Fe—C16	2.0472 (17)	C7—C8	1.386 (2)
Fe—C17	2.0495 (16)	C7—H7	0.917 (10)
Fe—C23	2.0494 (16)	C5—H5	0.979 (9)
Fe—C19	2.0496 (16)	C13—H13A	0.979 (9)
P2—O2	1.4753 (11)	C13—H13C	0.975 (19)
P2—O1	1.6085 (11)	C13—H13B	0.980 (9)
P2—N3	1.6509 (13)	N3—C12	1.444 (2)
P2—C14	1.7663 (16)	C10—C9	1.383 (3)
O1—C5	1.4701 (18)	C10—C11	1.391 (2)
C18—C17	1.420 (2)	C10—H10	0.920 (10)
C18—C14	1.433 (2)	C16—H16	0.929 (9)
C18—H18	0.932 (9)	C11—H11	0.929 (9)
C4—N3	1.4753 (19)	C20—C21	1.427 (2)
C4—C13	1.514 (2)	C20—H20	0.920 (10)
C4—C5	1.548 (2)	C8—C9	1.388 (3)
C4—H4	0.976 (9)	C8—H8	0.922 (10)
C19—C20	1.415 (2)	C21—C22	1.413 (2)
C19—C23	1.423 (2)	C21—H21	0.936 (9)
C19—H19	0.928 (9)	C12—H12B	0.972 (9)
C15—C16	1.417 (2)	C12—H12A	0.972 (9)
C15—C14	1.444 (2)	C12—H12C	0.979 (9)
C15—H15	0.922 (9)	C22—H22	0.929 (9)
C6—C11	1.388 (2)	C9—H9	0.916 (10)

C15—Fe—C14	41.47 (6)	C18—C14—Fe	69.48 (9)
C15—Fe—C18	69.17 (7)	C15—C14—Fe	69.05 (8)
C14—Fe—C18	41.07 (6)	P2—C14—Fe	127.21 (8)
C15—Fe—C21	161.85 (7)	C11—C6—C7	119.03 (15)
C14—Fe—C21	154.50 (7)	C11—C6—C5	122.74 (14)
C18—Fe—C21	118.74 (7)	C7—C6—C5	118.22 (14)
C15—Fe—C22	156.19 (7)	C18—C17—C16	108.26 (15)
C14—Fe—C22	121.73 (7)	C18—C17—Fe	69.46 (9)
C18—Fe—C22	109.54 (7)	C16—C17—Fe	69.57 (10)
C21—Fe—C22	40.43 (7)	C18—C17—H17	120.9 (11)
C15—Fe—C20	124.68 (7)	C16—C17—H17	130.6 (12)
C14—Fe—C20	164.29 (6)	Fe—C17—H17	121.7 (11)
C18—Fe—C20	151.73 (7)	C22—C23—C19	108.25 (15)
C21—Fe—C20	40.83 (7)	C22—C23—Fe	69.58 (9)
C22—Fe—C20	68.18 (7)	C19—C23—Fe	69.69 (9)
C15—Fe—C16	40.61 (7)	C22—C23—H23	123.2 (13)
C14—Fe—C16	68.92 (6)	C19—C23—H23	128.2 (13)
C18—Fe—C16	68.59 (7)	Fe—C23—H23	121.5 (13)
C21—Fe—C16	124.23 (7)	C8—C7—C6	120.45 (16)
C22—Fe—C16	162.76 (7)	C8—C7—H7	122.5 (15)
C20—Fe—C16	104.92 (7)	C6—C7—H7	116.8 (15)
C15—Fe—C17	68.65 (7)	O1—C5—C6	110.31 (12)
C14—Fe—C17	68.78 (6)	O1—C5—C4	104.24 (11)
C18—Fe—C17	40.61 (6)	C6—C5—C4	116.39 (13)
C21—Fe—C17	105.93 (7)	O1—C5—H5	108.5 (10)
C22—Fe—C17	126.81 (7)	C6—C5—H5	107.7 (10)
C20—Fe—C17	116.60 (7)	C4—C5—H5	109.5 (9)
C16—Fe—C17	40.68 (7)	C4—C13—H13A	109.7 (10)
C15—Fe—C23	120.97 (6)	C4—C13—H13C	111.5 (11)
C14—Fe—C23	110.67 (6)	H13A—C13—H13C	109.8 (15)
C18—Fe—C23	129.76 (7)	C4—C13—H13B	114.8 (13)
C21—Fe—C23	68.13 (7)	H13A—C13—H13B	105.4 (15)
C22—Fe—C23	40.53 (7)	H13C—C13—H13B	105.4 (16)
C20—Fe—C23	67.97 (7)	C12—N3—C4	118.53 (13)
C16—Fe—C23	153.31 (7)	C12—N3—P2	124.51 (11)
C17—Fe—C23	165.84 (7)	C4—N3—P2	112.90 (10)
C15—Fe—C19	107.28 (7)	C9—C10—C11	120.26 (16)
C14—Fe—C19	128.32 (6)	C9—C10—H10	118.3 (13)
C18—Fe—C19	167.20 (7)	C11—C10—H10	121.4 (13)

C21—Fe—C19	68.52 (7)	C15—C16—C17	108.40 (14)
C22—Fe—C19	68.43 (7)	C15—C16—Fe	69.31 (9)
C20—Fe—C19	40.43 (7)	C17—C16—Fe	69.75 (10)
C16—Fe—C19	117.29 (7)	C15—C16—H16	123.7 (12)
C17—Fe—C19	150.84 (7)	C17—C16—H16	127.6 (12)
C23—Fe—C19	40.64 (7)	Fe—C16—H16	131.0 (13)
O2—P2—O1	116.01 (7)	C6—C11—C10	120.41 (15)
O2—P2—N3	117.33 (7)	C6—C11—H11	118.6 (11)
O1—P2—N3	95.16 (6)	C10—C11—H11	121.0 (11)
O2—P2—C14	111.86 (7)	C19—C20—C21	108.39 (15)
O1—P2—C14	103.98 (7)	C19—C20—Fe	69.93 (9)
N3—P2—C14	110.74 (7)	C21—C20—Fe	69.55 (9)
C5—O1—P2	109.48 (9)	C19—C20—H20	129.1 (12)
C17—C18—C14	108.21 (14)	C21—C20—H20	122.5 (12)
C17—C18—Fe	69.94 (9)	Fe—C20—H20	125.0 (12)
C14—C18—Fe	69.45 (9)	C7—C8—C9	120.11 (16)
C17—C18—H18	129.6 (11)	C7—C8—H8	117.6 (13)
C14—C18—H18	122.2 (11)	C9—C8—H8	122.3 (13)
Fe—C18—H18	127.6 (10)	C22—C21—C20	107.68 (15)
N3—C4—C13	111.91 (12)	C22—C21—Fe	69.81 (10)
N3—C4—C5	102.52 (11)	C20—C21—Fe	69.62 (9)
C13—C4—C5	114.64 (13)	C22—C21—H21	125.8 (12)
N3—C4—H4	109.9 (10)	C20—C21—H21	126.6 (12)
C13—C4—H4	107.1 (9)	Fe—C21—H21	125.3 (11)
C5—C4—H4	110.7 (9)	N3—C12—H12B	110.2 (11)
C20—C19—C23	107.50 (15)	N3—C12—H12A	114.2 (12)
C20—C19—Fe	69.64 (10)	H12B—C12—H12A	108.4 (16)
C23—C19—Fe	69.67 (9)	N3—C12—H12C	112.2 (13)
C20—C19—H19	122.2 (12)	H12B—C12—H12C	109.8 (17)
C23—C19—H19	130.3 (12)	H12A—C12—H12C	101.6 (18)
Fe—C19—H19	126.3 (12)	C21—C22—C23	108.17 (15)
C16—C15—C14	107.93 (14)	C21—C22—Fe	69.76 (10)
C16—C15—Fe	70.08 (9)	C23—C22—Fe	69.88 (9)
C14—C15—Fe	69.48 (8)	C21—C22—H22	127.1 (13)
C16—C15—H15	129.0 (11)	C23—C22—H22	124.6 (13)
C14—C15—H15	122.9 (11)	Fe—C22—H22	123.1 (13)
Fe—C15—H15	129.2 (11)	C10—C9—C8	119.74 (16)
C18—C14—C15	107.20 (13)	C10—C9—H9	119.7 (13)
C18—C14—P2	127.40 (12)	C8—C9—H9	120.5 (13)

X-Ray Structure report for (2*S*,4*S*,5*R*)-3,4-Dimethyl-2-(α-(S_p)-diphenylphosphanyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (85)



Crystal and refinement data for 85: $C_{32}H_{31}FeNO_2P_2$, M = 579.37, orange prism, 0.28 × 0.26 × 0.23 mm^3, orthorhombic, space group $P2_12_12_1$, a = 12.0764(12), b = 13.3216(13), c = 17.3013(16) Å, V = 2783.4(5) Å^3, Z = 4, D_c = 1.383 g/cm^3, T = 110(2)K, 13337 reflections collected, 6011 unique, R_{int} = 0.0261, final $R1$ = 0.0317, $wR2$ = 0.0700, $GooF$ = 0.977, 376 parameters, 0 restraints, absolute structure parameter = 0.029(12), μ = 0.687 mm^{-1}.

Data collection, structure solution and refinement:

A suitable crystal was selected, mounted on a glass fibre and placed in a cold stream at 110K. Single crystal X-ray data were collected on a Bruker D8 diffractometer with an APEX CCD detector, and 1.5 kW graphite monochromated Mo radiation. The detector to crystal distance was 60 mm. Exposure times of 20 s per frame and scan widths of 0.3° were used throughout the data collection. The data collection was performed using three ω scans yielding data in the θ range 1.93 to 27.49° with an average completeness of 96%. The frames were integrated with the SAINT v6.45a (Bruker, 2005).[1] A semi-empirical absorption correction using multiple-reflections was carried out using the program SADABS (Bruker, 2004)[2], that implements an algorithm published by Blessing[3]. The structure was solved and refined with X-SEED,[4] a graphical interface to SHELX97 (Sheldrick, 1997).[5] In the final cycles of refinement all non-hydrogen atoms were refined anisotropically, and the hydrogen atoms refined with constraints.

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[1] Bruker (2005). SAINT V6.45a, BRUKER AXS Inc., Madison, WI, USA.

[2] Bruker (2004), SADABS, BRUKER AXS Inc., Madison, WI, USA.

[3] Blessing, R. H. *Cryst. Rev*. **1987**, *1*, 3-58; Blessing, R. H. (1989) *J. Appl. Cryst*. **1989**, *22*, 396-397.

[4] Barbour, L. J. "X-Seed - A software tool for supramolecular crystallography" *J. Supramol. Chem*. **2001**, *1*, 189-191.

[5] Sheldrick, G. SHELX-97 Programs for Solving and Refining Crystal Structures, Institüt für Anorganische Chemie der Universität, Tammanstrasse 4, D-3400 Gottingen, Germany (1997).

Table 2.1 - Crystal data and structure refinement for **85**.

Identification code	cmn130f2	
Empirical formula	C32 H31 Fe N O2 P2	
Formula weight	579.37	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P212121	
Unit cell dimensions	a = 12.0764(12) Å	α= 90°.
	b = 13.3216(13) Å	β= 90°.
	c = 17.3013(16) Å	γ = 90°.
Volume	2783.4(5) Å^3	
Z	4	
Density (calculated)	1.383 Mg/m^3	
Absorption coefficient	0.687 mm^{-1}	
F(000)	1208	
Crystal size	0.28 x 0.26 x 0.23 mm^3	
Theta range for data collection	1.93 to 27.49°.	
Index ranges	-11<=h<=15, -16<=k<=16, -21<=l<=17	
Reflections collected	13337	
Independent reflections	6011 [R(int) = 0.0261]	
Completeness to theta = 27.49°	96.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8579 and 0.8309	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6011 / 0 / 376	
Goodness-of-fit on F^2	0.977	
Final R indices [I>2sigma(I)]	R1 = 0.0317, wR2 = 0.0700	
R indices (all data)	R1 = 0.0376, wR2 = 0.0717	
Absolute structure parameter	0.029(12)	
Largest diff. peak and hole	0.539 and -0.221 e.Å^{-3}	

Table 2.2 - Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **85**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Fe	4053(1)	1769(1)	9445(1)	21(1)
P(1)	2067(1)	1448(1)	8098(1)	19(1)
P(2)	3016(1)	3911(1)	8565(1)	19(1)
O(1)	1898(1)	365(1)	8493(1)	21(1)
O(2)	1295(1)	2253(1)	8301(1)	25(1)
N(1)	1967(2)	1020(1)	7210(1)	23(1)
C(1)	1346(2)	-324(2)	7958(1)	21(1)
C(2)	1834(2)	-64(2)	7161(1)	23(1)
C(3)	1939(2)	1634(2)	6513(1)	29(1)
C(4)	2906(2)	-620(2)	6970(1)	26(1)
C(5)	1475(2)	-1386(2)	8229(1)	22(1)
C(6)	2207(2)	-1660(2)	8810(1)	26(1)
C(7)	2290(2)	-2655(2)	9045(2)	33(1)
C(8)	1644(2)	-3385(2)	8693(2)	37(1)
C(9)	920(2)	-3113(2)	8112(2)	35(1)
C(10)	827(2)	-2119(2)	7882(2)	28(1)
C(11)	3451(2)	1781(2)	8356(1)	17(1)
C(12)	3851(2)	2766(2)	8561(1)	17(1)
C(13)	5006(2)	2660(2)	8736(1)	19(1)
C(14)	5309(2)	1641(2)	8648(1)	22(1)
C(15)	4364(2)	1093(2)	8412(1)	21(1)
C(16)	2799(2)	1305(2)	10132(2)	45(1)
C(17)	3149(2)	2267(2)	10372(1)	38(1)
C(18)	4282(2)	2189(2)	10581(2)	36(1)
C(19)	4613(3)	1192(2)	10470(2)	44(1)
C(20)	3693(3)	641(2)	10189(2)	46(1)
C(21)	2931(2)	4121(2)	7513(1)	20(1)
C(22)	1950(2)	4502(2)	7218(2)	28(1)
C(23)	1840(2)	4693(2)	6434(2)	33(1)
C(24)	2700(2)	4476(2)	5934(2)	31(1)
C(25)	3679(2)	4087(2)	6216(1)	27(1)
C(26)	3798(2)	3922(2)	7010(1)	22(1)
C(27)	4056(2)	4851(2)	8843(1)	20(1)
C(28)	4320(2)	5675(2)	8388(2)	25(1)
C(29)	4992(2)	6438(2)	8667(2)	30(1)
C(30)	5410(2)	6389(2)	9411(2)	29(1)
C(31)	5169(2)	5568(2)	9870(2)	30(1)
C(32)	4492(2)	4812(2)	9593(1)	25(1)

Table 2.3 - Bond lengths [Å] and angles [°] for **87**.

Fe-C(11)	2.020(2)	Fe-C(16)	2.021(3)
Fe-C(12)	2.040(2)	Fe-C(17)	2.050(2)
Fe-C(13)	2.059(2)	Fe-C(18)	2.061(3)
Fe-C(14)	2.057(2)	Fe-C(19)	2.047(3)
Fe-C(15)	2.036(2)	Fe-C(20)	2.026(3)

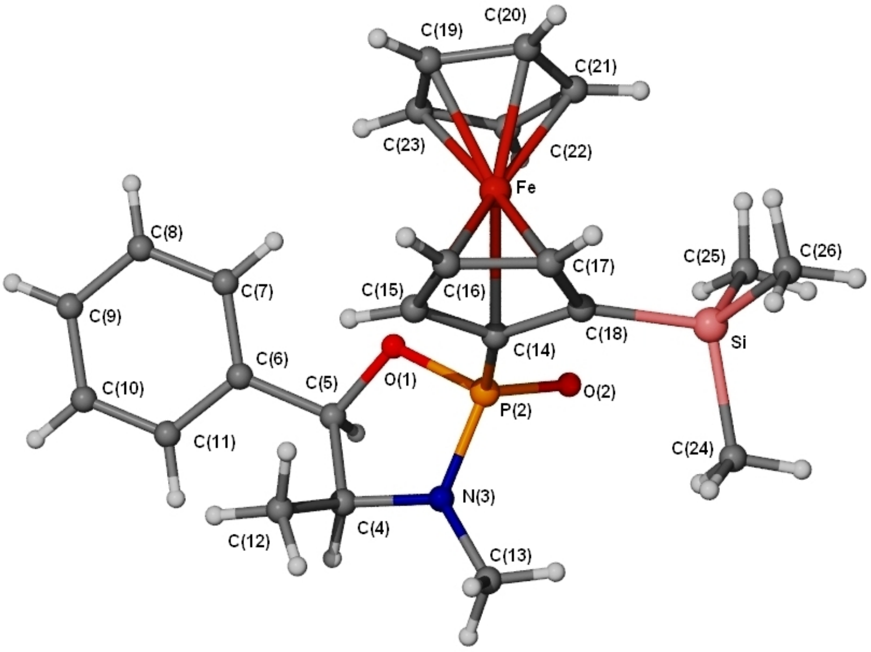
P(1)-O(1)	1.6093(16)
P(1)-O(2)	1.4639(16)
P(1)-N(1)	1.643(2)
P(1)-C(11)	1.786(2)
P(2)-C(12)	1.829(2)
P(2)-C(21)	1.844(2)
P(2)-C(27)	1.837(2)
O(1)-C(1)	1.464(3)
N(1)-C(2)	1.454(3)
N(1)-C(3)	1.458(3)
C(1)-C(2)	1.539(3)
C(1)-C(5)	1.499(3)
C(2)-C(4)	1.528(3)
C(5)-C(6)	1.387(3)
C(5)-C(10)	1.388(3)
C(6)-C(7)	1.391(3)
C(7)-C(8)	1.387(4)
C(8)-C(9)	1.380(4)
C(9)-C(10)	1.387(3)
C(11)-C(12)	1.443(3)
C(11)-C(15)	1.437(3)
C(12)-C(13)	1.435(3)
C(13)-C(14)	1.415(3)
C(14)-C(15)	1.414(3)
C(16)-C(17)	1.412(4)
C(16)-C(20)	1.399(4)
C(17)-C(18)	1.419(3)
C(18)-C(19)	1.400(4)
C(19)-C(20)	1.417(5)
C(21)-C(22)	1.385(3)
C(21)-C(26)	1.387(3)
C(22)-C(23)	1.387(4)
C(23)-C(24)	1.382(4)
C(24)-C(25)	1.380(3)
C(25)-C(26)	1.398(3)
C(27)-C(28)	1.388(3)
C(27)-C(32)	1.403(3)
C(28)-C(29)	1.387(3)
C(29)-C(30)	1.384(4)
C(30)-C(31)	1.383(4)
C(31)-C(32)	1.383(3)
C(1)-H(1)	1.0000
C(2)-H(2)	1.0000
C(3)-H(3A)	0.9800
C(3)-H(3B)	0.9800
C(3)-H(3C)	0.9800
C(4)-H(4A)	0.9800
C(4)-H(4B)	0.9800
C(4)-H(4C)	0.9800
C(6)-H(6)	0.9500
C(7)-H(7)	0.9500
C(8)-H(8)	0.9500
C(9)-H(9)	0.9500
C(10)-H(10)	0.9500
C(13)-H(13)	0.9500
C(14)-H(14)	0.9500
C(15)-H(15)	0.9500
C(16)-H(16)	0.9500
C(17)-H(17)	0.9500
C(18)-H(18)	0.9500
C(19)-H(19)	0.9500
C(20)-H(20)	0.9500
C(22)-H(22)	0.9500
C(23)-H(23)	0.9500
C(24)-H(24)	0.9500
C(25)-H(25)	0.9500
C(26)-H(26)	0.9500
C(28)-H(28)	0.9500
C(29)-H(29)	0.9500
C(30)-H(30)	0.9500
C(31)-H(31)	0.9500
C(32)-H(32)	0.9500
C(11)-Fe-C(12)	41.64(9)
C(11)-Fe-C(13)	68.95(9)
C(11)-Fe-C(14)	68.93(8)
C(11)-Fe-C(15)	41.48(9)

C(11)-Fe-C(16)	106.30(9)
C(11)-Fe-C(17)	122.40(9)
C(11)-Fe-C(18)	159.32(10)
C(11)-Fe-C(19)	158.34(10)
C(11)-Fe-C(20)	121.40(11)
C(12)-Fe-C(13)	40.97(8)
C(12)-Fe-C(14)	68.89(8)
C(12)-Fe-C(15)	69.63(9)
C(12)-Fe-C(16)	123.37(9)
C(12)-Fe-C(17)	108.20(9)
C(12)-Fe-C(18)	123.66(10)
C(12)-Fe-C(19)	158.95(10)
C(12)-Fe-C(20)	158.98(11)
C(13)-Fe-C(14)	40.20(9)
C(13)-Fe-C(15)	68.19(9)
C(13)-Fe-C(16)	160.98(10)
C(13)-Fe-C(17)	125.29(10)
C(13)-Fe-C(18)	109.68(9)
C(13)-Fe-C(19)	123.22(11)
C(13)-Fe-C(20)	157.84(12)
C(14)-Fe-C(15)	40.41(9)
C(14)-Fe-C(16)	157.01(10)
C(14)-Fe-C(17)	160.73(10)
C(14)-Fe-C(18)	124.23(9)
C(14)-Fe-C(19)	107.77(12)
C(14)-Fe-C(20)	121.47(11)
C(15)-Fe-C(16)	121.23(10)
C(15)-Fe-C(17)	158.11(9)
C(15)-Fe-C(18)	158.69(9)
C(15)-Fe-C(19)	122.17(10)
C(15)-Fe-C(20)	105.60(10)
C(16)-Fe-C(17)	40.59(10)
C(16)-Fe-C(18)	67.90(10)
C(16)-Fe-C(19)	67.92(12)
C(16)-Fe-C(20)	40.45(12)
C(17)-Fe-C(18)	40.39(10)
C(17)-Fe-C(19)	67.69(11)
C(17)-Fe-C(20)	68.21(11)
C(18)-Fe-C(19)	39.86(11)
C(18)-Fe-C(20)	67.95(11)
C(19)-Fe-C(20)	40.72(13)
O(1)-P(1)-O(2)	118.32(9)
O(1)-P(1)-N(1)	94.41(9)
O(1)-P(1)-C(11)	103.60(9)
O(2)-P(1)-N(1)	115.58(9)
O(2)-P(1)-C(11)	110.71(10)
N(1)-P(1)-C(11)	112.87(10)
C(12)-P(2)-C(21)	98.87(10)
C(12)-P(2)-C(27)	101.12(9)
C(21)-P(2)-C(27)	101.12(10)
P(1)-O(1)-C(1)	110.55(13)
P(1)-N(1)-C(2)	114.01(15)
P(1)-N(1)-C(3)	125.47(16)
C(2)-N(1)-C(3)	120.41(19)
O(1)-C(1)-C(2)	104.53(17)
O(1)-C(1)-C(5)	110.23(18)
C(2)-C(1)-C(5)	116.96(19)
N(1)-C(2)-C(1)	102.36(18)
N(1)-C(2)-C(4)	113.58(18)
C(1)-C(2)-C(4)	114.14(19)
C(1)-C(5)-C(6)	122.8(2)
C(1)-C(5)-C(10)	118.0(2)
C(6)-C(5)-C(10)	119.3(2)
C(5)-C(6)-C(7)	120.5(2)
C(6)-C(7)-C(8)	120.0(2)
C(7)-C(8)-C(9)	119.5(2)
C(8)-C(9)-C(10)	120.7(2)
C(5)-C(10)-C(9)	120.1(2)
Fe-C(11)-P(1)	124.65(11)
Fe-C(11)-C(12)	69.94(12)
Fe-C(11)-C(15)	69.89(12)
P(1)-C(11)-C(12)	126.91(16)
P(1)-C(11)-C(15)	125.24(17)
C(12)-C(11)-C(15)	107.84(17)
Fe-C(12)-P(2)	127.34(11)
Fe-C(12)-C(11)	68.43(12)

Fe-C(12)-C(13)	70.22(12)
P(2)-C(12)-C(11)	125.14(15)
P(2)-C(12)-C(13)	128.13(16)
C(11)-C(12)-C(13)	106.72(18)
Fe-C(13)-C(12)	68.81(12)
Fe-C(13)-C(14)	69.83(12)
C(12)-C(13)-C(14)	108.86(18)
Fe-C(14)-C(13)	69.97(12)
Fe-C(14)-C(15)	69.01(12)
C(13)-C(14)-C(15)	108.51(19)
Fe-C(15)-C(11)	68.63(12)
Fe-C(15)-C(14)	70.58(13)
C(11)-C(15)-C(14)	108.1(2)
Fe-C(16)-C(17)	70.79(14)
Fe-C(16)-C(20)	69.97(16)
C(17)-C(16)-C(20)	108.8(2)
Fe-C(17)-C(16)	68.62(14)
Fe-C(17)-C(18)	70.23(14)
C(16)-C(17)-C(18)	107.3(2)
Fe-C(18)-C(17)	69.38(14)
Fe-C(18)-C(19)	69.53(16)
C(17)-C(18)-C(19)	108.1(2)
Fe-C(19)-C(18)	70.61(16)
Fe-C(19)-C(20)	68.87(16)
C(18)-C(19)-C(20)	108.3(3)
Fe-C(20)-C(16)	69.57(15)
Fe-C(20)-C(19)	70.42(16)
C(16)-C(20)-C(19)	107.6(2)
P(2)-C(21)-C(22)	117.82(17)
P(2)-C(21)-C(26)	123.20(17)
C(22)-C(21)-C(26)	119.0(2)
C(21)-C(22)-C(23)	120.6(2)
C(22)-C(23)-C(24)	120.1(2)
C(23)-C(24)-C(25)	120.0(2)
C(24)-C(25)-C(26)	119.7(2)
C(21)-C(26)-C(25)	120.5(2)
P(2)-C(27)-C(28)	123.24(17)
P(2)-C(27)-C(32)	118.26(16)
C(28)-C(27)-C(32)	117.9(2)
C(27)-C(28)-C(29)	121.1(2)
C(28)-C(29)-C(30)	120.2(2)
C(29)-C(30)-C(31)	119.7(2)
C(30)-C(31)-C(32)	120.1(2)
C(27)-C(32)-C(31)	121.1(2)
O(1)-C(1)-H(1)	108.00
C(2)-C(1)-H(1)	108.00
C(5)-C(1)-H(1)	108.00
N(1)-C(2)-H(2)	109.00
C(1)-C(2)-H(2)	109.00
C(4)-C(2)-H(2)	109.00
N(1)-C(3)-H(3A)	110.00
N(1)-C(3)-H(3B)	109.00
N(1)-C(3)-H(3C)	109.00
H(3A)-C(3)-H(3B)	110.00
H(3A)-C(3)-H(3C)	109.00
H(3B)-C(3)-H(3C)	109.00
C(2)-C(4)-H(4A)	109.00
C(2)-C(4)-H(4B)	109.00
C(2)-C(4)-H(4C)	110.00
H(4A)-C(4)-H(4B)	109.00
H(4A)-C(4)-H(4C)	109.00
H(4B)-C(4)-H(4C)	109.00
C(5)-C(6)-H(6)	120.00
C(7)-C(6)-H(6)	120.00
C(6)-C(7)-H(7)	120.00
C(8)-C(7)-H(7)	120.00
C(7)-C(8)-H(8)	120.00
C(9)-C(8)-H(8)	120.00
C(8)-C(9)-H(9)	120.00
C(10)-C(9)-H(9)	120.00
C(5)-C(10)-H(10)	120.00
C(9)-C(10)-H(10)	120.00
Fe-C(13)-H(13)	127.00
C(12)-C(13)-H(13)	126.00
C(14)-C(13)-H(13)	126.00
Fe-C(14)-H(14)	127.00

C(13)-C(14)-H(14)	126.00
C(15)-C(14)-H(14)	126.00
Fe-C(15)-H(15)	126.00
C(11)-C(15)-H(15)	126.00
C(14)-C(15)-H(15)	126.00
Fe-C(16)-H(16)	125.00
C(17)-C(16)-H(16)	126.00
C(20)-C(16)-H(16)	126.00
Fe-C(17)-H(17)	126.00
C(16)-C(17)-H(17)	126.00
C(18)-C(17)-H(17)	126.00
Fe-C(18)-H(18)	127.00
C(17)-C(18)-H(18)	126.00
C(19)-C(18)-H(18)	126.00
Fe-C(19)-H(19)	126.00
C(18)-C(19)-H(19)	126.00
C(20)-C(19)-H(19)	126.00
Fe-C(20)-H(20)	125.00
C(16)-C(20)-H(20)	126.00
C(19)-C(20)-H(20)	126.00
C(21)-C(22)-H(22)	120.00
C(23)-C(22)-H(22)	120.00
C(22)-C(23)-H(23)	120.00
C(24)-C(23)-H(23)	120.00
C(23)-C(24)-H(24)	120.00
C(25)-C(24)-H(24)	120.00
C(24)-C(25)-H(25)	120.00
C(26)-C(25)-H(25)	120.00
C(21)-C(26)-H(26)	120.00
C(25)-C(26)-H(26)	120.00
C(27)-C(28)-H(28)	119.00
C(29)-C(28)-H(28)	119.00
C(28)-C(29)-H(29)	120.00
C(30)-C(29)-H(29)	120.00
C(29)-C(30)-H(30)	120.00
C(31)-C(30)-H(30)	120.00
C(30)-C(31)-H(31)	120.00
C(32)-C(31)-H(31)	120.00
C(27)-C(32)-H(32)	120.00
C(31)-C(32)-H(32)	119.00

X-Ray Structure report for (2*S*,4*S*,5*R*)-3,4-Dimethyl-2-(α-(S_p)-trimethylsylanylferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide (87)



Crystal data for **87**: $C_{23}H_{30}FeNO_2PSi$, M = 467.39, orange prismatic, 0.36 × 0.34 × 0.23 mm^3, monoclinic, space group $P2_1$ (No. 4), a = 10.0000(7), b = 11.0730(7), c = 10.832(2) Å, β = 109.495(10)°, V = 1130.7(3) Å^3, Z = 2, D_c = 1.373 g/cm^3, F_{000} = 492, Bruker D8 diffractometer with APEX detector, MoKα radiation, λ = 0.71073 Å, T = 110(2)K, $2\theta_{max}$ = 54.6º, 7948 reflections collected, 4724 unique (R_{int} = 0.0238). Final *GooF* = 1.054, *R1* = 0.0353, *wR2* = 0.0727, *R* indices based on 4424 reflections with I >2sigma(I) (refinement on F^2), 267 parameters, 1 restraint. Lp and absorption corrections applied, μ = 0.810 mm^{-1}. Absolute structure parameter = 0.048(14) (Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876-881).

Table 3.1 - Crystal data and structure refinement for **87**.

Identification code	CMN103F2	
Empirical formula	C23 H30 Fe N O2 P Si	
Formula weight	467.39	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21	
Unit cell dimensions	a = 10.0000(7) Å	α= 90°.
	b = 11.0730(7) Å	β= 109.495(10)°.
	c = 10.832(2) Å	γ = 90°.
Volume	1130.7(3) Å^3	
Z	2	
Density (calculated)	1.373 Mg/m^3	
Absorption coefficient	0.810 mm^{-1}	
F(000)	492	
Crystal size	0.36 x 0.34 x 0.23 mm^3	
Theta range for data collection	1.99 to 27.31°.	
Index ranges	-12<=h<=12, -13<=k<=14, -9<=l<=13	
Reflections collected	7948	
Independent reflections	4724 [R(int) = 0.0238]	
Completeness to theta = 27.31°	98.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8356 and 0.7592	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4724 / 1 / 267	
Goodness-of-fit on F^2	1.054	
Final R indices [I>2sigma(I)]	R1 = 0.0353, wR2 = 0.0727	
R indices (all data)	R1 = 0.0383, wR2 = 0.0739	
Absolute structure parameter	0.048(14)	
Largest diff. peak and hole	0.373 and -0.257 e.Å^{-3}	

Table 3.2 - Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **87**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Fe	5357(1)	2468(1)	8679(1)	18(1)
P(2)	1853(1)	2581(1)	6846(1)	16(1) S
Si	4699(1)	3787(1)	5553(1)	21(1)
O(2)	1691(2)	3829(2)	6371(2)	23(1)
O(1)	1586(2)	2292(2)	8198(2)	17(1)
C(18)	4698(2)	2494(3)	6675(2)	17(1)
C(14)	3605(2)	2032(2)	7149(3)	15(1)
C(17)	5889(3)	1706(2)	7203(3)	19(1)
N(3)	623(2)	1641(2)	5970(2)	18(1)
C(26)	6491(3)	3838(3)	5379(3)	29(1)
C(4)	12(3)	889(2)	6753(3)	18(1) S
C(23)	5119(4)	2859(3)	10420(3)	41(1)
C(7)	1187(3)	1404(2)	10424(3)	22(1)
C(19)	6495(3)	2449(4)	10626(3)	45(1)
C(16)	5543(3)	799(2)	7964(3)	20(1)
C(15)	4153(3)	990(2)	7936(3)	17(1)
C(6)	229(3)	1086(2)	9214(3)	18(1)
C(5)	235(3)	1688(2)	7968(3)	18(1) R
C(10)	-914(3)	-254(3)	10302(3)	26(1)
C(24)	3361(3)	3427(3)	3925(3)	31(1)
C(9)	34(3)	65(3)	11506(3)	24(1)
C(11)	-824(3)	247(3)	9167(3)	22(1)
C(20)	7123(3)	3236(4)	9962(4)	48(1)
C(8)	1083(3)	899(3)	11564(3)	26(1)
C(13)	365(3)	1364(3)	4606(3)	29(1)
C(25)	4321(3)	5299(3)	6109(3)	36(1)
C(21)	6140(4)	4126(3)	9360(3)	46(1)
C(22)	4899(4)	3888(4)	9637(3)	42(1)
C(12)	639(3)	-381(3)	6976(3)	23(1)

Table 3.3 - Bond lengths [Å] and angles [°] for **87**.

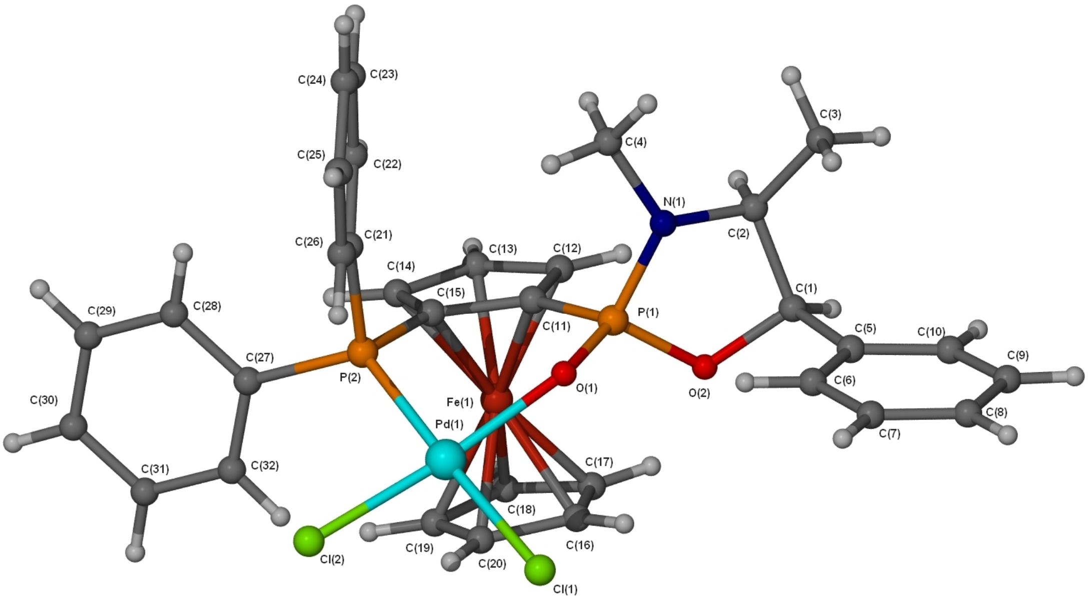
Fe-C(22)	2.019(3)	P(2)-O(1)	1.6054(18)
Fe-C(23)	2.024(3)	P(2)-N(3)	1.649(2)
Fe-C(14)	2.027(2)	P(2)-C(14)	1.778(2)
Fe-C(17)	2.030(3)	Si-C(25)	1.860(3)
Fe-C(15)	2.032(3)	Si-C(26)	1.863(3)
Fe-C(20)	2.033(3)	Si-C(24)	1.867(3)
Fe-C(21)	2.035(3)	Si-C(18)	1.879(3)
Fe-C(19)	2.036(3)	O(1)-C(5)	1.453(3)
Fe-C(16)	2.036(3)	C(18)-C(17)	1.433(4)
Fe-C(18)	2.047(2)	C(18)-C(14)	1.447(3)
P(2)-O(2)	1.465(2)	C(14)-C(15)	1.430(4)

C(17)-C(16)	1.414(4)
C(17)-H(17)	0.9500
N(3)-C(13)	1.445(3)
N(3)-C(4)	1.461(3)
C(26)-H(26A)	0.9800
C(26)-H(26B)	0.9800
C(26)-H(26C)	0.9800
C(4)-C(12)	1.526(4)
C(4)-C(5)	1.539(4)
C(4)-H(4)	1.0000
C(23)-C(22)	1.394(5)
C(23)-C(19)	1.394(5)
C(23)-H(23)	0.9500
C(7)-C(6)	1.386(4)
C(7)-C(8)	1.391(4)
C(7)-H(6)	0.9500
C(19)-C(20)	1.405(5)
C(19)-H(19)	0.9500
C(16)-C(15)	1.396(4)
C(16)-H(16)	0.9500
C(15)-H(15)	0.9500
C(6)-C(11)	1.393(4)
C(6)-C(5)	1.507(4)
C(5)-H(5)	1.0000
C(10)-C(9)	1.378(4)
C(10)-C(11)	1.379(4)
C(10)-H(9)	0.9500
C(24)-H(24A)	0.9800
C(24)-H(24C)	0.9800
C(24)-H(24B)	0.9800
C(9)-C(8)	1.383(4)
C(9)-H(8)	0.9500
C(11)-H(10)	0.9500
C(20)-C(21)	1.391(5)
C(20)-H(20)	0.9500
C(8)-H(7)	0.9500
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800
C(25)-H(25A)	0.9800
C(25)-H(25B)	0.9800
C(25)-H(25C)	0.9800
C(21)-C(22)	1.396(5)
C(21)-H(21)	0.9500
C(22)-H(22)	0.9500
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(22)-Fe-C(23)	40.32(14)
C(22)-Fe-C(14)	108.86(12)
C(23)-Fe-C(14)	118.29(12)
C(22)-Fe-C(17)	153.22(14)
C(23)-Fe-C(17)	164.96(13)
C(14)-Fe-C(17)	68.86(10)
C(22)-Fe-C(15)	128.66(13)
C(23)-Fe-C(15)	107.62(12)
C(14)-Fe-C(15)	41.25(10)
C(17)-Fe-C(15)	68.26(11)
C(22)-Fe-C(20)	67.51(15)
C(23)-Fe-C(20)	67.64(13)
C(14)-Fe-C(20)	167.07(15)
C(17)-Fe-C(20)	108.41(12)
C(15)-Fe-C(20)	150.72(15)
C(22)-Fe-C(21)	40.28(15)
C(23)-Fe-C(21)	67.69(14)
C(14)-Fe-C(21)	129.36(14)
C(17)-Fe-C(21)	119.34(13)
C(15)-Fe-C(21)	167.29(14)
C(20)-Fe-C(21)	39.98(15)
C(22)-Fe-C(19)	67.65(16)
C(23)-Fe-C(19)	40.17(13)
C(14)-Fe-C(19)	151.19(13)
C(17)-Fe-C(19)	127.53(13)
C(15)-Fe-C(19)	117.04(15)
C(20)-Fe-C(19)	40.40(15)
C(21)-Fe-C(19)	67.63(17)

C(22)-Fe-C(16)	165.36(14)
C(23)-Fe-C(16)	127.03(13)
C(14)-Fe-C(16)	68.68(10)
C(17)-Fe-C(16)	40.70(11)
C(15)-Fe-C(16)	40.14(10)
C(20)-Fe-C(16)	118.09(14)
C(21)-Fe-C(16)	152.09(13)
C(19)-Fe-C(16)	107.12(15)
C(22)-Fe-C(18)	119.08(15)
C(23)-Fe-C(18)	152.64(13)
C(14)-Fe-C(18)	41.61(9)
C(17)-Fe-C(18)	41.14(11)
C(15)-Fe-C(18)	69.68(11)
C(20)-Fe-C(18)	128.13(13)
C(21)-Fe-C(18)	108.68(14)
C(19)-Fe-C(18)	165.86(12)
C(16)-Fe-C(18)	69.35(12)
O(2)-P(2)-O(1)	118.39(11)
O(2)-P(2)-N(3)	114.79(12)
O(1)-P(2)-N(3)	94.61(10)
O(2)-P(2)-C(14)	111.96(11)
O(1)-P(2)-C(14)	102.56(11)
N(3)-P(2)-C(14)	112.97(12)
C(25)-Si-C(26)	108.19(15)
C(25)-Si-C(24)	109.81(15)
C(26)-Si-C(24)	108.74(14)
C(25)-Si-C(18)	115.60(14)
C(26)-Si-C(18)	107.25(12)
C(24)-Si-C(18)	107.06(12)
C(5)-O(1)-P(2)	111.34(15)
C(17)-C(18)-C(14)	105.6(2)
C(17)-C(18)-Si	122.81(18)
C(14)-C(18)-Si	131.5(2)
C(17)-C(18)-Fe	68.79(14)
C(14)-C(18)-Fe	68.47(14)
Si-C(18)-Fe	128.84(16)
C(15)-C(14)-C(18)	108.2(2)
C(15)-C(14)-P(2)	122.93(19)
C(18)-C(14)-P(2)	128.9(2)
C(15)-C(14)-Fe	69.55(14)
C(18)-C(14)-Fe	69.93(13)
P(2)-C(14)-Fe	126.78(14)
C(16)-C(17)-C(18)	109.4(2)
C(16)-C(17)-Fe	69.88(15)
C(18)-C(17)-Fe	70.07(14)
C(16)-C(17)-H(17)	125.3
C(18)-C(17)-H(17)	125.3
Fe-C(17)-H(17)	126.3
C(13)-N(3)-C(4)	120.4(2)
C(13)-N(3)-P(2)	124.56(18)
C(4)-N(3)-P(2)	113.69(18)
Si-C(26)-H(26A)	109.5
Si-C(26)-H(26B)	109.5
H(26A)-C(26)-H(26B)	109.5
Si-C(26)-H(26C)	109.5
H(26A)-C(26)-H(26C)	109.5
H(26B)-C(26)-H(26C)	109.5
N(3)-C(4)-C(12)	112.8(2)
N(3)-C(4)-C(5)	101.5(2)
C(12)-C(4)-C(5)	117.4(2)
N(3)-C(4)-H(4)	108.2
C(12)-C(4)-H(4)	108.2
C(5)-C(4)-H(4)	108.2
C(22)-C(23)-C(19)	108.1(3)
C(22)-C(23)-Fe	69.64(18)
C(19)-C(23)-Fe	70.34(17)
C(22)-C(23)-H(23)	125.9
C(19)-C(23)-H(23)	125.9
Fe-C(23)-H(23)	125.7
C(6)-C(7)-C(8)	120.3(3)
C(6)-C(7)-H(6)	119.8
C(8)-C(7)-H(6)	119.8
C(23)-C(19)-C(20)	107.6(3)
C(23)-C(19)-Fe	69.49(17)
C(20)-C(19)-Fe	69.72(19)
C(23)-C(19)-H(19)	126.2

C(20)-C(19)-H(19)	126.2
Fe-C(19)-H(19)	126.1
C(15)-C(16)-C(17)	108.4(2)
C(15)-C(16)-Fe	69.77(15)
C(17)-C(16)-Fe	69.42(15)
C(15)-C(16)-H(16)	125.8
C(17)-C(16)-H(16)	125.8
Fe-C(16)-H(16)	126.6
C(16)-C(15)-C(14)	108.4(2)
C(16)-C(15)-Fe	70.09(15)
C(14)-C(15)-Fe	69.21(14)
C(16)-C(15)-H(15)	125.8
C(14)-C(15)-H(15)	125.8
Fe-C(15)-H(15)	126.5
C(7)-C(6)-C(11)	118.6(3)
C(7)-C(6)-C(5)	121.8(2)
C(11)-C(6)-C(5)	119.4(2)
O(1)-C(5)-C(6)	109.4(2)
O(1)-C(5)-C(4)	105.8(2)
C(6)-C(5)-C(4)	118.0(2)
O(1)-C(5)-H(5)	107.8
C(6)-C(5)-H(5)	107.8
C(4)-C(5)-H(5)	107.8
C(9)-C(10)-C(11)	120.7(3)
C(9)-C(10)-H(9)	119.6
C(11)-C(10)-H(9)	119.6
Si-C(24)-H(24A)	109.5
Si-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
Si-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
H(24C)-C(24)-H(24B)	109.5
C(10)-C(9)-C(8)	119.1(3)
C(10)-C(9)-H(8)	120.4
C(8)-C(9)-H(8)	120.4
C(10)-C(11)-C(6)	120.7(3)
C(10)-C(11)-H(10)	119.7
C(6)-C(11)-H(10)	119.7
C(21)-C(20)-C(19)	108.2(3)
C(21)-C(20)-Fe	70.07(19)
C(19)-C(20)-Fe	69.88(18)
C(21)-C(20)-H(20)	125.9
C(19)-C(20)-H(20)	125.9
Fe-C(20)-H(20)	125.7
C(9)-C(8)-C(7)	120.5(3)
C(9)-C(8)-H(7)	119.7
C(7)-C(8)-H(7)	119.7
N(3)-C(13)-H(13A)	109.5
N(3)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
N(3)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
Si-C(25)-H(25A)	109.5
Si-C(25)-H(25B)	109.5
H(25A)-C(25)-H(25B)	109.5
Si-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5
H(25B)-C(25)-H(25C)	109.5
C(20)-C(21)-C(22)	107.8(3)
C(20)-C(21)-Fe	69.95(19)
C(22)-C(21)-Fe	69.25(19)
C(20)-C(21)-H(21)	126.1
C(22)-C(21)-H(21)	126.1
Fe-C(21)-H(21)	126.3
C(23)-C(22)-C(21)	108.3(3)
C(23)-C(22)-Fe	70.0(2)
C(21)-C(22)-Fe	70.47(19)
C(23)-C(22)-H(22)	125.9
C(21)-C(22)-H(22)	125.9
Fe-C(22)-H(22)	125.2
C(4)-C(12)-H(12A)	109.5
C(4)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(4)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5

X-Ray Structure report for Dichloro[(2*R*,4*S*,5*R*)-3,4-dimethyl-2-(α-(R_p)-diphenyl-phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide] palladium II (Pd-90)



Crystal Data for* Pd-90*: 2($C_{32}H_{31}Cl_2FeNO_2P_2Pd$), C_7H_5N, CH_2Cl_2, M = 1701.38, orange block, 0.20 × 0.20 × 0.10 mm^3, monoclinic, space group $P2_1$ (No. 4), a = 9.459(2), b = 19.219(4), c = 19.677(4) Å, V = 3550.5(12) Å^3, Z = 2, D_c = 1.591 g/cm^3, T = 110(2)K, 19537 reflections collected, 13146 unique, R_{int} = 0.0406. Final *GooF* = 1.011, *R1* = 0.0517, *wR2* = 0.1042, μ = 1.266 mm^{-1}, absolute structure parameter = 0.01(2) μ = 1.266 mm^{-1}.

***Data collection, structure solution and refinement*:**

A suitable crystal was selected, mounted on a glass fibre and placed in a cold stream at 110K. Single crystal X-ray data were collected on a Bruker D8 diffractometer with an APEX CCD detector, and 1.5 kW graphite monochromated Mo radiation. The detector to crystal distance was 60 mm. Exposure times of 10 s per frame and scan widths of 0.3° were used throughout the data collection. The crystal was twinned, and the twinning resolved using CELL-NOW and TWINABS. The twin was non-interpenetrating, each component was scaled separately using singles in TWINABS.

An aim of the analysis was to determine the absolute configuration of the molecule by anomalous dispersion. Three 180° ω scans in the θ range 1.04 to 27.53° provided data with an average completeness of 95%. The frames were integrated with the SAINT v6.45a (Bruker, 2005).[6] A semi-empirical absorption correction using multiple-reflections was carried out using the program TWINABS V1.05 (Bruker, 2003)[7]. The structure was solved and

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[6] Bruker (2005). SAINT V6.45a, BRUKER AXS Inc., Madison, WI, USA.

[7] Bruker (2003), TWINABS V1-05, BRUKER AXS Inc., Madison, WI, USA.

refined with X-SEED,[8] a graphical interface to SHELX97 (Sheldrick, 1997).[9] The hydrogen atoms were either constrained or refined with restraints. In the final cycles of refinement all non-hydrogen atoms were refined anisotropically. The value of the absolute structure parameter (0.01(1)) confirms that assignment of the absolute structure is correct.

Table 4.1 - Crystal data and structure refinement for **Pd-90**.

Identification code	129pdclm	
Empirical formula	C72 H69 Cl6 Fe2 N3 O4 P4 Pd2	
Formula weight	1701.38	
Temperature	110(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 9.4590(19) Å	α= 90°.
	b = 19.219(4) Å	β= 96.99(3)°.
	c = 19.677(4) Å	γ = 90°.
Volume	3550.5(12) Å^3	
Z	2	
Density (calculated)	1.591 Mg/m^3	
Absorption coefficient	1.266 mm^{-1}	
F(000)	1720	
Crystal size	0.20 x 0.20 x 0.10 mm^3	
Theta range for data collection	1.04 to 27.53°.	
Index ranges	-6<=h<=12, -24<=k<=20, -25<=l<=19	
Reflections collected	19537	
Independent reflections	13146 [R(int) = 0.0406]	
Completeness to theta = 27.53°	95.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8839 and 0.7859	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	13146 / 1 / 842	
Goodness-of-fit on F^2	1.011	
Final R indices [I>2sigma(I)]	R1 = 0.0517, wR2 = 0.1042	
R indices (all data)	R1 = 0.0731, wR2 = 0.1115	
Absolute structure parameter	-0.01(2)	
Largest diff. peak and hole	1.330 and -0.792 e.Å^{-3}	

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[8] Barbour, L. J. "X-Seed - A software tool for supramolecular crystallography" *J. Supramol. Chem.* **2001**, *1*, 189-191.

[9] Sheldrick, G. SHELX-97 Programs for Solving and Refining Crystal Structures, Institüt für Anorganische Chemie der Universität, Tammanstrasse 4, D-3400 Gottingen, Germany (1997).

Table 4.2 - Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Pd(1)	3541(1)	2120(1)	6231(1)	19(1)
Pd(12)	6286(1)	2282(1)	1809(1)	21(1)
Fe(1)	6843(1)	3499(1)	6235(1)	21(1)
Fe(12)	3375(1)	1564(1)	2977(1)	25(1)
Cl(22)	8414(2)	1767(1)	2143(1)	30(1)
Cl(2)	1347(2)	2594(1)	6001(1)	30(1)
P(1)	4092(2)	2909(1)	7051(1)	20(1)
P(12)	6187(2)	2674(1)	2865(1)	21(1)
P(2)	6964(2)	1830(1)	6723(1)	21(1)
Cl(1)	3070(2)	1264(1)	5370(1)	33(1)
Cl(12)	6317(2)	1862(1)	691(1)	40(1)
P(22)	2962(2)	2800(1)	1772(1)	24(1)
O(2)	5453(4)	1622(2)	6543(2)	27(1)
O(22)	4389(4)	2822(2)	1519(2)	26(1)
Cl(2S)	10064(3)	-9(2)	874(1)	74(1)
Cl(1S)	11363(6)	941(2)	23(3)	158(2)
C(16)	6488(7)	3858(3)	7183(3)	24(2)
C(14)	7074(6)	2722(3)	6939(3)	20(1)
C(23)	6689(7)	3037(4)	5277(3)	26(2)
O(12)	1801(4)	2322(2)	1356(2)	26(1)
C(24)	4066(7)	2492(3)	7870(3)	23(2)
C(27)	4106(8)	1777(4)	9115(4)	40(2)
O(1)	8001(4)	1704(2)	6159(2)	29(1)
C(42)	540(7)	3392(4)	1464(4)	33(2)
C(5)	9158(7)	1203(4)	6386(4)	34(2)
C(312)	6484(7)	4004(4)	2318(4)	29(2)
C(242)	7440(6)	2346(4)	3566(3)	24(1)
C(262)	9570(7)	2468(4)	4334(3)	30(2)
C(30)	3133(6)	3723(3)	7053(4)	23(2)
C(152)	4444(6)	2487(3)	3102(3)	19(1)
C(33)	1724(8)	4994(4)	7028(5)	42(2)
C(11)	7476(7)	201(4)	6014(4)	39(2)
C(162)	4057(6)	2261(4)	3754(3)	25(1)
N(32)	2073(6)	3544(3)	1651(3)	29(1)
C(12)	9988(8)	607(4)	7539(4)	41(2)
C(302)	6311(7)	3625(3)	2901(3)	25(2)
N(3)	7795(5)	1325(3)	7315(3)	25(1)
C(232)	3369(8)	921(4)	2144(4)	35(2)
C(22)	7863(8)	3505(4)	5370(4)	31(2)
C(62)	590(7)	2823(4)	289(4)	29(2)
C(222)	2162(8)	803(4)	2479(5)	44(2)
C(292)	7245(7)	1688(4)	3825(3)	27(2)
C(18)	8358(7)	3144(4)	6992(3)	24(2)
C(4)	9269(7)	1230(4)	7172(4)	32(2)
C(31)	2708(7)	4064(4)	6440(4)	31(2)
C(26)	5047(7)	2300(5)	9041(3)	38(2)
C(202)	4142(8)	593(4)	3235(4)	42(2)
C(21)	7344(8)	4173(4)	5491(4)	35(2)
C(35)	2845(7)	4023(4)	7670(4)	34(2)
C(34)	2143(8)	4669(4)	7651(4)	45(2)
C(6)	8813(7)	500(4)	6070(4)	29(2)
C(25)	5035(7)	2668(4)	8429(3)	33(2)
C(15)	5930(6)	3176(3)	7057(3)	21(1)

C(122)	-251(8)	3989(4)	1101(4)	47(2)
C(182)	1986(7)	2371(4)	3020(3)	26(2)
C(132)	2474(8)	4132(4)	2108(4)	42(2)
C(172)	2587(7)	2179(4)	3699(3)	28(2)
C(29)	3100(7)	1958(4)	7943(3)	30(2)
C(19)	5436(7)	3415(4)	5355(3)	27(2)
C(252)	8597(6)	2747(4)	3810(3)	28(2)
C(28)	3101(8)	1596(4)	8558(4)	38(2)
C(52)	539(7)	2720(4)	1036(4)	30(2)
C(332)	6267(7)	5066(4)	2942(4)	37(2)
C(32)	2012(7)	4708(4)	6437(5)	39(2)
C(192)	4601(8)	791(4)	2614(4)	38(2)
C(3S)	5316(13)	9(6)	529(6)	82(4)
C(1S)	10085(13)	849(6)	557(6)	86(4)
C(20)	5842(8)	4125(4)	5478(3)	32(2)
C(322)	6471(8)	4719(4)	2352(4)	35(2)
C(92)	522(9)	3099(4)	-1119(4)	43(2)
C(82)	1761(9)	3159(5)	-681(4)	51(2)
C(282)	8206(7)	1428(4)	4348(3)	31(2)
C(17)	7982(7)	3828(4)	7139(3)	28(2)
C(72)	1794(8)	3008(4)	5(4)	36(2)
C(342)	6113(7)	4691(4)	3519(4)	33(2)
C(10)	7268(9)	-466(4)	5745(5)	49(2)
C(9)	8343(9)	-835(4)	5536(4)	42(2)
C(8)	9700(9)	-538(4)	5592(4)	46(2)
C(13)	7445(9)	1326(5)	8015(4)	47(2)
C(102)	-693(8)	2885(5)	-845(4)	50(2)
C(352)	6137(6)	3971(3)	3512(4)	25(2)
C(212)	2636(9)	601(4)	3160(5)	49(2)
C(7)	9910(8)	124(4)	5841(4)	40(2)
C(272)	9385(8)	1815(4)	4602(4)	34(2)
C(142)	3144(7)	2544(3)	2639(3)	27(2)
C(4S)	4262(12)	-354(6)	792(6)	75(3)
C(7S)	5163(17)	-802(8)	-418(6)	100(5)
C(6S)	4136(17)	-1142(8)	-137(9)	113(6)
C(5S)	3650(14)	-888(7)	420(7)	95(4)
C(112)	-657(7)	2745(4)	-161(4)	40(2)
C(2S)	5756(12)	-216(6)	-90(6)	70(3)
C(8S)	6800(19)	123(9)	-377(8)	110(5)
N(1S)	7773(18)	353(10)	-649(8)	170(7)

Table 4.3 - Bond lengths [Å] and angles [°] for **Pd-90**.

Pd(1)-Cl(1)	2.3637(19)
Pd(1)-Cl(2)	2.2617(18)
Pd(1)-P(1)	2.2287(18)
Pd(1)-O(2)	2.072(4)
Pd(12)-O(22)	2.091(4)
Pd(12)-Cl(12)	2.3470(19)
Pd(12)-Cl(22)	2.2675(18)
Pd(12)-P(12)	2.2240(17)
Fe(1)-C(15)	2.023(6)
Fe(1)-C(16)	2.055(6)
Fe(1)-C(17)	2.064(6)
Fe(1)-C(14)	2.032(6)
Fe(1)-C(22)	2.056(8)
Fe(1)-C(23)	2.073(6)
Fe(1)-C(19)	2.058(6)
Fe(1)-C(18)	2.055(6)
Fe(1)-C(21)	2.052(8)
Fe(12)-C(162)	2.075(7)
Fe(12)-C(172)	2.056(7)
Fe(12)-C(222)	2.036(8)
Fe(12)-C(232)	2.053(8)
Fe(12)-C(202)	2.043(8)
Fe(12)-C(182)	2.041(7)
Fe(12)-C(192)	2.065(8)
Fe(12)-C(152)	2.042(6)
Fe(12)-C(212)	2.026(8)
Fe(12)-C(142)	2.001(6)
Cl(1S)-C(1S)	1.705(13)
Cl(2S)-C(1S)	1.764(12)
P(1)-C(24)	1.804(6)
P(1)-C(30)	1.809(6)

Fe(1)-C(20)	2.053(7)
P(1)-C(15)	1.811(6)
P(2)-O(1)	1.586(4)
P(2)-O(2)	1.484(4)
P(2)-C(14)	1.767(6)
P(2)-N(3)	1.642(6)
P(12)-C(152)	1.803(6)
P(12)-C(242)	1.817(6)
P(12)-C(302)	1.833(6)
P(22)-O(12)	1.581(4)
P(22)-O(22)	1.495(4)
P(22)-N(32)	1.661(6)
P(22)-C(142)	1.765(6)
O(1)-C(5)	1.485(8)
O(12)-C(52)	1.491(8)
N(3)-C(13)	1.455(10)
N(3)-C(4)	1.467(8)
N(32)-C(132)	1.465(10)
N(32)-C(42)	1.481(9)
N(1S)-C(8S)	1.20(2)
C(4)-C(12)	1.516(11)
C(4)-C(5)	1.538(11)
C(5)-C(6)	1.506(11)
C(6)-C(7)	1.384(10)
C(6)-C(11)	1.381(10)
C(7)-C(8)	1.369(11)
C(8)-C(9)	1.397(12)
C(9)-C(10)	1.345(12)
C(10)-C(11)	1.392(11)
C(14)-C(15)	1.431(8)
C(14)-C(18)	1.454(9)
C(15)-C(16)	1.424(8)
C(16)-C(17)	1.428(9)
C(17)-C(18)	1.401(11)
C(19)-C(20)	1.430(11)
C(19)-C(23)	1.414(10)
C(20)-C(21)	1.421(11)
C(21)-C(22)	1.405(11)
C(22)-C(23)	1.424(10)
C(24)-C(25)	1.385(9)
C(24)-C(29)	1.393(10)
C(25)-C(26)	1.395(9)
C(26)-C(27)	1.362(11)
C(27)-C(28)	1.404(11)
C(28)-C(29)	1.396(10)
C(30)-C(31)	1.389(11)
C(30)-C(35)	1.400(11)
C(31)-C(32)	1.402(11)
C(32)-C(33)	1.344(13)
C(33)-C(34)	1.390(12)
C(34)-C(35)	1.406(11)
C(4)-H(4)	1.0000
C(5)-H(5)	1.0000
C(7)-H(7)	0.9500
C(8)-H(8)	0.9500
C(9)-H(9)	0.9500
C(10)-H(10)	0.9500
C(11)-H(11)	0.9500
C(12)-H(12A)	0.9800
C(12)-H(12C)	0.9800
C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800
C(13)-H(13A)	0.9800
C(16)-H(16)	0.9500
C(17)-H(17)	0.9500
C(18)-H(18)	0.9500
C(19)-H(19)	0.9500
C(20)-H(20)	0.9500
C(21)-H(21)	0.9500
C(22)-H(22)	0.9500
C(23)-H(23)	0.9500
C(25)-H(25)	0.9500
C(26)-H(26)	0.9500
C(27)-H(27)	0.9500
C(28)-H(28)	0.9500
C(29)-H(29)	0.9500
C(31)-H(31)	0.9500
C(32)-H(32)	0.9500
C(33)-H(33)	0.9500
C(34)-H(34)	0.9500
C(35)-H(35)	0.9500
C(42)-C(52)	1.542(11)
C(42)-C(122)	1.502(11)
C(52)-C(62)	1.490(11)
C(62)-C(112)	1.394(10)
C(62)-C(72)	1.375(10)
C(72)-C(82)	1.377(11)
C(82)-C(92)	1.373(12)
C(92)-C(102)	1.390(11)
C(102)-C(112)	1.369(11)
C(42)-H(42)	1.0000
C(142)-C(182)	1.440(9)
C(142)-C(152)	1.443(9)
C(152)-C(162)	1.443(8)
C(52)-H(52)	1.0000
C(162)-C(172)	1.390(9)
C(172)-C(182)	1.435(9)
C(72)-H(72)	0.9500
C(82)-H(82)	0.9500
C(92)-H(92)	0.9500
C(192)-C(202)	1.398(11)
C(192)-C(232)	1.419(11)
C(102)-H(102)	0.9500
C(202)-C(212)	1.414(12)
C(2S)-C(3S)	1.403(17)
C(2S)-C(7S)	1.383(19)
C(2S)-C(8S)	1.36(2)
C(3S)-C(4S)	1.369(17)
C(4S)-C(5S)	1.350(18)
C(5S)-C(6S)	1.33(2)
C(6S)-C(7S)	1.34(2)
C(112)-H(112)	0.9500
C(212)-C(222)	1.415(14)
C(122)-H(14C)	0.9800
C(122)-H(14B)	0.9800
C(222)-C(232)	1.405(11)
C(122)-H(14A)	0.9800
C(132)-H(15C)	0.9800
C(132)-H(15A)	0.9800
C(132)-H(15B)	0.9800

C(12)-H(12B)	0.9800
C(242)-C(252)	1.376(9)
C(242)-C(292)	1.384(11)
C(252)-C(262)	1.402(9)
C(162)-H(182)	0.9500
C(262)-C(272)	1.381(11)
C(272)-C(282)	1.382(10)
C(172)-H(192)	0.9500
C(182)-H(202)	0.9500
C(282)-C(292)	1.381(9)
C(192)-H(242)	0.9500
C(202)-H(252)	0.9500
C(302)-C(352)	1.401(9)
C(302)-C(312)	1.385(10)
C(3S)-H(3S)	0.9500
C(4S)-H(4S)	0.9500
C(5S)-H(5S)	0.9500
C(6S)-H(6S)	0.9500
C(7S)-H(7S)	0.9500
C(312)-C(322)	1.376(11)
C(212)-H(212)	0.9500
C(222)-H(222)	0.9500
C(322)-C(332)	1.373(11)
C(232)-H(232)	0.9500
C(332)-C(342)	1.368(11)
C(342)-C(352)	1.384(10)
C(252)-H(372)	0.9500
C(262)-H(362)	0.9500
C(272)-H(352)	0.9500
C(282)-H(342)	0.9500
C(292)-H(332)	0.9500
C(312)-H(272)	0.9500
C(322)-H(282)	0.9500
C(332)-H(292)	0.9500
C(342)-H(302)	0.9500
C(352)-H(312)	0.9500
C(1S)-H(1S1)	0.9900
C(1S)-H(1S2)	0.9900

Cl(1)-Pd(1)-Cl(2)	92.77(7)
Cl(1)-Pd(1)-P(1)	177.27(7)
Cl(1)-Pd(1)-O(2)	88.44(12)
Cl(2)-Pd(1)-P(1)	89.94(7)
Cl(2)-Pd(1)-O(2)	172.82(12)
P(1)-Pd(1)-O(2)	88.91(12)
P(12)-Pd(12)-O(22)	87.41(12)
Cl(12)-Pd(12)-P(12)	178.32(7)
Cl(12)-Pd(12)-O(22)	91.35(12)
Cl(12)-Pd(12)-Cl(22)	90.53(7)
Cl(22)-Pd(12)-O(22)	176.10(12)
Cl(22)-Pd(12)-P(12)	90.78(7)
C(14)-Fe(1)-C(17)	68.6(3)
C(14)-Fe(1)-C(16)	69.1(2)
C(14)-Fe(1)-C(23)	107.1(3)
C(15)-Fe(1)-C(16)	40.9(2)
C(14)-Fe(1)-C(18)	41.7(3)
C(14)-Fe(1)-C(19)	121.4(3)
C(14)-Fe(1)-C(20)	158.0(3)
C(14)-Fe(1)-C(21)	159.3(3)
C(14)-Fe(1)-C(22)	123.1(3)

C(15)-Fe(1)-C(23)	127.3(3)
C(16)-Fe(1)-C(17)	40.6(3)
C(16)-Fe(1)-C(18)	68.3(3)
C(16)-Fe(1)-C(19)	129.1(3)
C(16)-Fe(1)-C(20)	110.5(3)
C(16)-Fe(1)-C(21)	120.9(3)
C(16)-Fe(1)-C(22)	153.5(3)
C(16)-Fe(1)-C(23)	165.6(3)
C(17)-Fe(1)-C(18)	39.8(3)
C(17)-Fe(1)-C(19)	165.0(3)
C(17)-Fe(1)-C(20)	126.3(3)
C(17)-Fe(1)-C(21)	106.3(3)
C(17)-Fe(1)-C(22)	117.6(3)
C(17)-Fe(1)-C(23)	152.5(3)
C(18)-Fe(1)-C(19)	155.0(3)
C(18)-Fe(1)-C(20)	160.1(3)
C(18)-Fe(1)-C(21)	121.7(3)
C(18)-Fe(1)-C(22)	104.2(3)
C(18)-Fe(1)-C(23)	118.9(3)
C(19)-Fe(1)-C(20)	40.7(3)
C(19)-Fe(1)-C(21)	68.4(3)
C(19)-Fe(1)-C(22)	68.0(3)
C(19)-Fe(1)-C(23)	40.1(3)
C(20)-Fe(1)-C(21)	40.5(3)
C(20)-Fe(1)-C(22)	67.6(3)
C(20)-Fe(1)-C(23)	67.5(3)
C(21)-Fe(1)-C(22)	40.0(3)
C(21)-Fe(1)-C(23)	67.6(3)
C(22)-Fe(1)-C(23)	40.3(3)
C(15)-Fe(1)-C(20)	123.8(3)
C(15)-Fe(1)-C(21)	157.3(3)
C(15)-Fe(1)-C(22)	162.3(3)
C(15)-Fe(1)-C(17)	68.5(3)
C(15)-Fe(1)-C(18)	69.2(2)
C(15)-Fe(1)-C(19)	110.7(3)
C(182)-Fe(12)-C(212)	116.7(3)
C(182)-Fe(12)-C(222)	103.8(3)
C(182)-Fe(12)-C(232)	123.4(3)
C(192)-Fe(12)-C(232)	40.3(3)
C(202)-Fe(12)-C(212)	40.7(3)
C(202)-Fe(12)-C(222)	68.0(3)
C(202)-Fe(12)-C(232)	67.4(3)
C(192)-Fe(12)-C(202)	39.8(3)
C(192)-Fe(12)-C(212)	68.0(3)
C(192)-Fe(12)-C(222)	67.9(3)
C(152)-Fe(12)-C(202)	127.5(3)
C(152)-Fe(12)-C(212)	161.6(3)
C(152)-Fe(12)-C(222)	157.5(3)
C(152)-Fe(12)-C(232)	124.9(3)
C(162)-Fe(12)-C(172)	39.3(2)
C(162)-Fe(12)-C(182)	67.9(3)
C(162)-Fe(12)-C(192)	125.6(3)
C(162)-Fe(12)-C(202)	109.7(3)
C(162)-Fe(12)-C(212)	122.8(3)
C(162)-Fe(12)-C(222)	157.7(3)
C(162)-Fe(12)-C(232)	161.3(3)
C(172)-Fe(12)-C(182)	41.0(2)
C(212)-Fe(12)-C(222)	40.8(4)
C(212)-Fe(12)-C(232)	67.9(3)
C(222)-Fe(12)-C(232)	40.2(3)

C(14)-Fe(1)-C(15)	41.3(2)
C(172)-Fe(12)-C(232)	158.7(3)
C(182)-Fe(12)-C(192)	162.2(3)
C(182)-Fe(12)-C(202)	153.5(3)
C(142)-Fe(12)-C(152)	41.8(2)
C(142)-Fe(12)-C(162)	69.4(3)
C(142)-Fe(12)-C(172)	69.8(3)
C(142)-Fe(12)-C(182)	41.7(3)
C(142)-Fe(12)-C(192)	127.2(3)
C(142)-Fe(12)-C(202)	164.4(3)
C(142)-Fe(12)-C(212)	153.2(3)
C(142)-Fe(12)-C(222)	118.9(3)
C(142)-Fe(12)-C(232)	108.1(3)
C(152)-Fe(12)-C(162)	41.0(2)
C(152)-Fe(12)-C(172)	68.5(3)
C(152)-Fe(12)-C(182)	69.3(3)
C(152)-Fe(12)-C(192)	112.1(3)
C(172)-Fe(12)-C(222)	121.0(3)
C(172)-Fe(12)-C(212)	103.9(3)
C(172)-Fe(12)-C(192)	156.8(3)
C(172)-Fe(12)-C(202)	120.1(3)
Pd(1)-P(1)-C(15)	109.8(2)
Pd(1)-P(1)-C(24)	108.5(2)
Pd(1)-P(1)-C(30)	121.2(2)
C(15)-P(1)-C(24)	103.7(3)
C(15)-P(1)-C(30)	103.7(3)
C(24)-P(1)-C(30)	108.7(3)
O(1)-P(2)-N(3)	97.1(2)
O(2)-P(2)-C(14)	110.2(3)
O(1)-P(2)-C(14)	107.0(3)
O(2)-P(2)-N(3)	112.0(3)
O(1)-P(2)-O(2)	116.9(2)
N(3)-P(2)-C(14)	113.2(3)
Pd(12)-P(12)-C(152)	108.5(2)
Pd(12)-P(12)-C(242)	119.6(2)
C(152)-P(12)-C(242)	105.5(3)
C(152)-P(12)-C(302)	104.2(3)
Pd(12)-P(12)-C(302)	111.3(2)
C(242)-P(12)-C(302)	106.5(3)
O(12)-P(22)-N(32)	96.8(3)
O(12)-P(22)-C(142)	108.6(3)
O(12)-P(22)-O(22)	116.3(2)
O(22)-P(22)-C(142)	110.1(3)
N(32)-P(22)-C(142)	111.5(3)
O(22)-P(22)-N(32)	113.0(3)
P(2)-O(1)-C(5)	112.6(4)
Pd(1)-O(2)-P(2)	136.6(2)
P(22)-O(12)-C(52)	113.0(4)
Pd(12)-O(22)-P(22)	132.4(2)
C(4)-N(3)-C(13)	120.9(6)
P(2)-N(3)-C(13)	121.8(5)
P(2)-N(3)-C(4)	108.8(5)
C(42)-N(32)-C(132)	118.5(6)
P(22)-N(32)-C(42)	109.2(5)
P(22)-N(32)-C(132)	119.2(5)
C(5)-C(4)-C(12)	115.1(6)
N(3)-C(4)-C(12)	112.9(6)
N(3)-C(4)-C(5)	104.3(6)
O(1)-C(5)-C(4)	103.8(5)
C(4)-C(5)-C(6)	115.5(6)
C(5)-C(6)-C(7)	118.0(6)
C(7)-C(6)-C(11)	118.2(7)
C(5)-C(6)-C(11)	123.8(6)
C(6)-C(7)-C(8)	121.3(7)
C(7)-C(8)-C(9)	120.0(7)
C(8)-C(9)-C(10)	118.8(7)
C(9)-C(10)-C(11)	121.7(8)
C(6)-C(11)-C(10)	120.0(7)
P(2)-C(14)-C(15)	127.4(4)
Fe(1)-C(14)-C(18)	70.0(4)
Fe(1)-C(14)-C(15)	69.0(3)
P(2)-C(14)-C(18)	125.7(5)
C(15)-C(14)-C(18)	106.9(5)
Fe(1)-C(14)-P(2)	123.5(3)
Fe(1)-C(15)-P(1)	125.8(3)
C(14)-C(15)-C(16)	108.6(5)
Fe(1)-C(15)-C(16)	70.8(3)
P(1)-C(15)-C(14)	124.8(4)
Fe(1)-C(15)-C(14)	69.7(3)
P(1)-C(15)-C(16)	126.7(5)
Fe(1)-C(16)-C(15)	68.4(3)
Fe(1)-C(16)-C(17)	70.1(4)
C(15)-C(16)-C(17)	107.5(5)
C(16)-C(17)-C(18)	109.2(6)
Fe(1)-C(17)-C(16)	69.4(3)
Fe(1)-C(17)-C(18)	69.8(4)
Fe(1)-C(18)-C(17)	70.5(4)
C(14)-C(18)-C(17)	107.9(6)
Fe(1)-C(18)-C(14)	68.3(3)
Fe(1)-C(19)-C(20)	69.5(4)
Fe(1)-C(19)-C(23)	70.6(4)
C(20)-C(19)-C(23)	107.3(6)
Fe(1)-C(20)-C(19)	69.8(4)
C(19)-C(20)-C(21)	108.2(6)
Fe(1)-C(20)-C(21)	69.7(4)
Fe(1)-C(21)-C(20)	69.8(4)
Fe(1)-C(21)-C(22)	70.1(4)
C(20)-C(21)-C(22)	107.9(7)
C(21)-C(22)-C(23)	108.4(7)
Fe(1)-C(22)-C(23)	70.5(4)
Fe(1)-C(22)-C(21)	69.9(4)
Fe(1)-C(23)-C(22)	69.2(4)
C(19)-C(23)-C(22)	108.2(7)
Fe(1)-C(23)-C(19)	69.4(4)
P(1)-C(24)-C(25)	121.4(5)
P(1)-C(24)-C(29)	120.0(5)
C(25)-C(24)-C(29)	118.5(6)
C(24)-C(25)-C(26)	119.8(7)
C(25)-C(26)-C(27)	122.0(6)
C(26)-C(27)-C(28)	119.2(7)
C(27)-C(28)-C(29)	118.8(7)
C(24)-C(29)-C(28)	121.7(6)
P(1)-C(30)-C(31)	119.9(6)
P(1)-C(30)-C(35)	120.6(6)
C(31)-C(30)-C(35)	119.5(6)
C(30)-C(31)-C(32)	120.4(7)
C(31)-C(32)-C(33)	120.1(8)
C(32)-C(33)-C(34)	120.9(7)
C(33)-C(34)-C(35)	120.2(7)
C(30)-C(35)-C(34)	118.8(7)

O(1)-C(5)-C(6)	110.0(5)
N(3)-C(4)-H(4)	108.00
C(5)-C(4)-H(4)	108.00
C(12)-C(4)-H(4)	108.00
O(1)-C(5)-H(5)	109.00
C(6)-C(5)-H(5)	109.00
C(4)-C(5)-H(5)	109.00
C(6)-C(7)-H(7)	119.00
C(8)-C(7)-H(7)	119.00
C(9)-C(8)-H(8)	120.00
C(7)-C(8)-H(8)	120.00
C(8)-C(9)-H(9)	121.00
C(10)-C(9)-H(9)	121.00
C(11)-C(10)-H(10)	119.00
C(9)-C(10)-H(10)	119.00
C(6)-C(11)-H(11)	120.00
C(10)-C(11)-H(11)	120.00
C(4)-C(12)-H(12B)	110.00
C(4)-C(12)-H(12C)	110.00
C(4)-C(12)-H(12A)	110.00
H(12A)-C(12)-H(12C)	109.00
H(12B)-C(12)-H(12C)	109.00
H(12A)-C(12)-H(12B)	109.00
N(3)-C(13)-H(13C)	110.00
H(13A)-C(13)-H(13B)	109.00
N(3)-C(13)-H(13A)	109.00
N(3)-C(13)-H(13B)	110.00
H(13A)-C(13)-H(13C)	109.00
H(13B)-C(13)-H(13C)	110.00
Fe(1)-C(16)-H(16)	127.00
C(17)-C(16)-H(16)	126.00
C(15)-C(16)-H(16)	126.00
C(16)-C(17)-H(17)	125.00
C(18)-C(17)-H(17)	125.00
Fe(1)-C(17)-H(17)	127.00
C(14)-C(18)-H(18)	126.00
C(17)-C(18)-H(18)	126.00
Fe(1)-C(18)-H(18)	127.00
C(23)-C(19)-H(19)	126.00
Fe(1)-C(19)-H(19)	125.00
C(20)-C(19)-H(19)	126.00
Fe(1)-C(20)-H(20)	126.00
C(19)-C(20)-H(20)	126.00
C(21)-C(20)-H(20)	126.00
C(22)-C(21)-H(21)	126.00
Fe(1)-C(21)-H(21)	126.00
C(20)-C(21)-H(21)	126.00
C(23)-C(22)-H(22)	126.00
C(21)-C(22)-H(22)	126.00
Fe(1)-C(22)-H(22)	125.00
Fe(1)-C(23)-H(23)	127.00
C(22)-C(23)-H(23)	126.00
C(19)-C(23)-H(23)	126.00
C(24)-C(25)-H(25)	120.00
C(26)-C(25)-H(25)	120.00
C(27)-C(26)-H(26)	119.00
C(25)-C(26)-H(26)	119.00
C(26)-C(27)-H(27)	120.00
C(28)-C(27)-H(27)	120.00
C(27)-C(28)-H(28)	121.00

C(28)-C(29)-H(29)	119.00
C(24)-C(29)-H(29)	119.00
C(32)-C(31)-H(31)	120.00
C(30)-C(31)-H(31)	120.00
C(31)-C(32)-H(32)	120.00
C(33)-C(32)-H(32)	120.00
C(32)-C(33)-H(33)	120.00
C(34)-C(33)-H(33)	120.00
C(35)-C(34)-H(34)	120.00
C(33)-C(34)-H(34)	120.00
C(34)-C(35)-H(35)	121.00
C(30)-C(35)-H(35)	121.00
N(32)-C(42)-C(52)	103.7(5)
N(32)-C(42)-C(122)	112.6(6)
C(52)-C(42)-C(122)	114.4(6)
O(12)-C(52)-C(42)	104.6(5)
O(12)-C(52)-C(62)	111.4(5)
C(42)-C(52)-C(62)	115.5(6)
C(52)-C(62)-C(72)	124.3(7)
C(52)-C(62)-C(112)	119.1(6)
C(72)-C(62)-C(112)	116.6(7)
C(62)-C(72)-C(82)	122.1(7)
C(72)-C(82)-C(92)	120.9(8)
C(82)-C(92)-C(102)	117.7(7)
C(92)-C(102)-C(112)	121.1(7)
C(62)-C(112)-C(102)	121.4(7)
Fe(12)-C(142)-P(22)	125.3(3)
Fe(12)-C(142)-C(152)	70.6(3)
Fe(12)-C(142)-C(182)	70.6(4)
P(22)-C(142)-C(152)	127.4(5)
P(22)-C(142)-C(182)	125.3(5)
C(152)-C(142)-C(182)	107.3(5)
N(32)-C(42)-H(42)	109.00
C(52)-C(42)-H(42)	109.00
C(122)-C(42)-H(42)	109.00
P(12)-C(152)-C(142)	123.9(4)
P(12)-C(152)-C(162)	128.9(4)
C(142)-C(152)-C(162)	107.2(5)
C(62)-C(52)-H(52)	108.00
Fe(12)-C(152)-C(162)	70.7(4)
Fe(12)-C(152)-P(12)	126.7(3)
Fe(12)-C(152)-C(142)	67.6(3)
O(12)-C(52)-H(52)	108.00
C(42)-C(52)-H(52)	108.00
Fe(12)-C(162)-C(172)	69.6(4)
Fe(12)-C(162)-C(152)	68.3(3)
C(152)-C(162)-C(172)	108.9(5)
C(62)-C(72)-H(72)	119.00
Fe(12)-C(172)-C(162)	71.1(4)
Fe(12)-C(172)-C(182)	69.0(4)
C(162)-C(172)-C(182)	108.8(6)
C(82)-C(72)-H(72)	119.00
Fe(12)-C(182)-C(172)	70.1(4)
C(142)-C(182)-C(172)	107.7(6)
Fe(12)-C(182)-C(142)	67.7(4)
C(72)-C(82)-H(82)	120.00
C(92)-C(82)-H(82)	119.00
C(82)-C(92)-H(92)	121.00
C(102)-C(92)-H(92)	121.00
C(202)-C(192)-C(232)	107.4(7)

C(29)-C(28)-H(28)	121.00
Fe(12)-C(192)-C(202)	69.3(4)
Fe(12)-C(192)-C(232)	69.4(4)
C(92)-C(102)-H(102)	119.00
C(112)-C(102)-H(102)	119.00
C(192)-C(202)-C(212)	108.8(7)
Fe(12)-C(202)-C(192)	70.9(5)
Fe(12)-C(202)-C(212)	69.0(4)
C(7S)-C(2S)-C(8S)	118.0(12)
C(3S)-C(2S)-C(8S)	121.3(12)
C(3S)-C(2S)-C(7S)	120.7(11)
C(2S)-C(3S)-C(4S)	118.6(11)
C(3S)-C(4S)-C(5S)	117.8(11)
C(4S)-C(5S)-C(6S)	123.8(13)
C(5S)-C(6S)-C(7S)	120.0(14)
C(2S)-C(7S)-C(6S)	118.5(13)
N(1S)-C(8S)-C(2S)	173.0(19)
Fe(12)-C(212)-C(202)	70.3(5)
Fe(12)-C(212)-C(222)	70.0(5)
C(202)-C(212)-C(222)	107.5(7)
C(62)-C(112)-H(112)	119.00
C(102)-C(112)-H(112)	119.00
H(14A)-C(122)-H(14B)	110.00
H(14A)-C(122)-H(14C)	109.00
H(14B)-C(122)-H(14C)	109.00
C(42)-C(122)-H(14C)	109.00
C(42)-C(122)-H(14A)	109.00
Fe(12)-C(222)-C(212)	69.3(5)
C(212)-C(222)-C(232)	107.9(7)
Fe(12)-C(222)-C(232)	70.6(5)
C(42)-C(122)-H(14B)	109.00
N(32)-C(132)-H(15B)	110.00
Fe(12)-C(232)-C(192)	70.3(4)
Fe(12)-C(232)-C(222)	69.3(5)
N(32)-C(132)-H(15A)	109.00
H(15A)-C(132)-H(15B)	109.00
H(15A)-C(132)-H(15C)	109.00
N(32)-C(132)-H(15C)	110.00
H(15B)-C(132)-H(15C)	110.00
C(192)-C(232)-C(222)	108.4(7)
P(12)-C(242)-C(252)	119.2(5)
P(12)-C(242)-C(292)	119.5(5)
C(252)-C(242)-C(292)	121.3(6)
C(242)-C(252)-C(262)	117.7(7)
C(172)-C(162)-H(182)	126.00
Fe(12)-C(162)-H(182)	128.00
C(152)-C(162)-H(182)	125.00
C(252)-C(262)-C(272)	121.7(7)
C(262)-C(272)-C(282)	119.0(7)
Fe(12)-C(172)-H(192)	126.00
C(162)-C(172)-H(192)	126.00
C(182)-C(172)-H(192)	126.00
Fe(12)-C(182)-H(202)	128.00
C(272)-C(282)-C(292)	120.2(7)
C(172)-C(182)-H(202)	126.00
C(142)-C(182)-H(202)	126.00
C(202)-C(192)-H(242)	126.00
C(232)-C(192)-H(242)	126.00
C(242)-C(292)-C(282)	120.0(6)
Fe(12)-C(192)-H(242)	127.00
P(12)-C(302)-C(312)	120.4(5)
C(312)-C(302)-C(352)	119.9(6)
C(212)-C(202)-H(252)	126.00
Fe(12)-C(202)-H(252)	126.00
P(12)-C(302)-C(352)	119.5(5)
C(192)-C(202)-H(252)	126.00
C(4S)-C(3S)-H(3S)	121.00
C(2S)-C(3S)-H(3S)	121.00
C(3S)-C(4S)-H(4S)	121.00
C(5S)-C(4S)-H(4S)	121.00
C(6S)-C(5S)-H(5S)	118.00
C(4S)-C(5S)-H(5S)	118.00
C(7S)-C(6S)-H(6S)	120.00
C(5S)-C(6S)-H(6S)	120.00
C(6S)-C(7S)-H(7S)	121.00
C(2S)-C(7S)-H(7S)	121.00
C(202)-C(212)-H(212)	126.00
Fe(12)-C(212)-H(212)	125.00
C(302)-C(312)-C(322)	118.8(7)
C(222)-C(212)-H(212)	126.00
C(212)-C(222)-H(222)	126.00
C(312)-C(322)-C(332)	122.0(7)
C(232)-C(222)-H(222)	126.00
Fe(12)-C(222)-H(222)	126.00
C(222)-C(232)-H(232)	126.00
C(322)-C(332)-C(342)	119.1(7)
C(192)-C(232)-H(232)	126.00
Fe(12)-C(232)-H(232)	126.00
C(332)-C(342)-C(352)	121.0(7)
C(242)-C(252)-H(372)	121.00
C(302)-C(352)-C(342)	119.1(7)
C(262)-C(252)-H(372)	121.00
C(252)-C(262)-H(362)	119.00
C(272)-C(262)-H(362)	119.00
C(282)-C(272)-H(352)	120.00
C(262)-C(272)-H(352)	121.00
C(272)-C(282)-H(342)	120.00
C(292)-C(282)-H(342)	120.00
C(282)-C(292)-H(332)	120.00
C(242)-C(292)-H(332)	120.00
Cl(1S)-C(1S)-Cl(2S)	110.8(7)
C(322)-C(312)-H(272)	120.00
C(302)-C(312)-H(272)	121.00
C(312)-C(322)-H(282)	119.00
C(332)-C(322)-H(282)	119.00
C(322)-C(332)-H(292)	120.00
C(342)-C(332)-H(292)	120.00
C(352)-C(342)-H(302)	120.00
C(332)-C(342)-H(302)	119.00
C(342)-C(352)-H(312)	120.00
C(302)-C(352)-H(312)	120.00
Cl(1S)-C(1S)-H(1S1)	109.00
Cl(1S)-C(1S)-H(1S2)	109.00
Cl(2S)-C(1S)-H(1S1)	109.00
Cl(2S)-C(1S)-H(1S2)	109.00
H(1S1)-C(1S)-H(1S2)	108.00