ENANTIOSELECTIVE CROSS COUPLING REACTIONS

A NEW ROUTE TO ENANTIOMERICALLY PURE α-ARYLPROPIONIC ACIDS

Henk van der Worp

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RIJKSUNIVERSITEIT GRONINGEN

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PROEFSCHRIFT

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HENDRIK VAN DER WORP

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te Hattem

Promotor: Prof. Dr. R.M. Kellogg

Ik wilde wijs worden en begrijpen waarom de mens zich dag en nacht aftobt en zich nooit rust gunt. Maar ik kwam tot de ontdekking dat de mens het handelen van God hier op aarde niet kan begrijpen. Hoe de mens zich ook inspant, hij komt er niet achter. Zelfs een wijs man kan

dat niet ook al zegt hij van wel.

Uit: de Bijbel, Prediker 8

Voorwoord

"Schrijven is als straten maken: op je knieën en achteruit kruipen", volgens de schrijver Harry Mulisch. Dit gaat zeker op voor romans, maar voor het schrijven van een proefschrift komt er nog meer om de straathoek kijken. Hoewel er maar één persoon op deze omslag staat vermeld, zijn er velen die, in welke vorm dan ook, een straatsteentje hebben bijgedragen, aangedragen, losgewrikt, verplaatst of aangedrukt. Of misschien hebben ze koffie aangereikt, interesse getoond, de zaak opgewaardeerd of gerelativeerd als dat nodig was, enzovoorts. Jullie waren onmisbaar tijdens de wegomlegging binnen het onderzoek. Ook tijdens een moeilijke periode, toen het op voorhand niet duidelijk was of ik ooit nog één steentje zou kunnen leggen, heb ik veel aan jullie gehad. Al de mensen die zich hierin voelen aangesproken wil ik van harte bedanken. Hoewel ik hierboven iedereen die heeft bijgedragen aan de totstandkoming van dit proefschrift bedankt heb, wil ik nadrukkelijk enkele personen met name noemen.

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hoofdvakonderzoek zijn in hoofdstuk 3 van dit proefschrift verwerkt.

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De unieke sfeer op het lab heb ik altijd zeer prettig gevonden. Mijn complexe associaties kregen een weerwoord of werden overtroffen. Organisch chemici blijken vaak hun experimentele handigheid om te kunnen zetten in gegoochel op vocabulair gebied. Ik betwijfel ernstig of ik deze specifieke humor, in deze mate en intensiteit, nog eens elders tegen zal komen. De collega's van de (tot Gebouw 14 verworden) A-vleugel in het bijzonder, maar ook de andere OMAC-kers, worden bedankt! Tijdens het schrijven heb ik met name veel gehad aan Bas Dros en Marc Veen, de laatste zeker niet alleen als regelmatige oppasser in huize Bekemaheerd.

Tenslotte wil ik in dit voorwoord mijn ouders bedanken voor de vele dingen die niet beschreven hoeven worden. De aanstekelijke inventiviteit die mijn vader bezat mag hier echter niet onvermeld blijven. Mijn drang om zulks op moleculair niveau voort te zetten vindt mede in hem zijn oorsprong. Het is duidelijk dat hij op de dag van de promotie extra zal worden gemist.

Henk

Contents

Chapter 1: Introduction

Chapter 2: Asymmetric Cross Coupling Reactions

Chapter 3: Ligands for Asymmetric Catalysed Cross Coupling Reactions

Chapter 4: Asymmetric Cross Coupling Reactions With An Improved Grignard Reagent Solution

Chapter 5: Organozinc Reagents And Asymmetric Cross Coupling Reactions

Chapter 6: Towards Enantioselective S_N2' Reactions

Samenvatting

Chapter 1

Introduction

1.1 Profen Drugs

Introduction

Ibuprofen [(+/-)2-(4-isobutylphenyl)propionic acid, 1.1], is one of the most commonly used anti-inflammatory agents. It is considered to be the prototype for the family of synthetic 2-arylpropionic acids, profens, a sub-class of the non-steroidal anti-inflammatory drugs (NSAIDs). In recent years, the profens have come to dominate this therapeutic class. Ibuprofen, for example, is used to treat arthritis, muscular strain, cephalalgia, etcetera.

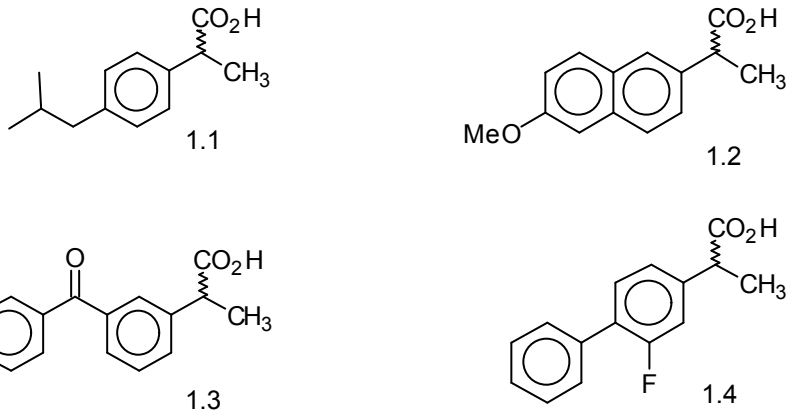


Figure 1.1

The profens have an asymmetric carbon centre attached to a carboxylic acid, a methyl, and an aryl group of varying structure. Some of the available profen drugs are depicted in Figure 1.1: ibuprofen (1.1), naproxen (1.2), ketoprofen (1.3), and flurbiprofen (1.4). Ibuprofen is distributed over the counter and naproxen belongs to the top-ten of drugs marketed worldwide in 1989.[1]

Profens as anti-inflammatory agents

NSAIDs exert their pharmacological and toxicological effects

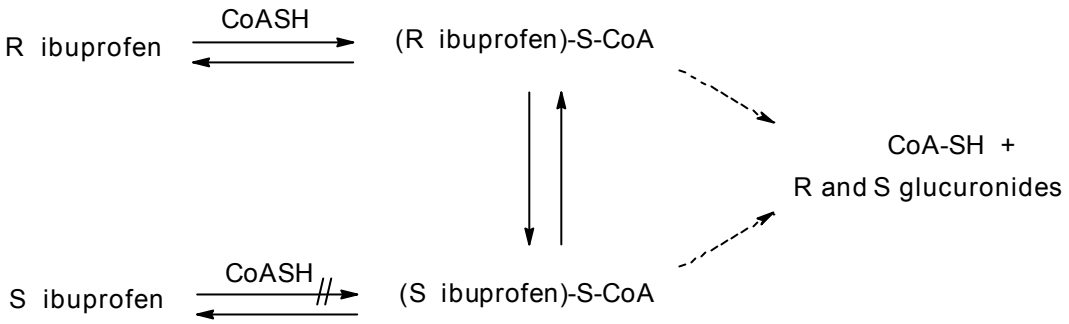
primarily by specifically inhibiting the binding of arachidonic acid[a] to the cyclo-oxygenase subunit of prostaglandin synthetase, thereby preventing the formation of various prostaglandins.[2,3] Effects on prostaglandin synthesis contribute to changes in inflammatory response. Evidence for this theory include a good rank-order correlation between inhibition of prostaglandin synthesis in vivo or ex vivo, and anti-inflammatory or analgesic effects in vivo.

In vivo behaviour of different profen drug enantiomers

The enantiomers of profens differ substantially in both their pharmacodynamics and pharmacokinetic properties.[4] It is generally recognized that the S profens are the enantiomers that inhibit prostaglandin synthetase. The absolute configuration, as well as the conformation of this isomer is important for the interactions with the cell receptors responsible for the therapeutic anti-inflammatory activity.[5] Prior to the early nineties the S enantiomer was regarded as the eutomer (the biological active enantiomer) of the profens and the R form as the distomer (the biological inactive enantiomer).[6] Observations in the late eighties made this dissimilarity less clear (vide infra). In practice, the profens are generally administered as racemic mixture.[b] In vivo, however, some of the profens can undergo, to a certain extent, a unidirectional inversion from the R to the S form, leading to an enantiomeric excess of the S form when a racemate of the drug is administered. This unique process was supposed to enhance the effectiveness of profen racemates as chiral drugs.

[a] $CH_3(CH_2)_3(CH_2{-}CH{=}CH)_4(CH_2)_3CO_2H$

[b] Except for naproxen (1.2), which is administered in the S form because of the undesirable side effects of the R form and the burden on renal clearance.



Scheme 1.1

The most compelling mechanism for this inversion (Scheme 1.1), originally proposed by Nakamura et al.,[7] is a three step process which commences with the enantiospecific enzymatic formation of a thioester between the R enantiomer of the 2-arylpropionic acid and coenzyme A (CoA). This thioester may be hydrolysed to regenerate the R enantiomer or may undergo epimerization[c] to yield the thioester in which the 2-arylpropionyl moiety has the S configuration. Subsequent hydrolysis of this (S)-CoA thioester completes the inversion process. The epimerization step may proceed non-enzymatically, due to the acidic nature of the proton connected to the alpha carbon of the 2-arylpropionic acid substituent of the thioester. This process is clinically important because it generates an active cyclo-oxygenase inhibitor (S profen) from a relatively inactive precursor (R profen). The extent of this dynamic resolution, however, varies in vivo within and between individuals and is certainly not complete.[8,9] Moreover, this metabolic inversion occurs some time after administration in the elimination phase, when the plasma concentration of the initial S profen is lowered markedly, and the therapeutic effect has dropped considerably. Hence, the delayed S profen delivery[d] may not contribute to the therapeutic effect. This inversion phenomenon cannot be seen as a "prodrug principle"[10] and leads to great uncertainty in the actual dose of the

[c] CoA is an optically active molecule.

[d] From the inversion of initially R profen compounds.

active S form of the profen.

Through the above described metabolic pathway the R enantiomers can have pharmacological and toxicological effects related to inhibition of prostaglandin synthesis. The ability of the R enantiomers to form potentially reactive acylglucuronides, to form thioesters with coenzyme A, to be incorporated into triacylglycerols, and possibly to interfere with lipid metabolism and a host of biological membrane processes, makes the R enantiomers a pharmacological uncertainty, besides their non-inhibiting property of prostaglandin synthesis.

The importance of the S enantiomer

Although a patient is exposed to two distinct chemical entities, the R and S enantiomers, when a NSAID is given as a racemate, there is currently no compelling evidence to suggest that the R enantiomers pose significant toxicological hazards. The advantages in using the pure S enantiomer of a chiral arylalkanoic acid NSAID, however, comprise the following:

- The recipient would be exposed to less of the xenobiotic and therefore a reduced metabolic and renal load.
- Adverse effects which may be mediated by the R enantiomer or its metabolites, would be avoided.
- Side effects (altered physiology, diseases) and coadministration of other drugs on the pharmacokinetics of the NSAID, would be easier to assess and as a consequence more reliable dosage recommendations could be made.
- Interaction of the NSAID with other drugs might be reduced.
- Enantiomer-enantiomer pharmacokinetic interactions (which may lead to non-linearity in the pharmacokinetics of the active enantiomer) would be avoided.
- The pharmacokinetic properties and metabolic fate of the drug would be easier to define.
- For those α-arylpropionic acids, which undergo inversion (e.g. ibuprofen), the variability in fractional inversion within and between individuals would be avoided.
- Relationships between drug concentrations in plasma or

synovial fluid and therapeutic response would be easier to assess; enantioselective methods would not be required to measure total and unbound drug concentrations.[11]

- In vivo, the pure enantiomers of 2-arylpropionic acids are absorbed faster than the corresponding racemic compound.[12]
- Twice the dose of racemic ibuprofen is needed to attain the same plasma concentration of S form, as compared with the pure S enantiomer.[13,14]

The importance of the R enantiomer

Some observations in the late eighties revealed that part of the analgesic effects of NSAIDs are not completely explained by the prostaglandin synthesis inhibition effect of the S profen in inflamed tissue. This analgesic effect is attributed to the R profen. It is presumed to originate from the fact that the R form crosses the blood-brain barrier more easily than the S form, and possibly acts in the spinal cord or central nervous system (CNS).[15] This feature is in agreement with the different effects of salicylic acid and acetylsalicylic acid (aspirin). Salicylic acid exerts an analgesic effect at low doses, despite the lack of prostaglandin synthesis inhibition,[16] and does cross the blood-brain barrier, more readily than aspirin.[17,18] In summary, the R form is a good analgesic drug, however, for this specific therapeutic treatment, a profen drug must be chosen which does not exhibit R to S inversion in vivo.

The use of single R or S profens as drugs: an evaluation

It can be shown that a selective use of either the pure R or S enantiomers of the profens may be applicable: 1) the S form for curbing inflammation and pain in intensive inflammation, and 2) it may suffice to use pure R profens for suppressing simple pains, particularly by using those profens that do not encounter chiral inversion in man.[19] The use of terms 'eutomer' and 'distomer' for all chiral drugs therefore, does not apply to every case, in all circumstances.

In view of recent licence applications for single S or R

enantiomer formulations of chiral NSAIDs, it may not be long before single enantiomer administration is the rule, rather than exception for this important class of drugs. The reason for continued use of racemic NSAIDs today are probably chiefly economic.

Conclusions

As we have seen, the profens represent an important class of analgesic anti-inflammatory drugs. In the course of the last twenty years, observations have given deeper insight into their behaviour in man. Prior to the late eighties, the anti-inflammatory and analgesic S enantiomers were regarded as the only biologically active form, acting as inhibitors of prostaglandin synthesis, whilst the R forms were seen as contaminants which were lowered in concentration if they could be partially inverted to the S forms in vivo. Observations of more recent date have shown that the R enantiomers have analgesic properties as well, probably originating from activity in the CNS and/or the spinal cord.

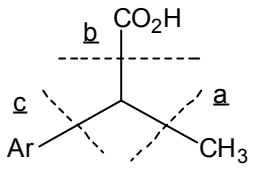
In conclusion, the profen drugs should be used as the pure, single enantiomers. More effective drug treatment could be established by using the required pure enantiomer for the specific medical condition.

1.2 Synthetic strategies towards optical active profens

Since profens have emerged as an important class of NSAIDs, publications, patents, and reviews have proliferated in this area. Most of the reviews essentially focus upon the synthesis of racemic profens. A review of Sonawane[20] concentrates on the methodologies developed to obtain chiral, non-racemic (scalemic) 2-arylpropionic acids and primarily deals with asymmetric syntheses among classical resolutions and enzymatic reactions. In this section, we evaluate a selection of the several synthetic strategies known at the start of this investigation. We do not imply to present a comprehensive list of strategies.

Asymmetric reactions

Retrosynthetic analysis of the key-profen molecule **1.5** suggests three possible disconnections: **a**) suggests an asymmetric methylation of 2-arylacetic acid, **b**) implies an asymmetric hydroformylation or hydrocarboxylation of the appropriate styrene derivative, and **c**) necessitates the formation of an asymmetric aryl alkyl coupling reaction or asymmetric alkylation of appropriate aromatic compounds.



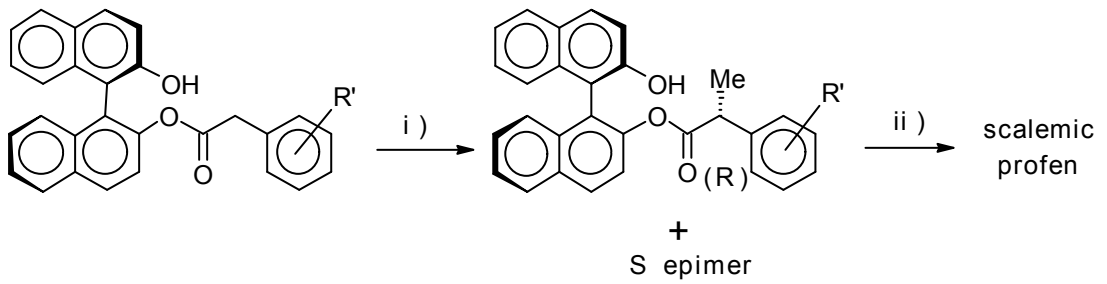
1.5

Figure 1.2

In addition to these asymmetric reactions, which approach the centre from one of the three possible sides, another class of reactions is the intramolecular stereospecific 1,2-aryl migration in chiral α-substituted acetals. In the following paragraphs several strategies are briefly discussed.

Methylation of 2-arylacetic acids

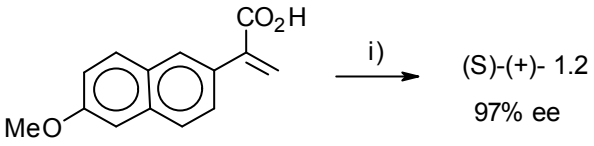
Synthesis of an optically active α-arylpropanoic acid via diastereoselective alkylation of binaphthyl esters of arylacetic acids has been reported by Fuji et al.[21] In general, bulky alkylating agents such as isopropyl and tert-butyl iodides are highly stereoselective in alkylation, although the enantioselectivity in methylation of binaphthyl esters of 2-arylacetic acid (Scheme 1.2) is not impressive (72% ee).



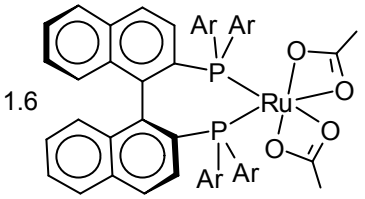
i) LDA, HMPA, THF, MeI, -78°C

ii) H^+, H_2O, recrystallization

Scheme 1.2



i) 14 mol% of 1.6, H_2, 30°C, 135 atm



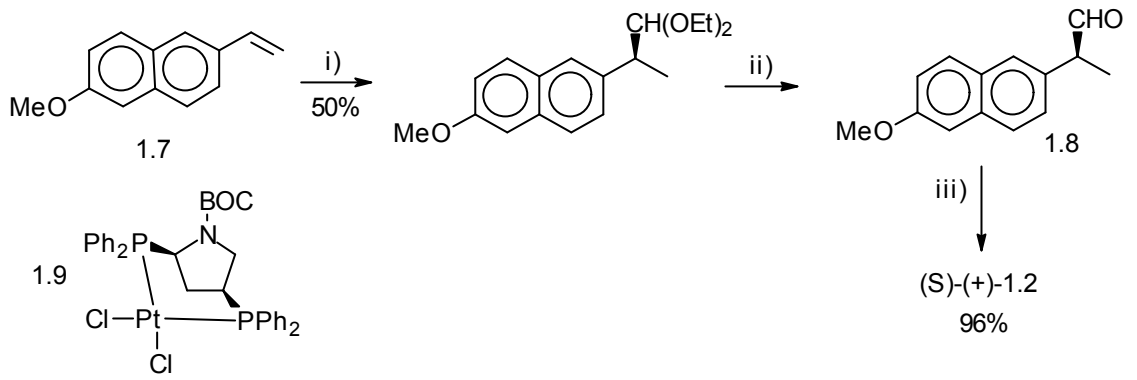
Scheme 1.3

Hydrogenation of 2-arylpropenoic acids

Optically active saturated acids, such as profens, are accessible from α,β-unsaturated acids by asymmetric hydrogenation (Scheme 1.3). [BINAP-Ru dicarboxylate] complexes, as **1.6**, hydrogenate prochiral arylpropenoic acids in a high yield (92%) and an enantiomeric purity of 97% under given conditions.[22]

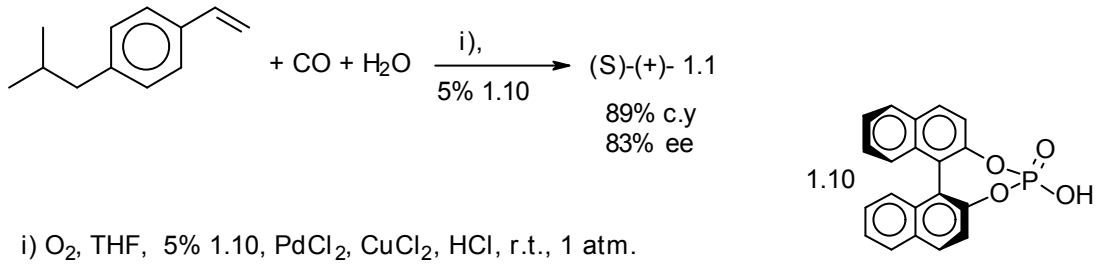
Hydroformylation of styrenes

The hydroformylation of styrene **1.7** (Scheme 1.4) yields the branched aldehyde **1.8** in 73% ee, when chiral Pt-catalyst **1.9** is used in the presence of $SnCl_2$.[23a] The ee was enhanced to 96% when triethylorthoformate is used, preventing the racemization of the aldehyde due to ketalization. Oxidation of the aldehyde with $KMnO_4$ gives the desired profen naproxen (**1.2**). A disadvantage of this method is the unfavourable branched/normal ratio of approximately 0.5. Recent developments are described in Catalytic Asymmetric Synthesis, edited by Ojima.[23b]



i) 1.9, H_2, CO, $HC(OEt)_3$, 2700 psi, 60°C, 20h; ii) pyridinium p-toluenesulphonate; iii) $KMnO_4$

Scheme 1.4



i) O_2, THF, 5% 1.10, $PdCl_2$, $CuCl_2$, HCl, r.t., 1 atm.

Scheme 1.5

Hydrocarboxylation of olefins

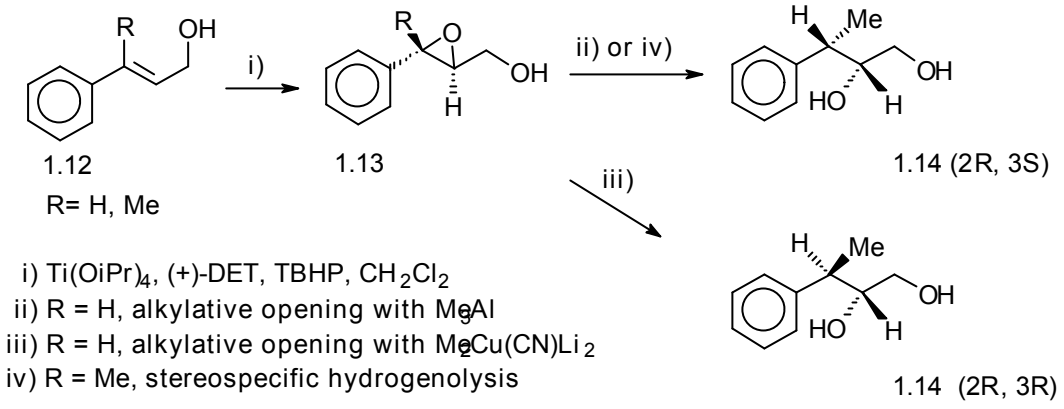
The hydrocarboxylation reaction in the presence of an asymmetric catalyst (e.g. **1.10**) affords exclusively branched acids in high yields under mild conditions (room temperature, atmospheric pressure), this makes the reaction an attractive reaction.[24]

Hydrovinylation

The hydrovinylation reaction is a useful reaction in homologation of olefins. Various catalysts have been developed to achieve asymmetric induction in the C-C bond formation. It is reported that ibuprofen precursor **1.11** has been obtained via this method in "high enantiomeric excess", though no data were given.[25] Compound **1.11** has been oxidized to ibuprofen with

high asymmetric induction.

Scheme 1.6



1.14 (2R, 3S) or (2R, 3R) ⟶ S-(+) or R-(-) 1.19 (Ar = Ph)

Scheme

1.7

Katsuki-Sharpless epoxidation

Chiral epoxy alcohols are versatile synthetic intermediates. Epoxidation of cinnamylalcohol **1.12** (R = H) by Katsuki-Sharpless method (Scheme 1.7)[e] followed by alkylative opening by MeI provides a chiral benzylic centre (**1.13**). Both enantiomers of **1.14** are accessible from the same oxirane ring depending on the choice of alkylating agent. Thus, on routine functional group manipulations both enantiomers of ibuprofen can be obtained.[26]

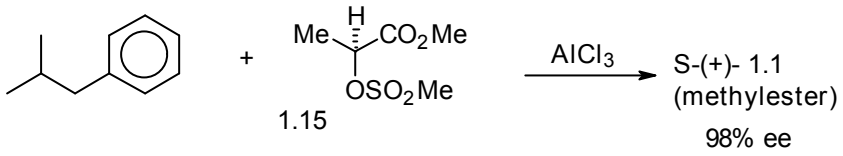
A variation is the hydrogenolysis of asymmetric epoxide **1.13** (R = Me) obtained from the olefin **1.12**, (R = Me) by Sharpless epoxidation. The diol **1.14** (2R, 3S) formed on oxidative cleavage affords the 2-phenylpropanoic acid in enantiomerically pure form.[27]

Friedel-Crafts alkylation of aromatics

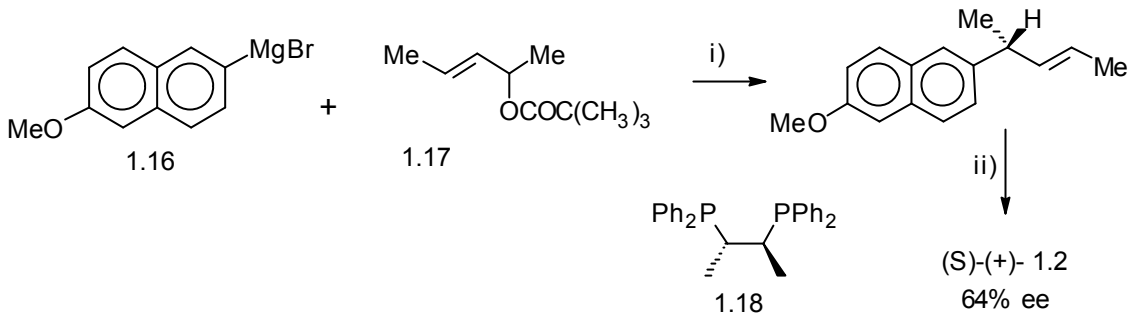
The acidic conditions of the Friedel-Crafts reaction would suggest that asymmetric alkylation is generally associated with racemization. Nevertheless, 98% ee could be obtained using a lactic acid derivative **1.15** as asymmetric

[e]The acronyms in Scheme 1.7 stand for: diethyltartrate (DET) and tert-butyl hydroperoxide (TBHP).

alkylating agent in the presence of $AlCl_3$, although the yield was low (50%).[28]



Scheme 1.8



i) [$NiCl_2$ -1.18], THF, r.t.; ii) oxidative cleavage ($NaIO_4$, $KMnO_4$)

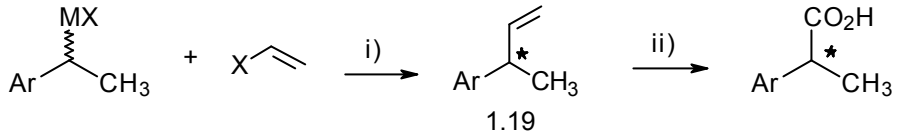
Scheme 1.9

Grignard coupling reactions

Naproxen has been formed in 64% ee in coupling **1.16** with **1.17** catalysed by a scalemic nickel-chiraphos complex (**1.18**).[29]

Asymmetric cross coupling reactions

One of the strategies of this thesis is to form a profen precursor in scalemic form via an asymmetric cross coupling reaction as depicted in Scheme 1.10. This reaction, established more than twenty years ago in its asymmetric version,[30] gives access to scalemic 3-aryl-1-butenes **1.19** in good to high yield (> 95%) and high enantiomeric purity (83% ee).[31] The mechanism of this reaction and associated parameters are discussed in detail in Chapters 2, 4, and 5. Oxidative cleavage of the butene moiety affords the desired profen in scalemic form.

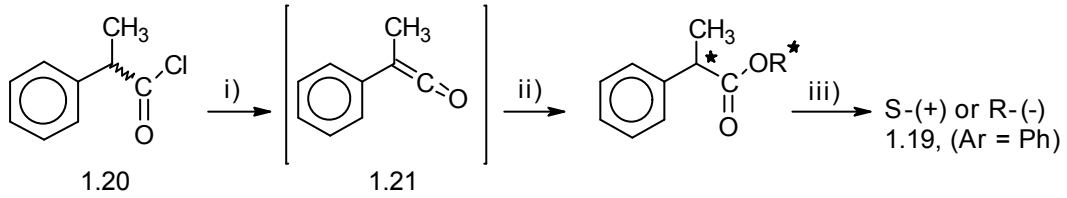


M = Mg, Zn, etc.; X = halide. i) 0.5% [L_2^*- $NiCl_2$] (L_2^* = chiral, non-racemic bidentate ligand); ii) oxidative cleavage.

Scheme 1.10

Enantioselective protonation

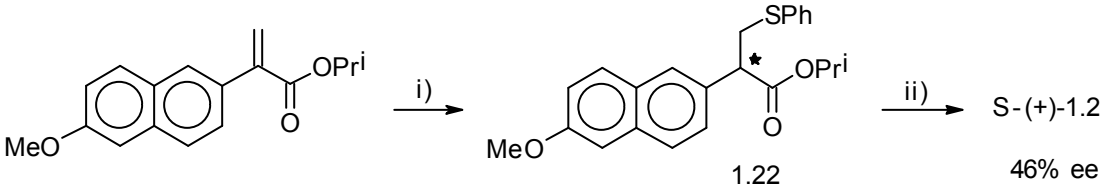
A racemic α-arylpropanoic acid chloride **1.20** has been converted into its corresponding (prochiral) ketene **1.21**. Addition of R*OH (scalemic α-hydroxyacids or ~lactones) to the ketene results in the ester of the corresponding α-arylpropanoic acid with high diastereoselectivity. Hydrolysis leads to the corresponding acid. When R pantolactone is used, almost exclusively R naproxen is formed.[32]



i) Et_3N, 25°C; ii) R*-OH, toluene, -78°C; AcOH, H_2O, 70°C; iii) AcOH, 2N HCl, 85°C

Scheme 1.11

With quinine as a catalyst, the asymmetric Michael addition of thiophenol to α-phenyl acrylates gives **1.22** (Scheme 1.12) in 50% ee. After hydrogenolysis under acidic conditions the profen compound is obtained.[33]

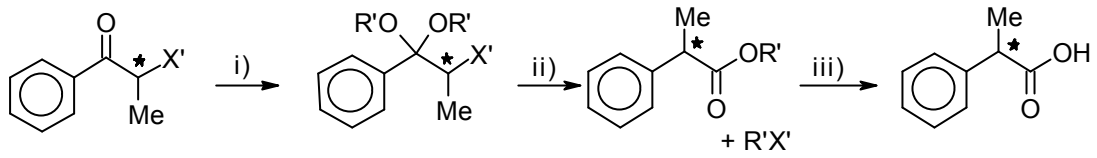


i) PhSH, quinine, toluene, r.t.; ii) Raney Nickel, AcOH-HCl

Scheme 1.12

1,2-Aryl migration

In a review article of Sonawane,[20] the broad scope of 1,2-aryl shifts leading to profen-precursors is reported. Most of the methods employed are based on Lewis acid promoted rearrangement of acetals of α-haloalkyl aryl ketones, as depicted in Scheme 1.13.

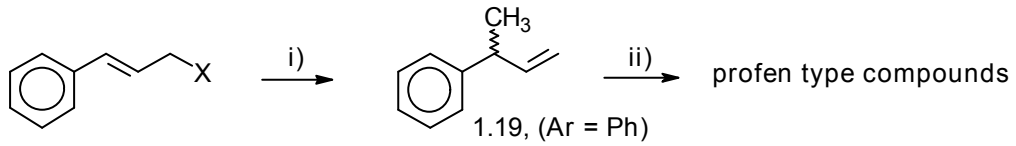


i) $HC(OR')_3$, p-TosOH; ii) Lewis acid (rearrangement); iii) hydrolysis.

Scheme 1.13

Bimolecular nucleophilic substitution with allylic rearrangement (S_N2' reaction)

In this thesis, a strategy is developed to obtain profen precursor **1.19** (3-aryl-1-butene; key compound with Ar = phenyl **1.20**) asymmetrically, based on the S_N2' reaction. This strategy will be discussed in Chapter 6.



i) CH_3MR, $Cu^{(I)}$-salt, ligand; ii) oxidative cleavage

Scheme 1.14

Resolution by diastereomeric salts; kinetic and enzymatic resolution.

In the quest for enantiomerically pure compounds, the classic resolution of racemates is still in fashion. Due to the loss of the unwanted enantiomers and chiral resolving agents on one hand and development of asymmetric synthesis on the other, the bias is shifting towards asymmetric synthesis.

Diastereomeric salt formation of racemic naproxen (**1.2**) with (-)-cinchonidine leads to resolution of optically pure S form in 49 % yield.[34] The diastereomeric mixture of the anhydride of (racemic) naproxen (**1.2**) can be kinetically resolved by reaction with (R)-(+)-1-(4-pyridyl)ethanol, yielding S-naproxen in 81%, with 55% ee.[35]

Enzymatic resolutions can be effected by different enzymes; the lipase from Candida cylindracea for instance, gives selectively the S acids from esters, although the use of activated esters was found to be necessary to obtain useful results; S-naproxen can be obtained in 39% yield and > 98% ee,[36] and with horse liver esterase the S ester is obtained in 31% yield and > 96% ee.[37]

1.3 Relationship to IOP Katalyse

The work described here, although it has a pronounced fundamental component, was of potential industrial interest at the time the work was begun. A brief discussion of this aspect and the relationship to the granting agency, IOP Katalyse, is necessary.

Profen drugs represent a significant share of the present pharmaceutical market. Virtually all examples of profens are currently marketed as racemates. Racemic profen drugs are a good illustration of so-called 'racemic switches'. Racemic switches are chiral drugs that have already been approved as racemates which have been redeveloped as single enantiomer. If the enantiomers are sufficiently different in pharmacological effects, it may be possible to get a patent on one or both. As discussed in this chapter, by preference both enantiomers of profen drugs should be used separately in different therapeutical treatments. However, all these deeper insights into the different behaviour of both profen enantiomers in human body has not resulted in production and marketing of single enantiomers on large scale. It is evident, however, that it is far better to use the specific active enantiomer in view of dosage and economic considerations.

In our research group, the development of the asymmetric cross coupling reaction to profen precursors has led to a procedure by which both enantiomers are accessible using only one asymmetric catalyst. The scope and limitations of this

finding are interesting and important, not only academically but practically. Industrial applications are not out of question.

This leads us to the framework within which this research has been carried out, and its character. The Netherlands Ministry of Economic Affairs set up Innovation Oriented Research Programmes on Catalysis (IOP-Catalysis) to promote mission-oriented research in the field of catalysis, in order to improve the Netherlands competitive position in international trade. The IOPs have funded research projects which are more specifically aimed at meeting the 'catalytic needs' of industry. In addition, it has been the intention to encourage greater collaboration between academia and industry. One of the main consequences for the research projects is indeed the "mission-oriented" character. In general, the aims of these programs involve innovation and development of catalytic reactions on an academic level, but with an eye towards industrial application of these processes. During the research projects, the course is outlined in a continuous dialogue with the industrial members of the specific IOP.

The asymmetric catalysed cross coupling reaction leading to profen precursors could not possibly be applied in an industrial process without deeper insight into the complex catalytic system involved. During the course of the work it became clear that the catalytic system was even more complex than first supposed. This thesis will deal for a large part with these complexities.

1.4 Incentives for this research

In our research group the design of ligands for use in the asymmetric catalysed cross coupling reaction, has been an area of intensive research (Scheme 1.10).[38] A remarkable phenomenon was observed, that when a stoichiometric amount of zinc halide was added to the Grignard reagent solution shortly before addition to the reaction mixture, the opposite enantiomer to that expected was formed.[38e,g] Thus, we have the opportunity to synthesize both enantiomers via one catalyst. The origin of this effect was one topic of this research. This will be discussed in Chapters 2, 4, and 5.

With our knowledge of aminophosphines derived from natural amino acids,[38a,f,g] we were interested in developing a new type of ligand. At DSM-Geleen, a procedure has been developed to give access to enantiomerically enriched α-methyl amino acids. Converting these into aminophosphines by readily available synthetic routes could lead to promising scalemic ligands for asymmetric cross couplings. Their synthesis will be discussed in Chapter 3, and application in Chapters 4 and 6.

In addition to the asymmetric cross couplings, we took the first step towards asymmetric catalysed S_N2' reactions. We postulated as to whether this catalysed reaction could be carried out asymmetrically, giving an alternative approach to the key target material: scalemic **1.20**. Chapter 6 deals with the development of S_N2' reactions towards scalemic **1.20**.

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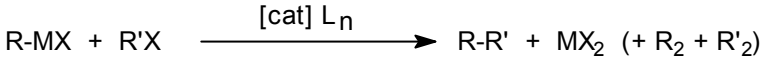
Chapter 2

Asymmetric Cross Coupling Reactions

2.1 Introduction

In Chapter 1 the asymmetric cross coupling reaction was introduced as a useful route to prepare profen precursors. The term 'cross coupling reaction' refers to the catalysed reaction of an organometallic species R**M**X with an organic halide R'X (or other leaving group), to join the two segments R and R'.



M = Mg, Zn, Al, B, Zr, Sn, etcetera
X = Cl, Br, I, OR, OP(O)(OR), SR, etcetera
R and R' = organic moieties, R' = alkenyl or aryl
cat = Ni, Pd, etcetera
L_n = n-dentate ligand

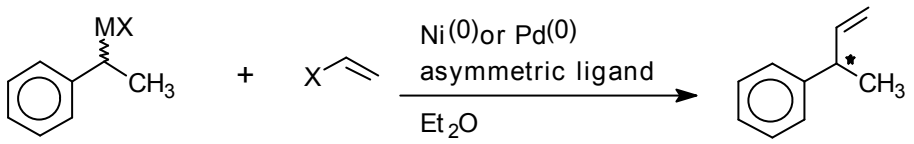
Scheme 2.1

The potential complexities of this method of carbon-carbon bond formation in terms of variation of R, **M**, X, and catalyst are evident in Scheme 2.1. Transition-metal catalysed reactions, known as the Kharash-type coupling reactions,[1] have been known for many decades. Various complications, such as homo coupling (formation of R_2 and $_2$R'), lack of chemoselectivity and halogen-metal exchange made applications of the cross coupling reaction limited until the mid-sixties when Cu-promoted reactions were developed.[2]

The cross coupling reaction can be markedly catalysed by Ni or Pd catalysts. In 1972 Corriu[3] and Kumada,[4] independently, reported that the cross coupling reaction was catalysed by nickel-phosphine complexes. With this change, the cross / homo coupling ratio could be greatly improved in favour of the cross coupling.[5]

This discovery was followed by the invention of Consiglio

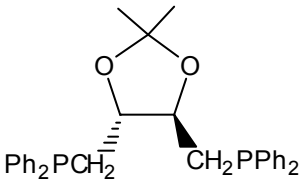
et al. of asymmetric catalysts for the cross coupling,[6] based on chiral diphosphines (e.g. DIOP, **2.3**, Scheme 2.2). Kumada and Hayashi have investigated this new area extensively and found that two types of phosphines were superior: β-aminophosphines (e.g. Valphos, **2.4** and Phephos, **2.4a**) derived from amino acids, and aminoalkylferrocenyl phosphine (e.g. (S)-(R)-PPFA **2.5**, (S)-(R)-BPPFA **2.6**).[7] In our group, aminophosphines derived from amino acids (homomethphos, **2.7**) and macrocylic compounds **2.8** were developed as ligands for Ni- and Pd catalysed asymmetric couplings.[8]



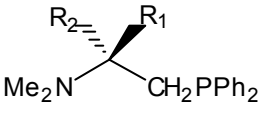
2.1a M=Mg
2.1b M=Zn

2.2

Asymmetric ligands:



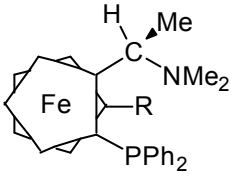
2.3 DIOP



2.4 S-Valphos
(R_1=2-propyl, R_2=H)

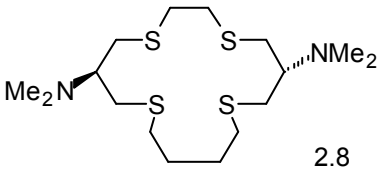
2.4a S-Phephos
(R_1=$PhCH_2$, R_2=H)

2.7 R-Homomethphos
(R_1=H, R_2=$CH_3S(CH_2)_3$)

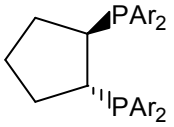


2.5 (S)-(R)-PPFA
(R=H)

2.6 (S)-(R)-BPPFA
(R=PPh_2)



2.8



2.9 a: Ar = Ph
b: Ar = p-$CH_3OC_6H_4$
c: Ar = o-$CH_3OC_6H_4$

Scheme 2.2

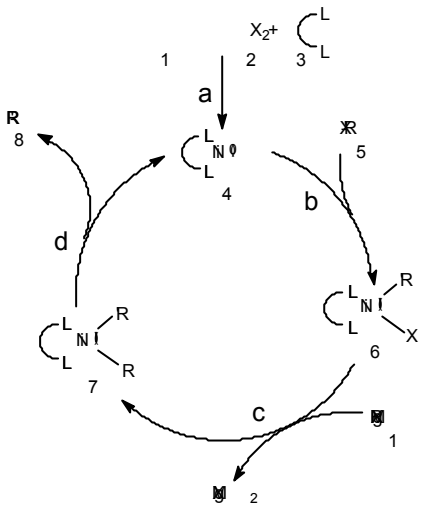
The discovery that the sense of enantioselectivity[8] in cross coupling reactions could be changed by addition of zinc halide beforehand to the Grignard reagent, led us to apply this reaction to profen synthesis. As we have seen in Chapter 1, each profen enantiomer has a different therapeutic activity. By means of this 'zinc halide' phenomenon, access to both profen precursors from one asymmetric catalyst is possible. Mechanistic insight into the causes of the phenomenon is not only interesting but also essential to further developments, such as rational design of ligand.

This chapter deals with the different aspects of the 'nutshell information' given above. In Section 2.2 the cross coupling, its mechanism, scope and limitations, and asymmetric induction will be discussed. We will focus upon the coupling between 1-phenylethyl halide and vinyl halide. In addition to asymmetric ligands other, often poorly defined, factors influence the enantioselection. These are not easily rationalized, particularly due to the uncertainty concerning the nature of the catalytic species,[9] and will be discussed in Section 2.3. Finally, the incentives, aims, and survey of this thesis will be discussed in Section 2.4 and Section 2.5.

2.2 Cross coupling reactions

Catalytic pathway

Although all details of the mechanism of the transition metal catalysed cross coupling reaction are not fully understood, an 'oxidative addition - transmetallation - reductive elimination' sequence appears plausible in many cases.[10] A catalytic cycle for the Ni-catalysed cross coupling reaction was suggested[4] in 1972 and this has not changed significantly since (Scheme 2.3).[11,12]



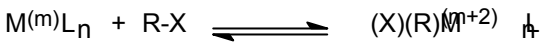
Scheme 2.3

The first catalytically active species is thought to be the Ni^0 intermediate **4**, formed from complexation of **2** and **3**, followed by reduction of Ni^{II} to Ni^0 by the Grignard reagent **1** (Scheme 2.3, step a). Thereafter, oxidative addition of an organic halide (or equivalent) R'X **5** to **4** leads to formation of **6** (step b). Transmetallation of **6** with **1** leads to formation of **7** (step c), which reductively eliminates **8** and regenerates **4** (step d) ready for the next catalytic cycle. The given sequences follow each other repeatedly: turnover numbers are often higher than 10,000. Analogous mechanisms have been proposed for the Pd-catalysed cross coupling reactions. We will comment briefly on the individual steps of the catalytic cycle.

Oxidative addition (Scheme 2.3, step b)

Oxidative addition is formally defined in Scheme 2.4, where **M** is a coordinatively unsaturated metal complex that adds the two fragments R and X from rupture of the R-X bond.[13]

The new ligands are formally considered to be negatively charged, so the oxidation state of the metal increases by formally 2. This change means that a metal complex must have a stable oxidation state two units higher to undergo oxidative addition



M = Pd, Ni
L_n = n-dentate ligand
R-X = organohalide

Scheme 2.4

The oxidative addition reaction of Ni or Pd complexes with unsaturated organic halides bears the hallmarks of a concerted process that can proceed with complete retention of the stereochemistry of alkenyl halides.[15b] The relative rates of oxidative addition to unsaturated organic halides are as follows: for the catalytic centre: Ni > Pd; for the organic halides: I > Br > Cl >> F; in case of phosphine as ligand: PEt_3 > PPh_3. The active catalytic species under catalytic conditions may well be $Pd^0[L]_n$ or $Ni^0[L]_n$ where [L] denotes a ligand, such as a monodentate, bidentate, or a more complicated ligating group. There are various factors that affect the oxidative addition of organic halides with Pd or Ni. For more detailed information on the broad scope of this step, the reader is referred to numerous articles summarized in reviews.[13,14,14]

Transmetallation (Scheme 2.3, step c)

Catalytic complex **6** is alkylated by the organometallic compound **1** with formation of unsymmetrical dialkyl transition metal complex **7** and a metal halide (Scheme 2.3). In other words, the catalytic complex **6** is alkylated by the alkylating agent **1**, to yield **7**. The rate-determining step in the cross coupling reaction may be the transmetallation step, although the exact nature of this step is not clear.[15b]

Reductive elimination (Scheme 2.3, step d)

For the crucial step in which the two organic moieties R and R' are joined, the most common starting point is a square

planar 16 electron, d^8 dialkyl complex **7** (the metal may also be Pd^{II}, Scheme 2.3). This is ligated by two other ligands L or a bidentate ligand L-L, typically (di)phosphine or aminophosphines.[7,15] In the case of Ni^{II} complexes, R-R' eliminates cleanly and easily, whereas for Pd^{II} complexes, kinetic evidence for a three coordinate intermediate like [L-Pd-RR'] is found.[12,16a,17a,b] When R and R' are cis-oriented on the transition metal centre **7**, C-C bond forming elimination is predominant. When the alkyl groups are trans-oriented, the elimination is less favoured.[14] Some β-elimination can occur, producing equimolar amounts of alkane and alkene. Slow trans-cis isomerization must occur before elimination can take place. The isomerization and elimination can occur via different mechanisms, depending on the metal. For various hypotheses, we refer to the literature.[14,15,16,16]

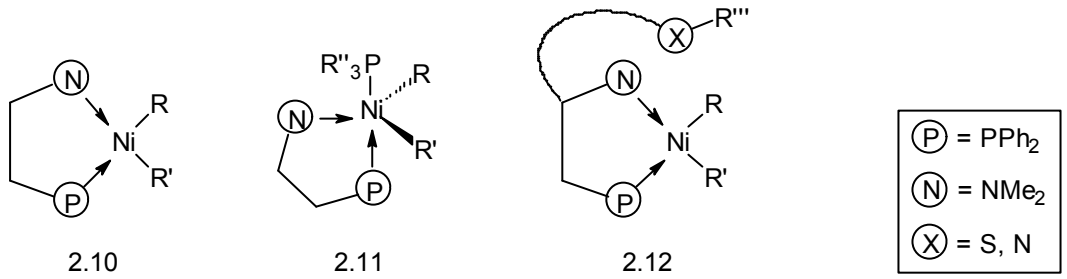


Figure 2.1

The reductive elimination from **2.10** (Figure 2.1) is known to be induced by tertiary phosphines.[17] It has been suggested that the dissociation occurs after pseudorotation of the intermediate that is formed on axial attack of the phosphine (**2.11**). This feature was used in the improvement of ligands to provide a manner to guide the reductive elimination. In our group, Vriesema et al.[8d] has developed aminophosphine ligands with a side-chain containing a heteroatom atom (**2.12**) which is supposed to act as a 'trigger', comparable with extra phosphine, but now intramolecularly.

The elimination step has been suggested to occur with high stereospecificity, very probably with complete retention of configuration, although this is unproven.[12]

Scope and limitations

Catalytic centres: transition metals

Nickel and palladium are effective catalytic centres in the cross coupling reaction.[18] For the catalytic cycle, Ni^0 or Pd^0 complexes can be used. Some of these **M**^{0} complexes are commercially available, but generally speaking, they are less stable than **M**^{II} complexes. Therefore, it is desirable to reduce in situ a **M**^{II} salt to **M**^{0} which is intercepted as soon as it is formed by ligands which are present, providing a [ligand]$_n$[**M**^{0}] complex. The reduction of the **M**^{II} salt can be carried out by the first drops of the organometallic reagent added to the catalytic mixture of **M**^{II} salt, ligand, and organo halide (Scheme 2.3, step a). After formation of complex **4** the catalytic cycle (depicted by Scheme 2.3) commences.

Organometallics R**M**X

The order in the reactivity of the organometallics R**M**X is interesting. Highly electropositive metals (**M** = K, Na, Li) are often far less effective than metals of intermediate electronegativity such as Zn, Al, Cd, Zr, or Cu; the former are rarely applied to cross coupling reactions. Organozinc, ~boron and ~aluminium species show high efficiency in reactions with organohalides. Organomagnesium compounds often produce homo coupled aryl halides and do not tolerate a wide variety of functional groups on either partner.[19]

Organic moiety R'X

Simple alkyl halides R'X are relatively unreactive towards Ni^0 and Pd^0 phosphine complexes, indicating that interaction with a π-system may be responsible for the observed facile oxidative addition processes. In fact, there does not appear to be any report on successful Pd- or Ni-catalysed cross coupling reactions with simple alkyl halides - a major limitation of this method. To circumvent this problem, the alkyl group (e.g. s-butyl-) can be introduced as a part of the organometallic (s-butyl-MgX) rather than organohalide (s-butyl-X). The electrophile is normally the unsaturated entity to avoid the complications arising from β-elimination.[19] β-Elimination from the alkyl part of the (di)organometallic compound is considerably slower than the reductive elimination

of it, resulting in the desired product.

The leaving group X in R'X is usually a halogen. The relative reactivity of leaving groups in oxidative addition is: I > Br > Cl. In cases where alkenyl and aryl halides are used, only iodides and highly active bromides participate in the Pd catalysed reactions, whereas the Ni catalysed reactions proceed readily with a wider range of bromides and chlorides.[20]

Summary

In a cross coupling reaction, two organic moieties R**M**X and R'X can be successfully joined under formation of a carbon-carbon bond by means of a transition metal catalyst. R can be a primary, secondary, or even a tertiary alkyl group. R'X typically contains a π-system, as an alkenyl or aryl group. The leaving group X is usually halogen.

Ligands and asymmetric induction

For non-stereoselective cross coupling reactions, very effective, simple, and suitable ligands for the catalyst are diaryl- and dialkyl phosphines, e.g. triphenylphosphine. In an early study, Kumada[4] demonstrated that a bidentate phosphine ligand exhibits remarkable catalytic activity in the Ni^0-phosphine catalysed coupling of n-butylmagnesium bromide with chlorobenzene. The activity of catalyst decreases in the order dpp > dpe > dmpe ≈ $(PPh_3)_2$ >> $(PEt_3)_2$ ≈ $(PPh_2Me)_2$.[a] This suggests that the cis-configuration of the organic groups R and R' in the intermediate RR'**M**L_2 is an important requisite of the catalyst.[21]

After the non-stereoselective Pd- or Ni-phosphine catalysed coupling was discovered in the early seventies, the invention of the asymmetric version followed promptly by using a chiral, non-racemic ligand L_2 (**3**, Scheme 2.3) for the catalytic centre.[6] Remembering the high turnover number of the Ni- and Pd catalysed reactions (> 10,000), this means that with a very small amount of chiral, non-racemic ligand a huge amount of scalemic product can be obtained.

For rational design of ligands for asymmetric synthesis,

[a] The acronyms stand for: 1,3-diphenylphosphinopropane (dpp), 1,2-diphenylphosphinoethane (dpe), dimethylphosphinoethane (dmpe).

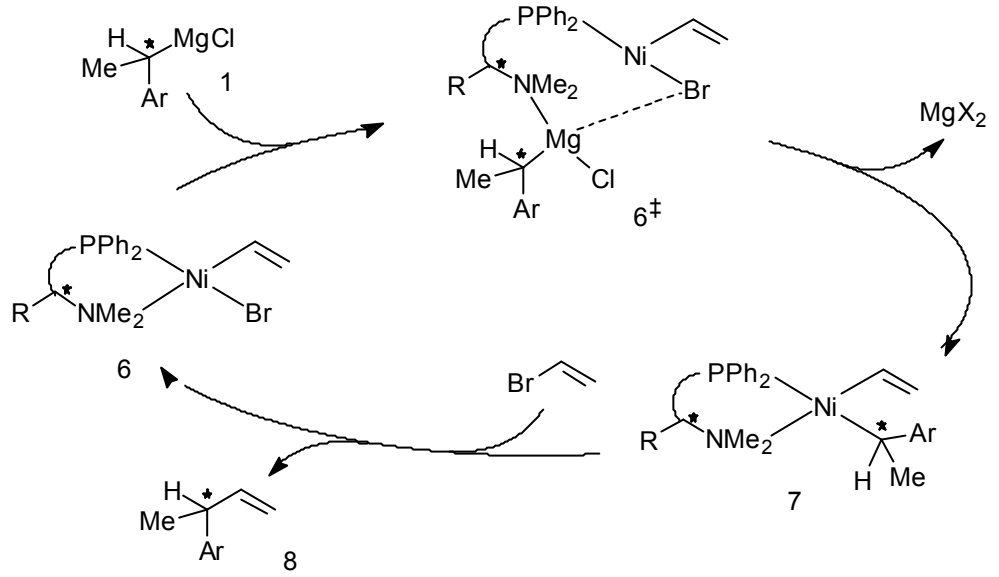
sufficient understanding of the mechanism of the reaction is required. Unfortunately, little is yet known about the mechanism of the rather fundamental asymmetric step. The intermediates of the cross coupling reaction cannot readily be isolated, and mechanistic interpretation involves considerable speculation. Certain trends in the behaviour of ligands, though, make the design of them not completely empirical and help uncover the mechanism.

Scheme 2.3 presents two steps (c,d) and one intermediate (**7**) that could be responsible for asymmetric induction. Alkylation of the catalytic species **6** by organometallic **1**, step c, epimerization of the asymmetric transition metal dialkyl intermediate **7**, and reductive elimination of **7** in the product forming step (step d). It is very likely that the configuration at carbon is determined in step c, the stage where L_2[Ni]RR' (**7**) is formed by transmetallation. Epimerization at the stage of **7**, however, cannot be excluded.[22] It is unlikely that step d, the C-C bond-forming step, is a significant source of stereochemical variation. This step is assumed to be stereospecific.[12,13,17b,23] Repeatedly, the nature and enantiomeric composition of the alkylating species **1** plays an arbitrary or important role in the stereochemistry. This will be discussed in Section 2.3.

A striking feature of the best ligands for asymmetric cross coupling reactions is that they bear little structural relationship to ligands for Rh or Ru catalysed hydrogenation, olefin isomerization, or Pt catalysed hydroformylation.[12,26] The latter reactions give highest optical yields with moderately rigid diphosphine chelates. Phosphines or diphosphines, preferentially carrying a potentially chelating tertiary amine or sulfide group, have demonstrated their superiority in the cross couplings.

Hayashi and Kumada performed coupling experiments catalysed by a series of optically pure ferrocenyl phosphine ligands. Among them, some were substituted with an aminoalkyl group, as depicted in Figure 2.1. These experiments demonstrated the high enantio-efficiency of a dimethylamino group. It was postulated that the configuration of the coupling product is already determined before the Ni-C bond is

formed, because of the opportunity for the dimethylamino group to complex with the Mg-atom in the Grignard reagent (**6**‡ in Scheme 2.5). With **2.6** as ligand, **2.2** (cross coupling product **8**, Ar = Ph) has been obtained in 65% optical yield.[24]



Scheme 2.5

Many scalemic aminophosphines derived from natural as well as synthetic amino acids have been developed as ligands, where optical yields of the cross coupling product have reached 94%.[b] Valphos (**2.4**), derived from the valine, yields **2.2** in 83% o.p. There is a remarkable consistency between ligand configuration and the configuration of the product obtained. This indicates that related ligands have similar coordination and comparable steric influence.

In our group, Vriesema et al. developed aminophosphines with a sulphur atom in the side chain. Homomethphos (**2.7**), a tridentate chelate, provides high optical yield (88%). The side chain hetero-atom probably participates as a built-in trigger,[8d] inducing reductive elimination of the organic

[b]Corrected for the optical purity (o.p.) of the ligand; the actual measured o.p. (misdenoted as "ee") is 83%.

moieties (see Section 2.2 Reductive elimination).

2.3 Extraneous influences upon enantioselection

Introduction

During the development of ligands for asymmetric cross coupling reactions, it appeared that the enantioselectivity not only depends on the asymmetric catalyst, but to a significant extent on other factors.[8e,g,9,25] These extraneous[5] factors can be, for instance, the composition of the organometallic solution,[26] the presence of other type of halide, or the addition of zinc halide. These parameters affect in some cases the optical yield, in other cases the absolute configuration of the product, vide infra. The extent of these effects differs among the systems, and depends on the combination of the extraneous factor and the type of asymmetric ligand.[26b] For instance, the presence of a few percent MgI_2 in the reaction mixture can lead to the other enantiomer. How these extraneous factors behave in the catalytic sequence, is not easily understood.

The comparison of the optical efficiency of the asymmetric ligands amongst research groups becomes dubious if these factors are not mentioned. It is of first importance that these factors should be defined and, if possible, minimized. The design of new ligands, therefore, requires careful analysis of the studies between ligand-structure and the ee of the product, to answer the question whether it is the ligand or something else that governs the stereoefficiency. Most of the factors that are known to influence the stereoselection, in addition to the chiral ligands, are discussed in the following sections.

I. Influence of the alkylating species RMX

The asymmetric cross coupling reaction is a kinetic resolution with respect to the chiral, racemic organometallic species, carried out by the asymmetric catalyst intermediate (**6**, Scheme 2.3). The alkylation of the transition metal catalyst **6** by the organometallic species **1** is suggested to be

[5] In this thesis, the term extraneous is applied to factors that influence enantioselection in ways that cannot be rationalized based on normal chemical knowledge.

responsible for asymmetric induction. The nature and enantiomeric composition of **1** may affect the stereochemistry in this step.

Variation in the nature of R**M**X during reaction

Consiglio observed that "all factors that are known to influence the structure of the Grignard reagent in solution also affect the extent of asymmetric induction, at least for the reaction catalysed by nickel diphosphine complexes".[9] The structure of the species, which can alkylate the transition metal catalyst, presumably changes with progress of the coupling reaction, owing to the formation of magnesium salts. Because of this structural change, it would be expected that the enantioselectivity would also change during the reaction - unless asymmetric induction is determined by the epimerization at the carbon-transition metal bond. Consiglio [26b] investigated the enantiomeric excess as a function of the degree of the conversion of the substrate, using chiral ligands **2.9 a-c** and **2.6** (Scheme 2.2). In the experiments where diphosphines **2.9 a-c** were used as ligands, the enantioselectivity changes during the reaction: the enantioselectivity depended on the extent of conversion. This non-linear behaviour is possibly related to the variation in the nature of the Grignard reagent as a consequence of the formation of magnesium halides or due to increased dilution, vide infra. The fact that **2.6**-$NiBr_2$ catalysed cross couplings showed linear behaviour is in agreement with the assumption that the NMe_2 group of the catalytic complex can interact with the magnesium atom of the Grignard reagent before alkylation of the transition metal.x This assumes that with aminophoshine ligands the nature of the species responsible for alkylation does not change during the course of the reaction (cf. Section 4.5-Varying halide in (vinyl halide - Grignard reagent) combinations).

Enantiomeric composition of R**M**X

The formation of Grignard reagents proceeds via trapping of radicals at the magnesium surface (see Section 4.2 The D-model). Because radicals are not configurationally stable, chiral secondary Grignard reagents are racemic, even when prepared from scalemic halides.[12] Racemization of a secondary

racemic Grignard reagent occurs at a moderate rate at ambient temperature.[27] If this rate of racemization is fast on the time scale of catalytic turnover, then one of the enantiomers may participate in asymmetric cross coupling preferentially, while the other inverts before reaction.[12] In other words, this is a form of dynamic kinetic resolution. Starting from a secondary Grignard reagent, the product can be obtained in 100% chemical and optical yield at least theoretically.

Secondary Grignard reagents, however, can be configurationally stable for hours (in favourable cases) at ambient temperature. More quantitative investigations demonstrated that the rate constant for interconversion of secondary Grignard reagents is much slower than for primary.[29,30] If this is supported under the conditions of catalytic cross coupling, then kinetic resolution of the Grignard reagent may make an important contribution to the ultimate optical yield. The influence of the enantiomeric composition of the Grignard reagent on the stereochemistry means that a low racemization rate of RMgX influences the extent of asymmetric induction.

Consiglio et al.[9] discovered that by increasing the ratio of RMgBr to R'Br, up to a 10-fold excess of the racemic Grignard reagent, the optical yield decreases in diphosphine-Ni complex catalysed couplings. In these experiments, the concentration of the Grignard reagent was maintained constant in order to ensure the presence of the same alkylating species. The association degree of the Grignard reagent is supposed to remain almost the same over a large concentration range, when X = Cl.[27] An influence of the racemization rate on the optical yield under these conditions cannot be excluded, since racemization is known to require more than one molecule.[29c] In the case of X = Br, the possible change of the structure of the alkylating species, due to dilution, must be considered. Dilution brings about a decrease in the optical yield of the coupling product, probably due to alterations in rate of epimerization. This phenomenon cannot be explained by simple mechanisms as given above. A competition amongst different pathways, or more complex catalytic species appear

more probable.[d]

II. Influence of the type of halide

In asymmetric couplings between RMgX and R'X', it appeared that different combinations of halides X and X' (X ≠ X' and X = X') provided different optical yields of R–R'. This occurrence has already been noted by Kumada,[28] where the observed differences in ee (amongst different halides, **2.3** as ligand) were small (≤ 4.2%). A study by Consiglio[26a] demonstrated that the optical purity of the product can be affected by the type of halogen in RMgX and R'X' under same catalytic conditions. The (erroneous) assumption that in some cases this effect could lead to reversal of the absolute configuration of the product, was corrected afterwards.[9] This reversal was found to originate from the presence of MgI_2 in the RMgX solution, formed by activation of magnesium turnings by I_2. Particularly when X = Cl in both RMgX and R'X, this effect is surprising. Addition of only 1 wt.% of MgI_2 to the asymmetric cross coupling reaction leads to reversal of the absolute configuration of the product, the optical purity remaining about the same. In all cases where the types of halide were varied independently, asymmetric cross coupling experiments of s-butyl-MgX with ArX' provided scalemic 2-aryl butane with different optical yields, in some cases with reversed absolute configurations. This effect appeared to be quite general, independent of the scalemic diphosphine ligand used. The effect on aminophosphine catalysed reactions will be discussed in Section 4.5-Varying halide in vinyl halide - Grignard reagent combinations.

III. Influence of solvent

The solvent is one of the most critical factors in successful asymmetric synthesis. The most successful asymmetric couplings are carried out in Et_2O whereas THF is less effective. The marked difference in optical efficiency between Et_2O and THF may relate to the structure of the Grignard reagents in those two solvents. In Et_2O the preferred

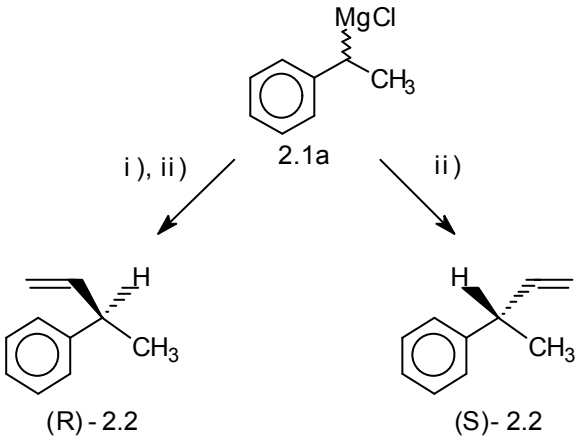
[d] Catalytic complexes containing the (diphosphine) ligands in a monodentate fashion have been suggested as a possibility by Consiglio (ref. 9).

form of RMgCl is a chloride bridged cyclic dimer, where solvated monomers are dominant in THF.[29]

IV. Influence of zinc halide

Negishi et al.[30] demonstrated that organozinc compounds can be used as alkylating species in cross coupling reactions. Kumada et al.[31] applied these compounds successfully in chiral ferrocenylphosphine-palladium complex catalysed cross couplings, providing higher enantiomeric purities than Grignard reagents. The organozinc species were generally prepared by mixing corresponding Grignard reagents to excess zinc halides. Direct preparation from zinc metal and organohalide led to low yields and poor reproducibility.

As asymmetric cross coupling reactions has been under investigations in our group,[8] analogously prepared organozinc species were used in couplings catalysed by nickel or palladium complexed to ligands derived from amino acid. A remarkable phenomenon was observed[8e,g] in the reversal of the enantioselection. The opposite enantiomer ((R)-**2.2**, Scheme 2.6) can be obtained under these conditions (**Cross**-conditions).[e] In other words, both enantiomers of **2.2** can be obtained with only one catalyst and the sign of the optical rotation depends on addition of ZnX_2.



i) $ZnBr_2$
ii) vinylhalide, $Ni^{(0)}$ or $Pd^{(0)}$ - asymmetric ligand

[e] The bold typed 'Cross' refers to Graham Cross, who discovered the previously described phenomenon of reversal of the enantioselection.

Scheme 2.6

The rate of the coupling increases on addition of zinc bromide. At low temperature (-34°C) and Ni-**2.7** as catalyst, practically no reaction takes place (0.4%), whereas addition of $ZnBr_2$ leads to 73% yield.

Addition of other salts (e.g. magnesium halide) neither inverted nor influenced the optical rotation of **2.2**.

When the **Cross**-mixture was allowed to stand for 1 h, no cross coupling could be detected.[8g] On basis of the report of Negishi et al.[33] that after stirring RMgX and ZnX_2 for one hour, the dialkylzinc species R_2Zn should be formed, the assumption was made that this species is apparently not very reactive. The appropriate balance of reactivity might be reached in the monoexchanged species RZnX.[8g]

A fast "Zn^{II}-induced pathway and a slower reaction involving the Grignard reagent" was proposed, and "the dialkylzinc species, if allowed to form, is apparently not very reactive. The appropriate balance of reactivity may be reached in RZnBr, the monoexchanged species. On the other hand, the formation of zincates may also influence the course of the reaction". The inhibitory effect on cross coupling when zinc chloride is used, is attributed to slower halide exchange reactions on Zn^{II} by chloride.[8 g]

In summary, the **Cross**-mixture is an alkylating agent that is formed after addition of a solution of 1-phenylethylmagnesium halide in Et_2O to a stoichiometric amount of anhydrous zinc halide. This **Cross**-mixture must be used freshly (< 1 h). Under these conditions and when amino acid derivatives are used as ligand for Ni- and Pd-catalysts, enantioselectivity is influenced.

Evaluation

The optical yield of asymmetric cross coupling reactions is easily influenced by many more factors than the asymmetric catalyst alone. For synthesis involving such a reaction step, these influencing factors, though intricate, must be recognized and minimized.

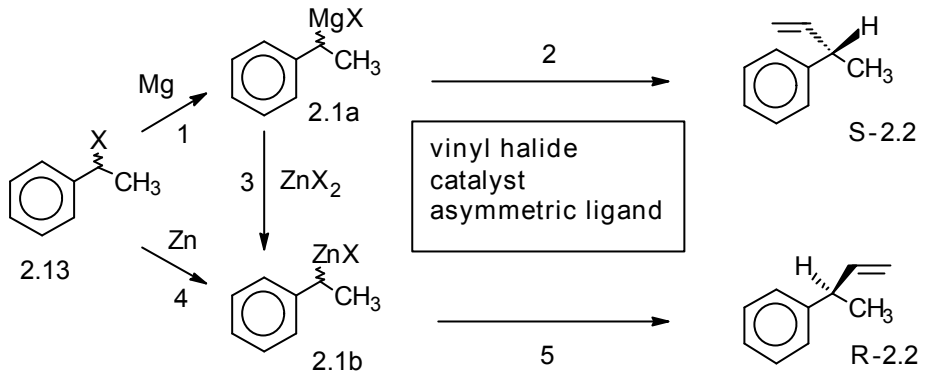
2.4 Incentives

Successful ligands derived from amino acids have been developed in our research group, such as homomethphos **2.7**, having a side-chain with a terminal sulphur group. We were intrigued by the effect of this ligand on optical yield, and speculated about the effect of homologation of this side-chain by one CH_2-group.

As amino acid derived ligands has been under investigation in our group,[8a,f,g] synthetic α-alkylated amino acids catched our attention. At DSM-Research Geleen a procedure has been developed to give access to enantiomerically enriched α-methyl amino acids. We considered that these compounds could be converted to promising ligands by readily available synthetic routes.

Asymmetric cross coupling reactions has provided us with a number of elusive or at least striking effects on enantioselection. In this field, Consiglio observed that all factors that are known to influence the structure of the Grignard reagent in solution also affect the extent of asymmetric induction in cross coupling reactions.[f] As a consequence, the alkylation of the transition metal catalyst is thought to be responsible for asymmetric induction (Scheme 2.3, **2**).[12,13,24,26b,32] Extrapolating this, the **Cross**-mixture is an alkylating species affected by zinc halide, generating either an organozinc compound RZnX by transmetallation or a zincate complex [$RMg\text{-}ZnX_3$]. Questions remain about the nature of this alkylating species in the **Cross**-mixture. Is it an organozinc reagent? And if so, in which form: RZnX or R_2Zn? Is it dependent on the formed magnesium salts, excluding alternative methods to form this organozinc species? Or is it something completely different: a zincate complex?

[f] At least for the Ni-diphosphine complex catalysed reactions.



Scheme 2.7

An interesting question remained whether a magnesium salt-free prepared organozinc species could carry out the cross coupling or not. We suggest pathways illustrated by Scheme 2.7. Step 1 leads from **2.13** to **2.1a**, followed by the classic asymmetric cross coupling, step 2. After addition of ZnX_2 (step 3) **2.1b** is formed, responsible for the cross coupling via an alternative stereoselective pathway. To verify this, **2.1b** should be prepared from **2.13** by an alternative method, under magnesium salts-free conditions, step 4.

2.5 Aims and survey

The principal aim in this thesis involves the synthesis of profen-precursor 3-phenyl-1-butene in enantiomeric excess via asymmetric catalysed reactions, such as asymmetric cross coupling.

In Chapter 3 the synthesis of α-methyl amino acid derived ligands is described. Further, syntheses of ligands are described that are developed to investigate the effect of the sulphur-containing side-chain of **2.7**. We focused on the optimum chain length and the function of the terminal sulphur moiety.

In Chapter 4 the improvement of the preparation of the Grignard reagent is discussed, preceded by a summary of preparation methods, and followed by the results of asymmetric

catalysed cross coupling reactions. Ligands for the catalyst in the couplings are derived from α-amino acids, the syntheses of which are described in Chapter 3. The couplings where the **Cross**-mixture is used as alkylating species are described as well. Use of the 'improved Grignard reagent solution' in **Cross-**mixtures leads to unprecedented results.

As outlined in this chapter, the asymmetric induction in cross coupling reactions is influenced by a number of factors. Some of these enigmatic factors, such as addition of zinc halide, are not easy to understand and needed further investigation. To determine the nature of the alkylating agent in the **Cross**-mixture, we investigated the preparation of organozinc compounds under magnesium salt-free conditions. This is described in Chapter 5.

The intricacy of the asymmetric cross coupling reaction prompted us to investigate an alternative asymmetric catalysed reaction towards the key-intermediate of profen-type compounds, **2.2**. Chapter 6 deals with bimolecular nucleophilic substitution reactions of methyl-metallic and cinnamyl moieties with allylic rearrangement (S_N2' reactions), leading to **2.2**. The S_N2' reaction has the preference above the S_N2 reaction when appropriate methylmetallic–catalyst combinations are used. The aim in Chapter 6 is to develop a catalyst-dependent S_N2' reaction being enantioselective by the use of proper asymmetric ligands.

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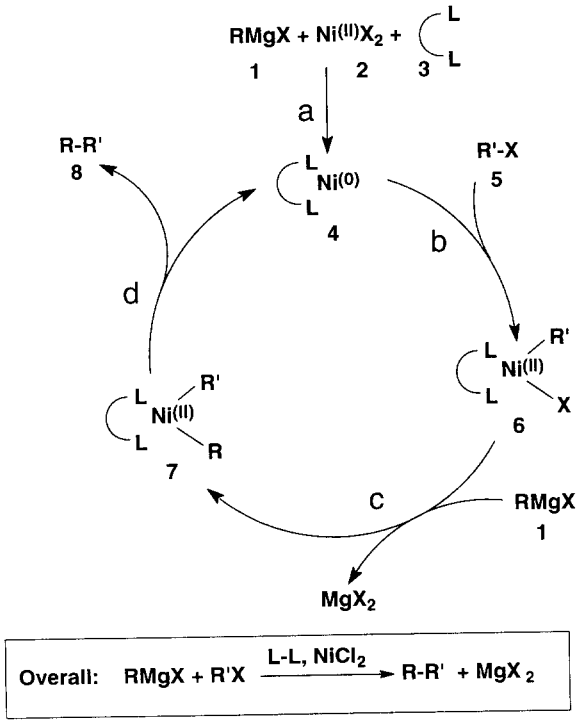
Chapter 3

Ligands for Asymmetric Catalysed Cross Coupling Reactions

3.1 Introduction

In Chapter 2 an overview is given of factors that have an influence upon enantioselection in asymmetric cross coupling reactions. In Section 2.2-*Ligands and asymmetric induction* we discussed some types of ligands used in cross coupling reactions, together with mechanistic interpretations. The step responsible for asymmetric induction is presumed to be the alkylation of **6** by **1** (Scheme 3.1).[a]



Scheme 3.1

[a] For convenience, the same proposed catalytic cycle of Scheme 2.3 is reproduced here as Scheme 3.1.

The stereochemical compositions of both 1 and 6 probably are of influence on the stereochemistry of asymmetric cross coupling reactions. The enantiomeric composition of 1 depends, among other factors, on the rate of racemization during the course of the cross coupling reaction. The Grignard reagent 1 is generally assumed to undergo inversion rapidly relative to coupling at a reaction temperature of –40°C, a criterion that has to be met if a high yield of chiral, non racemic (scalemic) product is to be obtained. Inversion of configuration of α-chiral primary Grignard reagents is known to be rapid on the NMR timescale,[1] although secondary Grignard reagents have been reported to be configurationally stable for hours at ambient temperature in favourable cases.[2,3]

The degree of chiral induction in the formation of 6 can be modified by use of various chiral, non racemic ligands. Selection of appropriate asymmetric ligands 3 potentially results in the formation of 8, where optical yields up to about 90% have been realized for R-R' = 3-phenyl-1-butene. As discussed in Section 2.2, little is known about the mechanism of the rather fundamental asymmetric step (Scheme 3.1, step c). Although considerable speculation about the mechanism is inevitable, certain trends in the behaviour of ligands make the design of them not completely empirical and may help unravel the mechanism.

In asymmetric cross coupling reactions aminophosphines are very effective as ligands for Ni and Pd catalysts and they give the best results in optical purity for R-R' = 3-phenyl-1-butene, as shown by Kumada and Hayashi.[4] These ligands involve scalemic β–aminophosphines derived from natural amino acids and aminoalkylferrocenylphosphines. In our research group Griffin, Vriesema, and Cross have developed aminophosphines, derived from natural as well as synthetic amino acids, in order to test various theories about the catalytic mechanism of the cross coupling reaction.[5] The remarkable stereochemical outcomes using this type of catalytic system,[b] and the questions that arose about the mechanism of cross couplings led us to continue with these types of ligands.

In this chapter, the incentives to and the syntheses of

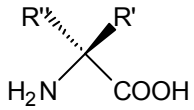
[b] See Chapter 4 and 5 for the specific composition of the catalytic systems used (transition metal, ligand, etcetera).

specific ligands will be described. We categorize these ligands in three subdivisions. Since we had access to synthetic α-methyl-α-amino acids, we have used this type of compounds as precursor for aminophosphines (Section 3.2) as well as aminosulphides (Section 3.3). In extrapolation of the successful homomethphos ligand[5e,f] (3.12, n = 3), we developed aminophosphines with various sulphur containing appendages (Section 3.4) to obtain more information about the optimum length of these appendages and the effect of substitution on sulphur.

3.2 β -Aminophosphines

Incentives and strategy

We have designed a promising new type of ligand for the nickel or palladium catalysed cross coupling reactions, based on the following rationale. When more rigid diphosphines were applied as ligands in cross couplings, the optical yield of 8 was found to improve.[6] Further, aminophosphine ligands have demonstrated their superiority to diphosphines in the cross couplings (see Chapter 2). It was postulated that the configuration of the coupling product is already determined before the Ni-C bond is formed. This assumption may be visualized by coordination of the amino moiety with the magnesium atom in the Grignard reagent.[7]



3.1 a: R' = CH_3, R'' = $PhCH_2$
b: R' = Ph, R'' = CH_3
c: R' = iPr, R'' = CH_3

natural amino acids: R' = alkyl, aryl, hydrogen, and R'' = hydrogen
α-methyl-α-amino acids: R' or R'' = alkyl, aryl, etcetera, and R'' or R' = methyl

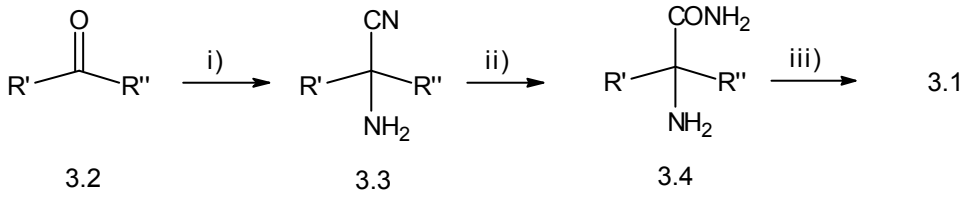
Figure 3.1

We expected that α-methyl substitution of the aminophosphine (3.9, R' or R'' = Me and R'' or R' = alkyl, aryl, Scheme 3.3) will combine the advantage of both rigidity and NMe_2 coordination, allowing a better degree of recognition of the chirality about the ligand. As we have seen in Chapter 2,

amino acids are potential precursors for aminophosphines. α-Methyl-α-amino acids are now accessible in enantiomerically enriched form via an enzymatic process, developed at DSM-Research Geleen.[8] These synthetic amino acids 3.1 (R' or R'' = Me and R'' or R' = alkyl, aryl) differ from natural amino acids by an α-methyl substituent, as depicted in Figure 3.1.

Synthesis of 3.9a and 3.9b

In a process developed at DSM-Research Geleen,[8] stereoselective hydrolysis of α-alkyl-α-amino acid amides can be performed by a biocatalyst from Mycobacterium neoaurum.[c] The synthesis of the racemic substrates involves a Strecker synthesis with a ketone (3.2), followed by hydrolysis of the resulting aminonitrile 3.3 to form the amino acid amide 3.4 (Scheme 3.2). Enzymatic hydrolysis of the amides results in the formation of the L-3.1, leaving D-3.4 unchanged. We obtained from DSM-Research Geleen, as a generous gift three enantiomerically enriched α-methyl-α-amino acids, namely D-α-methyl-phenylalanine (3.1a, R' = Me, R'' = $PhCH_2$), L-α-methyl-phenylglycine (3.1b, R' = Ph, R'' = Me), and L-α-methylvaline (3.1c, R' = iPr, R'' = Me).[d] To obtain the corresponding aminophosphines, we applied standard procedures to these α-methyl-α-amino acids.



i) HCN, NH_3; ii) HO^-, ketone; iii) enzymatic hydrolysis.

Scheme 3.2

In Scheme 3.3 two standard procedures for the conversion

Or from Ochrobactrum anthropi, see: Van den Tweel, W.J.J.; Van Dooren, T.J.G.M.; De Jonge, P.H.; Kaptein, B.; Duchateau, A.L.L.; Kamphuis, J. Appl. Microbiol. Biotechnol. 1993, 39, 296.

[d] All of the ligands discussed in this chapter are derived from amino acids. We have chosen to maintain the Fischer notation (D and L) for absolute configuration; each ligand is then a member of a homochiral family starting from a certain amino acid. In amino acids the Fischer system translates into Cahn-Ingold-Prelog stereochemical designators as L ≡ S and D ≡ R.

of α-amino acids to dimethylaminophosphines are depicted. Both involve four steps. Two routes, via 3.5 or 3.6 are possible.

Scheme 3.3

The amino group of compounds 3.1 were reductively methylated with formaldehyde, hydrogen and Pd/C, yielding 3.5, and the carboxylic acid group was subsequently reduced with $LiAlH_4$ to 3.7. When larger substituents R' (eg. Ph, $PhCH_2$)[4] in natural amino acids were involved, the route via 3.6 was preferred. In that case, the reductive alkylation was perfomed on 3.6 using the Eschweiler–Clarke procedure.[e] The resulting amino alcohol 3.7 was converted to mesylate 3.8 and in situ subjected to substitution with potassium diphenylphosphine, furnishing 3.9.

Conversion of D-α-methylphenylalanine (3.1a) to 2-methyl-(R)-phephos (3.9a) was accomplished by the standard route via 3.6a in 39% overall yield. 2-methyl-(S)-glyphos (3.9b) was obtained from L-α-methyl-phenylglycine (3.1b) via 3.6b in 25% overall yield. Several attempts to convert L-α-methyl-valine (3.1c) to 3.6c were unsuccessful. A better approach to 3.7c is probably the route via 3.5c. For several reasons,[f] progress with 3.1c were not made.

Instead of the standard work up procedure[9] of 3.6, we strongly recommend the use of Glauber's salt[g] to hydrolyse the excess of $LiAlH_4$.[10] We have used this superior work up procedure in other, not in this thesis described, experiments. The resulting precipitate can be extracted with chloroform (or another appropriate solvent) in a Soxhlet apparatus more readily.

3.3 β-Aminosulphides

Incentives and strategy

The cross coupling results obtained by using 3.9b (see Section 4.7) led us to use a chelating atom, other than

[e] This route has advantages in practical sense, since an Eschweiler Clarke alkylation does not require a Parr apparatus, hydrogen gas, and Pd/C.

[f] Among these reasons are the shortage of 3.1c and the fact that we changed to another chiral catalytic system in the preparation of enantiomerically enriched 3-phenyl-1-butene, as will be described in Chapter 6.

[g] $Na_2SO_4 \cdot 10\ H_2O$.

phosphorus. We decided to use sulphur as an alternative, maintaining the tertiary amine group. Aminosulphides have been used before as ligands, albeit with low enantioselectivity.[5e] Recently, Sharpless et al. discussed the high enantioselectivity of ligands bearing large, plate-like aromatic substituents in asymmetric dihydroxylation of olefins.[11] We expected this strategy to have a wider application, although the asymmetric catalytic reactions, dihydroxylation and cross coupling, are quite different. We chose to use naphthyl substituents on the sulphur moiety, as depicted in Figure 3.2. We further expected the configurationally differences between 3.10 and 3.11 to result in a significant effect on enantioselection in cross coupling reactions.

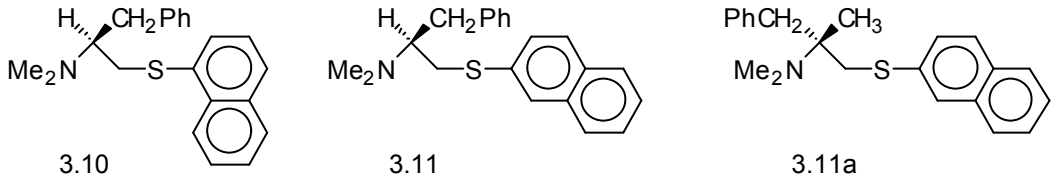


Figure 3.2

Synthesis of 3.10, 3.11, and 3.11a

The aminosulphides 3.10, 3.11 and 3.11a were prepared in yields of 68%, 92%, and 33%, respectively. They were synthesized from mesylates of amino alcohols 3.8 and 1- or 2-naphthalenethiol (cf. Section 3.2). For 3.10 and 3.11 this amino alcohol is L-2-(dimethylamino)-3-phenyl-1-propanol,[h] for 3.11a amino alcohol 3.7a. The synthetic route is analogous to the formation of aminophosphine as depicted in Scheme 3.3 except for step v), where Ph_2PH is replaced by 1- or 2-naphthalenethiol. A strong base like potassium tert-butoxide is not necessary, and was omitted in case of 1-naphthalenethiol to prevent disulphide formation. 1–Naphthalenethiol was most conveniently prepared[i] in a one

[h]Obtained in 73% overall yield from L-phenylalanine, according to the literature procedure of ref. 2.

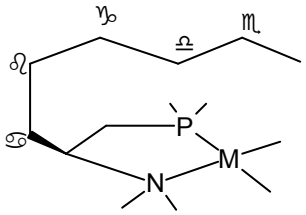
[i] 2-Naphthalenethiol is commercially available.

step reaction,[j] by addition of elementary sulphur to 1-naphthylmagnesium bromide. Because of the easy formation of disulphides, it was necessary to use freshly reduced 1–naphthalenethiol ($LiAlH_4$, THF) prior to reaction step vi, Scheme 3.3.

3.4 Ligands with sulphur containing appendages

Incentives and strategy

Aminophosphine ligands with a side chain containing sulphur as an extra heteroatom have been developed in our research group.[5e,f] Length and branching of the sulphur containing appendage were varied. In methphos (3.12, n = 2), the sulphur containing $(CH_2)_n$ side chain is too short to be placed properly above the catalytic centre (n = 2, sulphur in γ-position). Elongation of this side chain by one methylene group (3.12, n = 3, sulphur in δ-position) resulted in the most successful ligand, homomethphos, which provided ee in cross coupling higher than could be expected solely on basis of a steric effect (Figure 3.3).



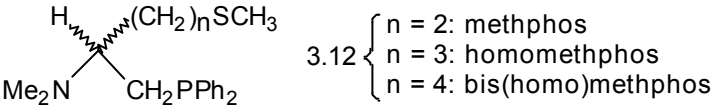


Figure 3.3

This indicates that the ee can be improved by other than simple steric means. Two possible explanations for the increase in ee were conceived, namely a ligating side arm that participates in the reductive elimination (Scheme 3.1, step d), or an (extra) coordinating site for the Grignard reagent that approaches the catalytic centre (Scheme 3.1 step c).[5e,f] Questions remain about the role of the sulphur moiety, since

[j] A two step preparation route of 1-naphthalenethiol by HCl-Zn reduction of 1-naphthalenesulphonyl chloride, which was previously prepared from 1-naphthalenesulphonic acid and $POCl_3$, was less successful.

X-ray studies of [3.12•$PdCl_2$] showed no coordination of the Pd^{II} centre to the sulphur atom.[5e,f]

We were interested in the optimum length of such sulphur containing side-chain on the aminophosphine ligand (eg. n = 4, sulphur in ε-position). Substitution of the methyl group on sulphur in 3.12, (n = 3) for a steric moiety like 2-propyl would give us more information about the role of this third hetero atom[k] in the catalytic proceedings. Substitution of the diphenylphosphine group of 3.12, (n = 4) for a 2-naphthalenethio group also has been considered and accomplished, in order to circumvent air sensitivity or instability of the diphenylphosphine group.

Synthesis and resolution of racemic amino acid amides

The syntheses of bis–(homo)methionine 3.16 and allylglycine 3.20 and the resolutions to L-3.16 and D-3.20, respectively, were accomplished by Ms. Agnes D. Cuiper at the Bio-Organic Chemistry (BOC) Section of DSM Research in Geleen. Syntheses of L-3.16, 3.12 (n = 4), 3.24, and 3.19 were also accomplished by Ms. Cuiper, and are described in the present thesis.

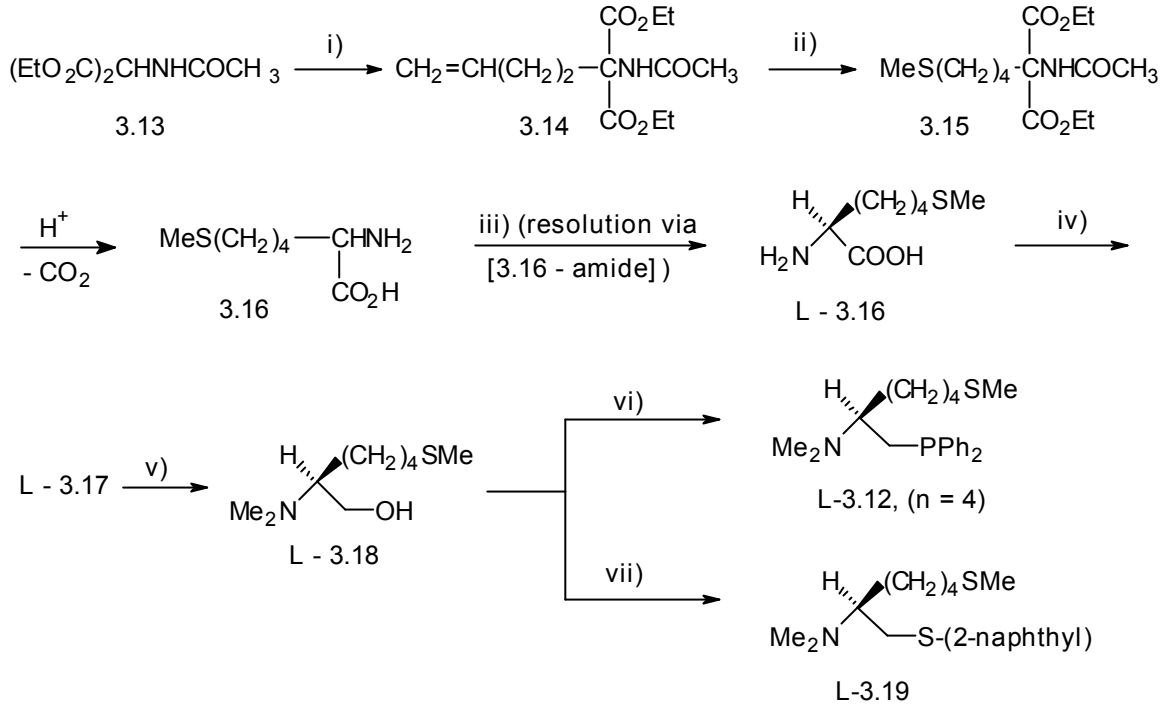
The synthesis of racemic 3.16 was accomplished analogously to the literature procedure that leads to homomethionine.[5] Compound 3.13 was deprotonated by sodium ethoxide and treated with 4-bromo-1-butene, to give 3.14 in quantitative yield (Scheme 3.4). A methylthio group was added in a free radical addition reaction in 70% yield to give 3.15, and racemic 3.16 was obtained in 90% yield by acid hydrolysis and decarboxylation. The synthesis is, just as the synthesis of homomethionine, easy to scale up.[5f,12]

In order to obtain a ligand comparable to 3.12, but more sterically hindered around sulphur, we chose for addition of 2-propanethiol to D-3.20 (vide infra). Racemic 3.20 was prepared in 85% overall yield by a literature procedure.[13]

Racemic 3.16 and racemic 3.20 were esterified by reaction with $SOCl_2$ in methanol. Attempts to synthesize amino acid amides from the methyl ester of 3.16 by reaction with aqueous ammonia were unsuccessful. Enhancing the solubility of the

[k]In addition to phosphorus and nitrogen.

methyl ester of 3.16 by



i) NaOEt, 4-bromo-1-butene; ii) $(PhCO)_2O_2$, $(CH_3CO_2)_2Hg$, MeSH, h■ iii) Pseudomonas Putida; iv) $LiAlH_4$; v) H_2CO, HCO_2H, ■ vi) MsCl, $Ph_2P^-K^+$; vii) MsCl, (2-naphthyl)-S^-K^+

Scheme 3.4

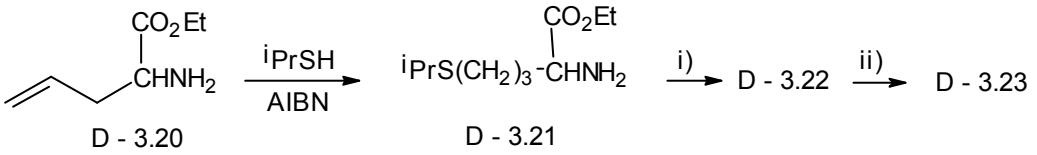
addition of a small amount of 1,4-dioxane gave a partial conversion to the amide of 3.16 (<30%). Reaction of the methyl ester of 3.16 with aqueous ammonia in a carius oven at 100°C resulted in decomposed material. Use of neat NH_3 in a carius oven at ambient temperature furnished the amide of 3.16 in less than 30% yield. On stirring the above mentioned amino acid esters for five days in methanol saturated with NH_3, the amino acid amides of 3.16 and 3.20 were realized in yields over 90%.

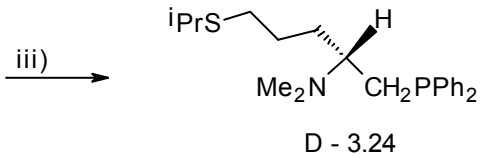
Enzymatic resolutions of the amino acid amides of 3.16 and 3.20 were accomplished with a crude peptidase from Pseudomonas Putida.[8] Since enzymatic resolution of racemic 3.16-amide did not furnish enantiomerically pure L-3.16 (71%

ee), classical resolution was considered. As resolving agent we chose chlocyphos,[l] developed by Ten Hoeve and Wynberg,[14] since this has been successfully applied to methionine (3.12, n = 2)[14] and homomethionine (3.12, n = 3). We obtained enantiomerically pure L-3.16 as judged from chiral TLC, though the yield of this (not optimized) resolution was low (9%). Therefore, enzymatically resolved 3.16 was used for further syntheses. In the case of the amide of 3.20, the enzymatic resolution was terminated at a conversion of 57%, yielding L-3.20 (75% ee) and D-3.20[m] (> 95% ee).

Aminophosphine and ~sulphide ligands bearing sulphur containing appendages

On addition of 2-propanethiol to the allylic position of D-3.20, compound D-3.21 was realized in 21% yield (Scheme 3.5). The amino acids L-3.16 and D-3.21 have been converted by the standard method (Section 3.2) to aminophosphines 3.12 (n = 4) (by way of amino alcohol L-3.17 and dimethylamino alcohol L-3.18) and D-3.24 (by way of amino alcohol D-3.22 and dimethylamino alcohol D-3.23). The syntheses of both L-3.12 (n = 4) and D-3.24 were accomplished in 52% overall yield. Analogous to the procedure described in Section 3.3, aminosulphide L-3.19 was obtained from L-3.18 in 42% yield.





i) $LiAlH_4$; ii) H_2CO, HCO_2H, iii) MsCl, $Ph_2P^-K^+$

[l] Chlocyphos is an acronym for (S)-(+)-4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,2,3-dioxaphosphorinane-2-oxide.

[m] After hydrolysis of the amide.

Scheme 3.5

3.5 Summary and conclusions

In this chapter the syntheses of amino acid derived β-aminophosphines and β-aminosulphides are described. Enantiomerically enriched α-methyl-β-aminophosphines and α-methyl-β-aminosulphides were synthesized in 4 steps from α-methyl-α-amino acids, affording 3.9a, 3.9b and 3.11a. We were not able to accomplish reduction of 3.1c to afford 3.6c; a promising route to 3.7c may proceed via 3.5c. β-Aminophosphines and β-aminosulphides with sulphur containing appendages were synthesized. We succeeded in the synthesis of the homologue 3.12 (n = 4) of homomethphos 3.12 (n = 3), which has proven to be a successful ligand in asymmetric cross couplings. A naphthalenesulphide analogue of 3.12 (n = 3) was realized in 3.19. We succeeded in the synthesis of 3.24, an analogue of homomethphos 3.12 (n = 3) with a sterically more hindered sulphur in the side chain. In how far these ligands have an influence upon the enantioselection in the asymmetric cross coupling reaction under investigation, is described in Chapter 4.

3.6 Experimental section

General remarks: All reactions were performed under a nitrogen atmosphere, unless stated otherwise. All reagents and solvents were purified and dried, following standard procedures.[15] All commercially available chemicals were purchased from Janssen Chimica (Acros), Aldrich or Fluka, and were used without further purification, unless stated otherwise. Melting points (uncorrected) were determined on a Mettler FP-2 melting point apparatus, equipped with a Mettler FP-21 microscope. ^{1}H NMR spectra were recorded on a Hitachi Perkin Elmer R-24B High Resolution NMR spectrometer (60 MHz), on a JEOL JNM-PMX60 si NMR spectrometer (60 MHz), on a Varian Gemini-200 (200 MHz) or on a Varian VXR-300 spectrometer (300 MHz). Chemical shifts are denoted in δ-units (ppm) relative to tetramethylsilane (TMS) as an internal standard (δ = 0 ppm) or relative to the solvent and converted to the TMS scale using δ ($CHCl_3$) = 7.26 ppm. ^{13}C NMR spectra were recorded in the APT mode on either a

Varian Gemini-200 (50.32 MHz) or a Varian VXR-300 (75.48 MHz) spectrometer. Chemical shifts are denoted in δ-units (ppm) relative to the solvent and converted to the TMS scale using δ ($CHCl_3$) = 76.91 ppm. The splitting patterns are designated as follows: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Mass spectra were recorded on a AEI-MS-902 mass spectrometer by Mr A. Kiewiet. Elemental analyses were performed in the Microanalytical Department of this laboratory by Mr H. Draayer, Mr J. Ebels, and Mr J. Hommes. Compound 3.20 was prepared according to literature procedure.[13]

Reduction of amino acid 3.1 to amino alcohol 3.6 (Procedure A) This reaction was performed in a three-necked flask (B24), equipped with a reflux condenser and a $CaCl_2$ drying tube. Amino acid 3.1 (1.0 eq.) was added under stirring in portions to a suspension of $LiAlH_4$ (1 M, 2.5 eq.) in THF at 0°C. The reaction mixture was refluxed overnight. After standard work up[9] and extraction with Et_2O, the combined organic layers were washed with water and brine, dried over Na_2SO_4, concentrated under reduced pressure, distilled by means of bulb to bulb distillation to give amino alcohol 3.6 (An alternative work up procedure[10] for the used standard work up procedure[9] is highly recommended, since complexation of the product to aluminium salts can be significant. This alternative method applies crystal water in Glauber salt, $Na_2SO_4 \bullet 10\ H_2O$, for hydrolysis of the excess hydride. The resulting salts can be extracted successfully, eventually followed by extensive extraction in a Soxhlet apparatus).

D-2-Amino-2-methyl-3-phenyl-1-propanol (3.6a, D-α-methyl-phenylalaninol)
Reduction of D-3.1a (4.9 g, 27.3 mmol) gave D-3.6a as a colourless oil in 75% yield (Procedure A); ^1H NMR ($CDCl_3$, 60 MHz): δ 1.00 (s, 3 H), 2.68 (s, 6 H), 3.35 (s, 2 H), 7.1-7.4 (m, 5 H).

L-2-Amino-2-methyl-2-phenyl-1-ethanol (3.6b, L-α-methyl-phenylglycinol)

Reduction of L-3.1b (4.13 g, 25 mmol) gave L-3.6b as a colourless oil in 54% yield (Procedure A). After prolonged extraction with Et_2O (40 h), the isolated yield was raised to 76%; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.47 (s, 3 H), 2.42 (br, 3 H), 3.59 (d, J = 11 Hz, 1 H), 7.23 - 7.46 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 26.8 (q), 56.7 (s), 71.4 (t), 125.3 (d), 127.0 (d), 128.5 (d), 145.7 (s).

Reductive alkylation (Eschweiler Clarke)[16] of 3.6 (Procedure B) Formic acid (4.4 eq.) and formaldehyde (2.2 eq., 37 wt.% solution in water) were added to amino alcohol 3.6 (neat, 1 eq.) at 0°C. The reaction mixture was refluxed overnight and subsequently poured on crushed ice. The mixture was made slightly basic with 15% NaOH and then extracted with Et_2O (3 x). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure and distilled by means of bulb to bulb distillation, to give 3.7.

D-2-Dimethylamino-2-methyl-3-phenyl-1-propanol (3.7a)
Reductive alkylation of D-3.6a (2.38 g, 20.45 mmol) gave D-3.7a as a colourless oil after bulb to bulb distillation in 61% yield (Procedure B); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.91 (s, 3 H), 2.34 (s, 6 H), 2.68 (d, $^2J_{AB}$ = 12.5 Hz, 1 H), 2.76 (d, $^2J_{AB}$ = 12.8 Hz, 1 H), 3.18 (d, J_{AB} = 10.6 Hz, 1 H), 3.18 (s, 1 H), 3.39 (d, J_{AB} = 10.6 Hz, 1 H), 7.17-7.28 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 16.4 (q), 37.8 (q), 38.5 (t), 60.0 (s), 64.1 (t), 125.9 (d), 127.8 (d), 130.4 (d), 138.0 (s).

L-2-Dimethylamino-2-methyl-2-phenyl-1-ethanol (3.7b)
Reductive alkylation of L-3.6b (1.24 g, 8.2 mmol) gave L-3.7b as a colourless oil after bulb to bulb distillation (100°C, 0.05 mbar) in 69% yield (Procedure B); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.36 (s, 3 H), 2.21 (s, 6 H), 3.62 (d, J = 10.6 Hz, 1 H), 3.69 (d, J = 10.6 Hz, 1 H), 7.34-7.49 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 14.4 (q), 38.5 (q), 63.4 (s), 68.7 (t), 126.9 (d), 127.0 (d), 128.2 (d), 143.3 (s).

Preparation of diphenylphosphine derivatives 3.9 from amino alcohol 3.7 (Procedure C)
Methanesulphonyl chloride (1.1 eq.) was added dropwise to a

stirred solution of N,N-dimethylamino alcohol 3.7 (1.0 eq., 1 M in THF) and 1.1 eq. triethylamine at 0°C. Stirring was continued at 0°C for 2 h, after which time the reaction was treated in one portion with a freshly prepared, bright deep red mixture of diphenylphosphine (1.0 eq.) and KO^{t}Bu (2.5 eq.) in THF (0.2 M to diphenylphosphine) at 0°C. The red colour faded on addition to give a yellow mixture which was stirred for an additional 2 hours at 0°C. The work up procedure includes evaporation of the major part of the organic solvent, after which the residue was shaken with 15% NaOH and benzene. The aqueous layer was extracted twice with benzene and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by means of bulb to bulb distillation (≈200°C, ≈0.005 mm Hg) to give N,N-dimethylaminophosphine 3.9.

D-2-Dimethylamino-2-methyl-1-diphenylphosphino-3-phenylpropane (3.9a)

Compound D-3.9a was synthesized from D-3.7a in 86% yield, by Procedure C and additional purification over a short column (Al_2O_3, Et_2O) to remove phosphine oxides; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.03 (s, 3 H), 2.18 (s, 6 H), 2.33-2.47 (m, 2 H), 2.82 (s, 2 H), 7.15-7.82 (m, 25 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 23.7 (q), 36.7 (t), 38.5 (q), 41.2 (t), 59.8 (s), 125.7 (d), 127.7 (d), 128.0 (d), 128.1 (d), 128.2 (d), 130.7 (d), 139.0 (s), 140.2 (s); ^{31}P NMR ($CDCl_3$, 121.4 MHz): δ -24.8.

L-2-Dimethylamino-2-methyl-1-diphenylphosphino-2-phenylethane (3.9b)

Compound L-3.9b was synthesized from L-3.7b by Procedure C and purified over a short column (Al_2O_3, Et_2O) to remove phosphine oxide (47%). The ^{31}P NMR spectrum contained R_3PO absorption if the material had been exposed to air; this indicates the sensitivity to oxidation; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.45 (s, 3 H), 2.23 (s, 6 H), 2.55-2.73 (m, 2 H), 7.15-8.86 (m, 25 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 18.2 (q) 29.5 (q), 47.1 (t), 70.3 (s), 124.6 (d), 126.7 (d), 127.8 (d), 128.0 (d), 128.1 (d), 128.4 (d), 143.1 (s), 148.0 (s); ^{31}P NMR ($CDCl_3$, 121.4 MHz): δ 21.3, -40.5 (major peaks).

L-2-Dimethylamino-1-(1-naphthylthio)-3-phenylpropane (3.10)
Freshly reduced 1-naphthalenethiol (304 mg, 1.9 mmol) in THF (10 mL) was added in one portion to the mesylate prepared in situ from L-2-(dimethylamino)-3-phenyl-1-propanol (see Footnote h) (340 mg, 1.9 mmol) and methanesulphonyl chloride (0.16 mL, 2.1 mmol) in THF (15 mL) at 0°C. Due to ready formation of the 1-naphthalene disulphide under basic conditions, no extra base, such as KO^{t}Bu, was added. The mixture was stirred overnight at ambient temperature. Work up procedure, as described for aminophosphines in Procedure C, afforded L-3.10 (68%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.46 (s, 6 H), 2.49-3.21 (m, 5 H), 7.18-8.44 (m, 12 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 34.6 (t), 35.0 (t), 40.6 (d), 65.8 (q), 125.1 (d), 125.5 (d), 126.2 (d), 126.4 (d), 126.7 (d), 128.5 (d), 128.6 (d), 129.2 (d), 129.4 (d), 130.3 (d), 132.8 (q), 133.4 (q), 134.1 (q), 139.6 (q).

L-2-Dimethylamino-1-(2-naphthylthio)-3-phenylpropane (3.11)
A mixture of 2-naphthalenethiol (304 mg, 1.9 mmol) and KO^{t}Bu (0.533 mg, 4.75 mmol) in THF (10 mL) was added in one portion to the in situ prepared mesylate from L-2-(dimethylamino)-3-phenyl-1-propanol (see Footnote h) (340 mg, 1.9 mmol) and methanesulphonyl chloride (0.16 mL, 2.1 mmol) in THF (15 mL) at 0°C. The mixture was stirred overnight at ambient temperature. The work up procedure, as described for aminophosphines in Procedure C, afforded L-3.11 (92%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.55 (s, 6 H), 2.76 (m, 1 H), 2.80-3.33 (m, 4 H), 7.26-8.13 (m, 12 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 34.1 (t), 34.4 (t) 40.7 (q), 65.5 (d), 125.4 (d), 126.2 (d), 126.3 (d), 126.4 (d), 127.0 (d), 127.7 (d), 128.2 (d), 128.6 (d), 129.0 (d), 129.3 (d), 131.3 (s), 133.9 (s), 134.8 (s), 139.8 (s).

D-2-Dimethylamino-2-methyl-1-(2-naphthylthio)-3-phenylpropane (3.11a)
2-Naphthalenethiol (320 mg, 2.0 mmol) in THF (5 mL) was added by syringe to D-3.8a, prepared from D-3.7a (387 mg, 2.0 mmol) and methanesulphonyl chloride (0.17 mL, 2.2 mmol), at 0°C. Additional triethylamine (0.1 mL) was added, and the mixture was stirred for 24 h at ambient temperature. The work up

procedure, as described for aminophosphines in Procedure C, afforded 632 mg crude material. This was filtered over a short column (Al_2O_3, basic; Et_2O/hexane 1:1) to give D-3.11a (33%); MS calcd. for $C_{22}H_{25}NS$: 335.171, found: 335.171; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.46 (s, 3 H), 2.41 (s, 6 H), 2.61 (s, 2 H), 3.08 (s, 2 H), 7.28-7.74 (m, 12 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 18.3 (q), 38.5 (q), 40.7 (t), 41.6 (t), 59.9 (s), 125.0 (d), 125.3 (d), 126.4 (d), 126.5 (d), 126.9 (d), 127.0 (d), 127.7 (d), 127.9 (d), 128.1 (d), 130.7 (d), 131.4 (s), 133.9 (s), 135.9 (s), 138.5 (s).

Diethyl-(4-butenyl)acetamidomalonate (3.14)
Compound 3.13 (86.6 g, 400 mmol) was added to a warm solution of of sodium (9.2 g, 400 mmol) in ethanol (abs) (500 mL) under a nitrogen atmosphere. After stirring for 15 minutes, the mixture was cooled to 10°C and 4-bromo-1-butene (54 g, 400 mmol) was added slowly. The mixture was stirred and refluxed for one night and evaporated to dryness. Water (200 mL) and chloroform (100 mL) were added. The aqueous layer was extracted twice with chloroform (100 mL). The combined chloroform fractions were washed with brine and dried ($MgSO_4$) and concentrated, to give crude 3.14 as a yellow liquid in quantitative yield, which was used without further purification, ^{1}H NMR ($CDCl_3$): δ 1.25 (t, 6 H), 1.28 (t, 2 H), 2.07 (s, 3 H), 2.2-2.6 (m, 2 H), 4.23 (q, 4 H), 4.8-6.0 (br m, 3 H), 6.8 (br s, 1 H).

Diethyl-(4-Methylthiobutanyl)acetamidomalonate (3.15)
Compound 3.14 (400 mmol) was added to a solution of ethanol (200 mL), benzoylperoxide (1.0 g, 4.1 mmol) and mercury$^{(II)}$ acetate (4.5 g, 14 mmol). The solution was cooled to –30°C. Methanethiol (25 mL) was added quickly and the whole mixture was irradiated with a high-pressure mercury lamp (Hanau TQ-150) equipped with a quartz filter for one night at –10°C. The resulting black mixture was filtered over Celite and dried, to give crude 3.15 as a light yellow solid in 70% yield, which was used without further purification; ^{1}H NMR ($CDCl_3$): δ 1.25 (t, 6 H), 1.28 (t, 2 H), 1.35 (m, 2 H), 2.03 (s, 6 H), 2.40 (m, 4 H), 4.20 (q, 4 H), 7.0 (br s, 1 H).

2-Amino-6-methylthio-1-hexanoic acid (3.16, racemic bis(homo)-methionine)
To 3.15 was added 4N HCl solution (400 mL), and the mixture was refluxed for 6 h. After the solvent was removed in vacuo, water (100 mL) was added. Under cooling and stirring, 10 N NaOH was added until pH 7. The white solid was filtered off, to give racemic 3.16 in 90% yield (63% overall yield); ^{1}H NMR (D_2O/DCl, 200 MHz): δ 1.45 (m, 2 H), 1.56 (m, 2 H), 1.92 (m, 2 H), 2.00 (s, 3 H), 2.47 (t, 2 H), 4.09 (t, 1 H). Further purification of a part was accomplished by recrystallization from water/methanol and water/acetone; mp > 200°C; MS calcd.

for $C_7H_{15}NO_2S$: 177.082, found 177.082; Analysis calculated for $C_7H_{15}NO_2S$: C 47.43, H 8.53, N 7.90, S 18.09; found: C 46.67, H 8.49, N 7.82, S 17.87.

Enzymatic resolution of 3.16 and 3.20
Standard enzymatic resolutions of the amino acid amides of 3.16 and 3.20 were realized according to the literature procedure[5e] with a crude peptidase from Pseudomonas Putida, affording L-3.16 (71% ee) and D-3.20 (> 95% ee). These resolutions are described in detail in the undergraduate report of Ms. Cuiper.

Resolution of 3.16 with chlocyphos[14]
Racemic 3.16 (532 mg, 3.0 mmol) and (S)-(+)-4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,2,3-dioxaphosphorinane-2-oxide (chlocyphos, 830 mg, 3.0 mmol) were dissolved in a mixture of warm water : ethanol of 2.7 : 1 v:v (18 mL). The solution was stirred for 7 days, after which the salt was filtered off and washed with water. The salt was stirred with HCl (2.4 M, 8 mL) for 24 h, and filtered off. The filtrate was evaporated to dryness, dissolved in 2 mL water : ethanol and neutralized with a NaOH solution (10 M). The precipitate was filtered off, washed with ethanol and dried to give D-3.16 in 8.6% chemical yield, in > 99% ee, as judged by chiral TLC (CHIRALPLATE, Machery Nagel, Duren) against racemic 3.16.

L-2-Amino-6-methylthio-1-hexanol (3.17)
Reduction of L-3.16 (3.0 g, 17 mmol) with $LiAlH_4$ gave L-3.17 in quantitative yield as a colourless oil (Procedure A); ^{1}H NMR ($CDCl_3$, 60 MHz): δ 1.6 (m, 8 H), 2.1 (s, 3 H), 2.4 (m, 3 H), 3.4 (m, 3 H).

L-2-Dimethylamino-6-methylthio-1-hexanol (3.18)
The crude L-3.17 was used as such, and gave L-3.18 in 80% yield as a colourless oil after purification by bulb to bulb distillation (120°C, 0.01 mm Hg) (Procedure B). The ee of L-3.18, 71%, was determined by ^{1}H NMR spectrum analysis of (S)-2-chloropropionyl coupled product;[17] ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.14 (m, 2 H), 1.34 (m, 2 H), 1.59 (m, 2 H), 2.09 (s, 2 H), 2.27 (s, 6 H), 2.49 (t, 2 H), 2.57 (m, 1 H), 3.25 (dd, 1 H),

3.53 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 15.4 (q), 23.6 (t), 26.0 (t), 29.2 (t), 33.8 (t), 39.9 (q), 60.7 (t), 64.4 (d).

L-2-Dimethylamino-1-diphenylphosphino-6-methylthiohexane (3.12 (n = 4), L-bis(homo)methphos)

Compound L-3.12 (n = 4) was synthesized from L-3.18 (0.62 g, 3.23 mmol, 71% ee) in 68% yield (Procedure C). A double Schlenk vessel was used owing to the extreme air sensitivity of the product. MS calcd. for $C_{21}H_{30}NPS$: 359.184, found: 359.183. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.41-1.51 (m, 6 H), 2.07 (s, 3 H), 2.15 (s, 6 H), 2.24-2.47 (m, 5 H), 7.26-7.49 (m, 10 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 15.50 (q), 26.12 (t), 28.30 (t), 29.19 (t), 30.78 (t), 34.08 (t), 39.91 (q), 61.03 (d), 128.37 (s), 132.67 (d), 133.06 (d), 138.80 (d), 139.30 (d); ^{31}P NMR ($CDCl_3$, 80.95 MHz): δ -20.23.

L-2-Dimethylamino-6-methylthio-1-(2-naphthylthio)-hexane (3.19)

A mixture of 2-naphthalenethiol (320 mg, 2.0 mmol) and KO^{t}Bu (0.560 mg, 5.0 mmol) in THF (10 mL) was added in one portion to the in situ prepared mesylate from L-3.18 (380 mg, 2.0 mmol) and methanesulphonyl chloride (0.17 mL, 2.2 mmol) in THF (15 mL). The mixture was stirred for 2 h at 0°C. Work up procedure, as described for aminophosphines in Procedure C, afforded a light yellow oil. The crude product was purified by column chromatography (Al_2O_3-neutral, Et_2O) to give L-3.19 (42%) as a colourless oil; ^{1}H NMR ($CDCl_3$ 200 MHz): δ 1.20-1.66 (m, 6 H), 2.06 (s, 3 H), 2.30 (s, 6 H), 2.47 (t, 2 H), 2.68 (m, 1 H), 2.92 (dd, 1 H), 3.25 (dd, 1 H), 7.2-7.8 (m, 7 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 15.3 (q), 25.8 (t), 28.8 (t), 33.7 (t), 40.2 (q), 63.6 (d), 125.8 (d), 126.6 (d), 127.0 (d), 127.3 (d), 127.4 (d), 127.6 (d), 128.5 (d), 131.7 (s), 133.3 (s), 133.6 (s); MS calcd. for $C_{19}H_{27}NS_2$: 333.158, found: 333.158.

D-2-Amino-5-(2-propylthio)-1-pentanoic acid (3.21)

D-3.20 (5.5 g, 47.8 mmol, 95% ee), 2-propanethiol (11 g, 143.5 mmol) and AIBN[n] (0.26 g, 1.4 mmol) in water-methanol 1:1 (200 mL) were refluxed for 48 hours. After 24 hours an additional portion of AIBN (0.26 g, 1.4 mmol) was added. The solvent and

[n] 2,2'-Azobis(2-methylpropionitrile).

excess of 2-propanethiol were evaporated under reduced pressure. Hot water was added, just enough to dissolve the residue, followed by acetone (200 mL). The white solid obtained was filtered and dried. Since this material included starting material (about 70%), the procedure was repeated with fresh 2-propanethiol and AIBN. The crude product was recrystallized from water-acetone and water-methanol to give (D)-3.21 (21%); mp > 200°C; ^{1}H NMR (D_2O/DCl, 200 MHz): δ 1.14 (d, 6 H), 1.67 (m, 2 H), 1.99 (m, 2 H), 2.56 (t, 2 H), 2.94 (sept, 1 H), 4.12 (t, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 27.5 (q), 29.4 (t), 33.4 (t), 38.4 (t), 39.3 (d), 57.4 (d),175.7 (s); MS calcd. for $C_8H_{17}NO_2S$: 191.098, found: 191.098; Analysis calculated for $C_8H_{17}NO_2S$: C 50.23, H 8.96, N 7.32, S 16.76, found: C 50.24, H 8.86, N 7.23, S 16.59.

D-2-Amino-5-(2-propylthio)-1-pentanol (3.22)
Reduction of D-3.21 (1.33 g, 6.97 mmol) gave D-3.22 in 82% yield as a colourless oil (Procedure A); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.86 - 3.65 (m, 12 H), 1.27 (d, 6 H), 2.88 (sept., 1 H).

D-2-Dimethylamino-5-(2-propylthio)-1-pentanol (3.23)
The crude D-3.22 was used as such, and gave D-3.23 in 79% yield as a colourless oil after purification by bulb to bulb distillation (120°C, 0.01 mm Hg) (Procedure B); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.26 (d, 6 H), 1.60 (m, 4 H), 2,28 (s, 6 H), 2.54 (m, 3 H), 2.91 (sept, 1 H), 3.26 (dd, 1 H), 3.53 (m, 2 H); ^{13}C NMR ($CDCl_3$): δ 23.3 (q), 23.5 (t), 27.2 (t), 30.6 (t), 34.8 (d), 40.0 (q), 60.8 (t), 64.3 (d); MS calcd. for $C_{10}H_{23}NOS$: 205.150, found: 205.150.

D-2-Dimethylamino-1-diphenylphosphino-5-(2-propylthio)-pentane (3.24)

Compound D-3.24 was synthesized from D-3.23 (0.83 g, 4.03 mmol) in 80% yield (Procedure C); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.23 (d, 6 H), 1.20-1.60 (m, 4 H), 2.14 (s, 6 H), 2.08-2.45 (m, 5 H), 2.86 (sept, 1 H), 7.25-7.49 (m, 10 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 23.35 (q), 27.01 (t), 28.27 (t), 30.40 (t), 30.45 (t), 34.58 (d), 39.79 (q), 60.69 (d), 128.27 (d), 132.57 (d), 133.01 (d), 138.57 (q), 139.25 (q); ^{31}P NMR ($CDCl_3$, 80.95 MHz): δ -20.40.

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Chapter 4

Asymmetric Cross Coupling Reactions With An Improved Grignard Reagent Solution

4.1 Introduction

In Chapter 2 the transition metal catalysed cross coupling reaction was discussed as a route to 3-phenyl-1-butene. When appropriate asymmetric ligands, as described in Sections 2.1 and 2.2, and Chapter 3, are used for the catalytic centre, this profen-precursor can be obtained in a chiral, non-racemic form. The enantioselectivity, although not absolute, is quite high, values of 80–90% ee being accessible. The enantioselectivity of asymmetric cross coupling reactions, however, is easily influenced by many more factors than the asymmetric catalytic complex alone, as we have discussed in Chapter 2. Some of these factors arise in the preparation of the Grignard reagent, and are often overlooked.

This chapter opens with mechanistic aspects of organomagnesium halide formation in Section 4.2, followed by the problems in practical sense in Section 4.3. The scope of methods to prepare a Mg surface for reaction with organohalides is discussed in Section 4.4 In a workable scheme for synthetic purposes, the ee values for the asymmetric cross coupled products must depend unambiguously on the scalemic catalyst and not on additional factors that influence enantioselectivity.[a] Some of these factors, originate from the composition of the Grignard reagent solution and its preparation, which will be described in Section 4.5. To exclude the influence of these factors adequately, the preparation of the magnesium surface prior to reaction with RX had to be improved. The development of a method to prepare improved Grignard reagent solutions is described in Section 4.6, as well as the different stereochemical consequences.

In Section 4.7 asymmetric cross coupling reactions will

[a] cf. Section 2.3-I Influence of the alkylating species RMX.

be discussed, in which use is made of the improved solution of **4.2**. The syntheses of the asymmetric ligands applied in these experiments were discussed in Chapter 3. In the present chapter, cross couplings with a mixture of Grignard reagent and zinc halide will be discussed as well. With regard to reactivity in cross couplings, a substantially different behaviour is found between mixtures of zinc halide with Grignard solutions prepared in the conventional and the improved manner. Cross couplings with RZnX solutions that have been prepared under magnesium salt-free conditions will be described separately in Chapter 5, since there is considerable difference between these organozinc reagents and the 'classic' mixture of Grignard reagent and zinc halide.

4.2 Grignard reagents - different mechanistic models

Introduction

The Grignard reagent is one of the most useful, perhaps the most useful, of all organometallic intermediates. In the last years of the nineteenth century, Victor Grignard (1871-1935) examined the so called Barbier synthesis[1] (Scheme 4.1, eq. 2) when working in the group of Barbier. Grignard proposed the reactive intermediate to be RMgX (Scheme 4.1, eq. 1) and although Barbier did not approve of the idea, Grignard carried out some experiments and demonstrated the formation of RMgX. Barbier broadmindedly commended Grignard upon the making of an important scientific discovery, and encouraged him to exploit it.[b] The first description of the new reagents, and of some of their properties and reactions, appeared in 1900.[2] The Barbier synthesis has later become a variation of the Grignard reaction. In 1954, Kharasch and Reinmuth stated that "it might be said that he who knows and understands the Grignard reactions has a fair grasp of organic chemistry, for most fundamental processes have prototypes or analogues in phenomena observable in Grignard systems".[3]

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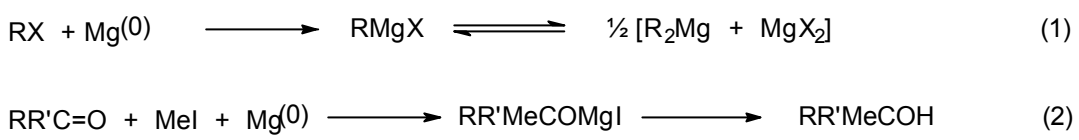
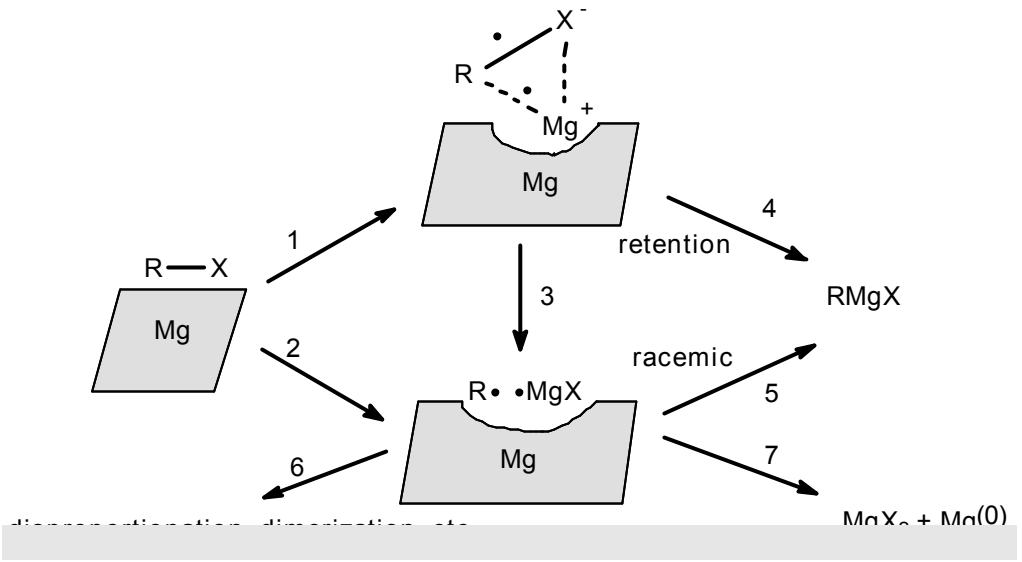
[b] The Barbier synthesis differs from the normal Grignard reaction in that the carbonyl compound is already present at the beginning of the reaction.



Scheme 4.1

More than 90 years after the initial reports,[2] the mechanism of the Grignard reagent formation has been and still is a topic of active interest.[4,5,6,7,8,9,10,11,12,13,14] There remain various unsettled questions about the mechanism. In the fifties Kharasch and Reinmuth already believed that alkyl radicals are intermediates and they suggested a mechanism which now is called the A (adsorption) model. Unfortunately, the Grignard reagent is formed in a heterogeneous reaction occurring at a solid-liquid interface and no nonelectrochemical organic reaction occurring at such an interface is understood at the mechanistic level that is typical for reactions in homogeneous solutions. This is due to the lack of kinetic studies at least up to the mid eighties. The first steps to fill up this gap were made by Garst et al., who proposed a mechanistic model using kinetics: the D (diffusion) model.[8,9,10,11,12]

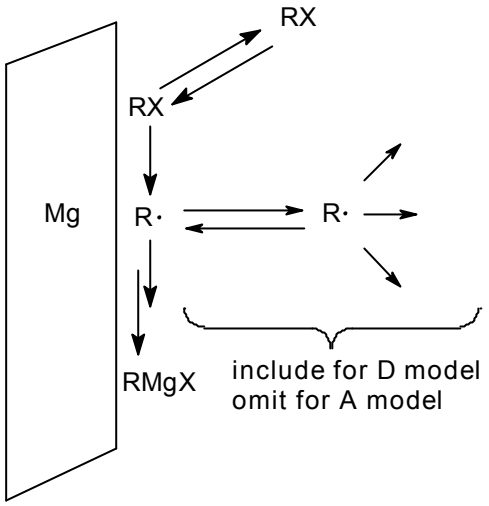
Even now, there is controversy on the surface nature of the radical, with Walborsky and Garst as protagonists for the A model and the D model, respectively. The models differ as to whether the intermediate radicals diffuse freely in solution, or remain adsorbed at the magnesium surface.



Scheme 4.2 Proposed Mechanism for Grignard Formation - The Adsorption Model

The A model

The A model is based on experimentally established product distributions and stereochemistry observed in the formation of the Grignard reagent. In the A model two species can be formed after the initial electron transfer: a tight radical-anion - radical-cation species (path 1), which can either collapse to form RMgX with conserved stereochemistry (path 4) or give a loose [R● MgX●] radical pair (path 3). Alternatively, a loose [R● MgX●] radical pair can be formed directly by an electron transfer (path 2). Grignard reagents formed via path 1 and 4 are presumed to be formed with retention of configuration, whereas via path 2 and 5 (or 1, 3, 5) RMgX is formed in racemic form. A more detailed discussion about the chirality of Grignard reagents is beyond the scope of this thesis. We refer the reader to the references about this subject.[5,6,7]



Scheme 4.3 Proposed Mechanism for Grignard Formation - The Diffusion Model

The D model

The D model is a mathematical model and based on a kinetic analysis of the product distribution.[8,9,10,11,12] In this model, it is assumed that only the electron transfer processes take place at the Mg surface, whereas the A model proposes that all reactions occur there. Although the difference is subtle, it is more than semantic, since in the D model radicals are predicted to get many molecular diameters out into the solution before reaction. To get an idea of the (mathematical) distance a radical can diffuse away and still come back to the magnesium surface, it has been calculated that n-octyl radicals can travel as far as 17,000 Å into the solution and still have a 40% chance of getting back to the magnesium surface before reacting with ether solvent. This is a result of the low reactivity between the radical and the solvent and, on the other hand the 'radical trapping ability' of the magnesium surface. Walborsky, on the other hand, proved experimentally that tertiary radicals (which are assumed to react even slower with the solvent than do n-octyl radicals) generated in solution within 1,500 Å of the Mg surface do not form a Grignard reagent and, consequently, magnesium does not

behave as an effective radical trap.[13]

In fact, two questions remain: does the Grignard formation proceed entirely via free radicals on the Mg surface or are other intermediates involved, such as radical anions. And: do these intermediates remain largely on the surface or do they diffuse freely in solution all the time? According to Garst, "the D model radicals are not 'in solution'; instead the radicals belong to surface-radical pairs. The behaviour of these type radicals is very different from those of both radical-radical pairs and individual radicals in solution".[8]

The A and D models have been reviewed by Walling,[14] who finally sympathized more with the D model than the A model. Simply, the D model is capable of quantitative predictions supported by mathematical analysis. The A model is based on experimental data; it is difficult to falsify for it invokes several additional reactions of poorly characterized species and has little predictive power. Both models have their incompletenesses.

This section has no direct relationship to the investigation which is described in this thesis. It illustrates the intricacy of (presumed) behaviour of organometal compounds at the metal suface, and gives a brief review of recent mechanistic models. Both the two models, A and D, have no consequence for the mechanism of the asymmetric cross coupling reaction, described in this thesis.

4.3 Grignard reagents - in practical sense

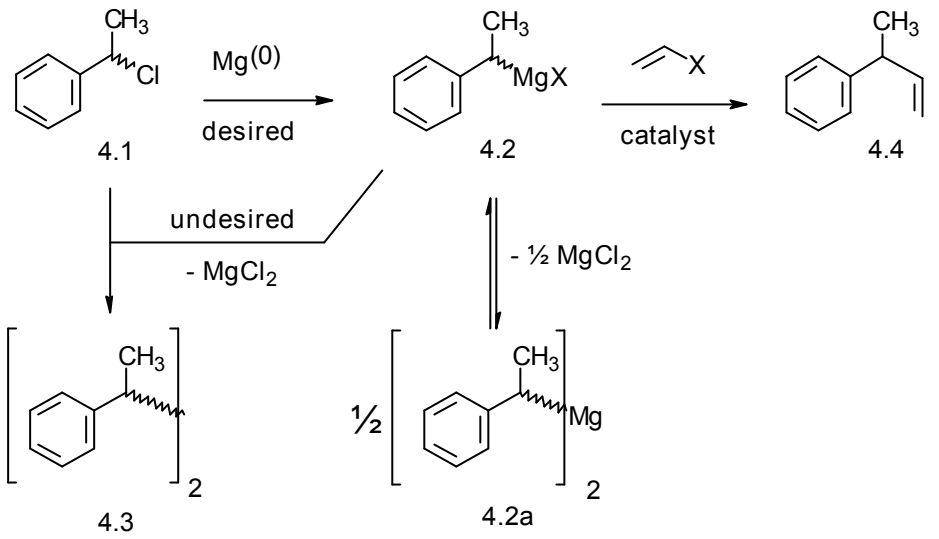
The Grignard reagent **4.2**, discussed in Chapter 2, was generally prepared from **4.1**, as depicted in Scheme 4.4,[15] in a routine procedure. This was accomplished with magnesium turnings which were pretreated by a crystal of elementary iodine. In the vast majority of the cases, we had to heat the flask locally to initiate the reaction, after addition of the first drops of halide. On completion of the preparation, the flask contains several compounds in a differing ratio: in addition to the Grignard reagent RMgX, homo coupled product R–R (**4.3**) and starting material (**4.1**) are present. As a result of the undesired homo coupling (**4.3**), magnesium salts are formed, which give the reaction mixture a cloudy, grey-white

appearance. This procedure was never satisfactory due to its low reproducibility. Yields of **4.2**, generally spoken, are low to moderate, up to 30%. The pretreatment of Mg needed improvement to circumvent the occurrence of homo-coupling problem (up to 40%), and the attendant problems of chemical activators, as will be discussed in Section 4.5.

To improve the preparation of a Grignard reagent with few side products, we focus on the problems of low reactivity between Mg and RX and formation of homo coupled product. The initial step requires electron transfer from the Mg surface to RX, leading to the formation of R●. According to D model theory, this step is limited by diffusion control and makes the available surface area of active magnesium a critical factor. It may give way to a mixture of compounds, due to incomplete conversion. Higher reaction temperatures favour another problem: if RX reacts slowly with the Mg surface, it may react with the already formed RMgX, yielding homo coupled product. (cf. Scheme 4.4) This is a severe problem with reactive allylic or benzylic halides. The competition will be in favour of the $Mg^{(0)}$, assuming its surface is active and sufficient available. The RMgX species is less jeopardized by RX if the concentration of both is kept low,[c] and the reaction temperature must be lowered to an optimum. Preparation of magnesium surface remains a major problem in the RMgX formation. In the next section, some of the Mg preparation techniques prior to the formation of RMgX are discussed. When some of the resulting Grignard reagent solutions[d] are applied in asymmetric cross coupling reactions, however, additional problems regarding stereoselectivity may arise, as we will see in Section 4.5. In order to solve the problems of insufficient active Mg surface, and the influence on enantioselection of chemical activators in RMgX solutions, we present an ultimate surface preparation technique in Section 4.6, which is indispensable to this type of chemistry.

The concentration of the reagent preferably should not exceed 25-30% volume of halide in solvent.

[d]The different Grignard reagent solutions may contain different contaminations (eg. as a result from surface preparation by chemicals).



Scheme 4.4

4.4 Methods to prepare magnesium surfaces

There are many ways to activate $Mg^{(0)}$, and the chemist who tries -without much success- to initiate Grignard reagent formation can reckon on well-intentioned colleagues suggesting a myriad of techniques, from the sublime to the strange; from adding a crystal elementary iodine, to the use of slightly wet solvent or the addition of some saliva.

To prepare magnesium surfaces reproducibly is notoriously difficult. Surface oxides, adsorbed insulating layers and crystal lattice orientation can affect the heterogeneous reaction rates. As a result, not only the initiation but also the reproduction of the Grignard reaction is difficult. The following survey of magnesium surface pretreatments is indicative, and does not claim to be complete; they can be divided in two types: mechanical and chemical.

Generally, magnesium turnings are sufficiently prepared for reactive halides after removal of surface oxides and contaminations by hand with pestle and mortar. It is suggested that bending magnesium strips would cause crystal lattice

dislocations, making them appropriate for Grignard reactions.[3,4i] Magnesium turnings can be activated by sonication; this method appears to be critically dependent on the water content of the ethereal solution. It is suggested that the function of the ultrasound is to disperse surface-bound water from the magnesium.[16] Sometimes, sonication is the preferred technique for effecting the Barbier variation of the Grignard reaction, where magnesium, organohalide and carbonyl compound are introduced concomitantly and the Grignard reagent is intercepted as fast as it is formed.[17]

Instead of mechanical activation, chemical activation with a crystal of elementary iodine is satisfactory in a fair number of the reactions. Among the numerous other chemical activators are bromine, iron trichloride, or a readily reactive alkyl halide (e.g. methyl iodide). A small portion of a preformed Grignard reagent (preferentially a left-over of a former experiment), is often successful.

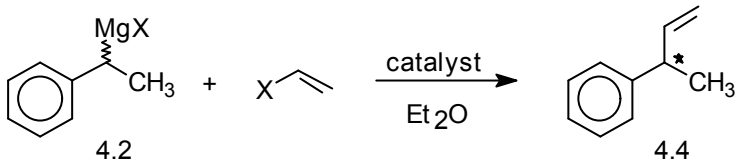
A well known activation procedure is Rieke's method, where magnesium halides are reduced in situ by metallic potassium, yielding a finely divided black powder of metallic magnesium.[18] An alternative method for the synthesis of finely divided magnesium requires the evaporative sublimation of high purity metal in vacuo with condensation into a solvent slurry at –196°C.[19]

Magnesium amalgam can be formed by dissolving magnesium powder in mercury, which appears to react slowly, but uniformly over the entire surface. Reduction of mercuric halides by magnesium furnishes an amalgam as well,[20] though contaminated with halides, a disadvantage, as we will see. In the next section, we discuss the influence of the composition of Grignard solutions on ee in asymmetric couplings.

4.5 Grignard reagent solutions in asymmetric cross coupling reactions

The broad scope of methods to prepare the surface of magnesium, however, is not a guarantee for success in preparation of Grignard reagent solutions that are acceptable for asymmetric cross coupling reactions. In the asymmetric

cross coupling reactions of this chapter, the chiral, racemic Grignard compound is subjected to kinetic resolution. In Section 2.3-I,II and III, several influences on ee have been discussed: higher amounts of RMgX versus R'X result in decrease of optical yields; dilution of the Grignard reagent lowers the optical purity; the type of ether solvent (Et_2O, THF, ^tBuOMe) also influence the optical yield.[21,22,23] These factors can be standardized relatively easy, although one would prefer that they were absent.



Scheme 4.5

Varying halide X in [vinyl halide - Grignard reagent] combinations

Remarkable is the influence on ee by the halogens X present in both moieties to be coupled, RMgX and R'X, as discussed in Section 2.3-II. Consiglio et al. reported[21] a phenomenal effect on ee by varying the combination of type of halides X in cross coupling 2-butyl-MgX with ArX, using the same chiral catalyst $NiCl_2$[(+)(R)-Prophos].[e] All nine combinations between 2-butyl-MgX and ArX (X = Cl, Br and I) resulted in different optical yields of the product 2-phenylbutane. Although it is evident now that the initially reported reverse of absolute configuration is due to the presence of MgI_2 (vide infra), the effect on optical purity[f] remains.[22]

More recently, Consigslio et al. established that the sense of enantioselectivity could change during asymmetric cross coupling experiments. This was attributed to the variation in the nature of the Grignard reagent as a consequence of the increased dilution and the formation of

[e] Prophos is an acronym for 1,2-bis(diphenylphosphino)propane.

[f] For example, with $NiCl_2$[(+)(R)-Prophos] as catalyst, the cross coupling between s-BuMgCl and PhCl afforded 2-phenylbutane in an optical purity of 14.4%, whereas s-BuMgBr and PhBr afforded 2-phenylbutane in 39.9%.

magnesium halides. The occurrence and the extent of this effect appears to be dependent on the diphopsphine ligand used. Remarkably, no such change in enantioselectivity was observed when the aminophosphine (S)-(R)-BPPFA was used. This was attributed to the proposed interaction between the dimethyl amino group and the Grignard reagent before alkylation of the transition metal.[23] Consiglio et al. assumed that the change in enantioselectivity during the reaction is a result of magnesium halide formation. They supposed the aminophosphine catalysed systems to be insensitive to this effect, due to interaction between the dimethyl amino group and the Grignard reagent, prior to alkylation of the transition metal.[23,24]

We were interested to know whether this effect applies to our catalytic system,[g] where the ligand contains a dimethylamino group. In the following indicative study, we varied the types of halide X of **4.2** and vinyl halide under further similar conditions. The valphos-$NiCl_2$ complex was chosen as archetype of these aminophosphine catalysts. The commercial availability of halides RX and R'X was limited to X = Cl and Br. We investigated several synthetic methods (vide infra) to synthesize the corresponding halides with X = I in Et_2O.

Haynes et al. reported that diiodophosporane (Ph_3PI_2) is able to convert primary and secondary alcohols into iodides.[25] We converted 1-phenylethyl alcohol into the corresponding iodide by this method, though incompletely. A 70 : 30 ratio of alcohol : iodide was the best we could reach. Further purification by distillation, under formation of styrene, did not lead to improvement (60 : 40 ratio). Since 1-phenylethyl iodide easily forms styrene and the corresponding Grignard reagent easily undergoes homo-coupling, no further attempts were made. We therefore have limited the range of the 1-phenylethyl halides to chloride and bromide.

We attempted to prepare vinyl iodide in Et_2O by addition of I_2 to vinyl magnesium bromide solution in Et_2O, but without success. The Grignard reagent of vinyl bromide is commercially

[g] Catalyst = amino acid derived dimethylaminophosphine complexed to Ni^0 centre; cross coupling reaction between 1-phenylethyl halide and vinyl halide.

available in THF (and not in Et_2O). Since THF may influence the enantioselectivity,[h] its presence as (co)solvent in these experiments is not desired. Isolation of vinyl iodide from THF by distillation is hampered by their close boiling points, respectively 56°C and 66°C. We expected that use of a higher-boiling solvent would give a better opportunity to isolate vinyl iodide by distillation. We then tried n-Bu_2O (bp 142–143°C) as solvent, but no vinyl iodide was distilled from the reaction mixture. On addition of elementary iodine to vinyl lithium, prepared from vinyl bromide and n-BuLi / KO^{t}Bu,[26,27] no vinyl iodide was obtained. Normant reported that olefinic iodides can be obtained on addition of I_2 to an olefinic cuprate intermediate. The cuprate was prepared from the corresponding Grignard and $Cu^{(I)}Br$.[28] We have performed analogous experiments with vinyl bromide as olefinic species, however, without success, since no vinylic proton signals were detected by ^{1}H NMR. Takagi et al. reported that olefinic bromides can be converted into iodides with an iodide ion in the presence of a nickel catalyst, composed of $NiBr_2$ and zinc dust as a reducing agent, in HMPA as solvent.[29] We have performed analogous experiments with vinyl bromide, but these failed. No trace of vinyl iodide was detected. Whatever the explanation, the attempts to prepare a vinyl iodide solution in Et_2O from vinyl metallic species and I_2 or I^-, were unsuccessful. We limited the range of vinyl halides to X = Cl and Br.

Table 4.1 Cross coupling reaction of **4.2** (X = Cl, Br) with vinyl-X (X = Cl, Br) catalysed by valphos-$NiCl_2$, to give **4.4** (% optical purity, configuration) (cf. Scheme 4.5).

		vinyl-X	
entry	**4.2**	Cl	Br
1	X = Cl	73 % o.p. (S)	57 % o.p. (S)
2	X = Br	–	66 % o.p. (S)

In Table 4.1 the results of the indicative study on the

[h] cf. Section 2.3 III-Influence of solvent.

influence of type of halide in **4.2** and vinyl halide on enantioselectivity are displayed. The Grignard reagent, **4.2**, was prepared from mechanically prepared magnesium turnings by a method that will be described in Section 4.6. It is obvious that the valphos-$NiCl_2$ complex catalysed system is sensitive to different halides or to the magnesium halides produced during the reaction. These results contradict the supposition of Consigllio et al. that the nature of the alkylating species RMgX in the aminophosphine catalysed reaction does not change due to the interaction between the dimethyl amino group and the Grignard reagent prior to alkylation (vide supra).[22] We assume that the supposition of Consiglio et al. is limited to (S)-(R)-BPPFA (**2.6**, Scheme 2.2), may be to the class of aminoalkylferrocenyl phosphines. It is certainly not applicable to all phosphine ligands that contain a dimethyl amino group.

Influence of extraneous compounds in the reaction mixture on ee

The previous mentioned influence of different halides on ee is most probably related to the formation of magnesium halides during the reaction. When a fixed set of halides (for instance RMgCl and R'Br) is used in the asymmetric cross coupling, one might assume that the influence of magnesium halides on enantioselection can be standardized. This assumption holds, in so far that no extra or other type of halides are present in solution. It must be taken into account that during the course of the reaction the composition of the alkylating species RMgX in solution changes, due to the formation of magnesium halides and dilution of the reaction mixture. This may influence the enantioselectivity during the reaction. Moreover, magnesium halides can be already present in the Grignard solution, for example MgI_2, as a result of Mg-surface activation with a crystal of elementary iodine. Consiglio et al. found that pretreatment of the Mg-surface with only 1% of I_2 yields a Grignard solution that can lead to reverse of absolute configuration of the cross coupled product.[22]

A valid conclusion may be that in asymmetric catalysed

cross coupling reactions 'xenohalophobia' is required.[i] The stereoselective pathway can be influenced by different halides in combination with some, but not all, scalemic catalysts. The extent of influence on enantioselection differs among classes of catalysts and within the subclass. This is not predictable, and the combinations should be screened thoroughly beforehand.

4.6 Improved Grignard reagent solution

As we have seen in Section 4.4, the surface of conventional magnesium turnings is generally covered with surface oxides, which preclude its ability to react with unreactive halides in the absence of initiators or mechanic pretreatment. Ultimately, when the reaction is initiated, the conditions to keep the reaction going may be so harsh that side reactions easily occur. In Section 4.5 we have demonstrated that halide-containing chemical activators can complicate a model-based interpretation of the ee values for the asymmetric catalysed couplings. Halide-free activation methods for the magnesium surface remain. These include sonication, 'Riekes magnesium', sublimation, Mg-amalgam and mechanical activation. Since the ultimate goal of this research is preparation of profen precursors, some of these methods are not applicable on a reasonable preparative scale. Under this condition, suitable mechanical activation scores well.

Mendel[30] discovered a facile mechanical activation method for preparing a Grignard reagent from p-(dimethylamino)-bromobenzene without the aid of an initiation agent. Brown et al. recently applied this technique to allylic and benzylic halides as **4.1** with success.[31] This procedure includes vigorous stirring of a five-fold excess of magnesium turnings with a Teflon stirring bar in a Schlenk vessel, without solvent, under an inert atmosphere. After two days, a mixture of darker grey black coloured powder and turnings of reduced size is formed. On addition of the ethereal solution of the halide slowly at 0°C, this procedure provides benzylic Grignard reagents in a good yield, free from homo coupling products

[i] Xeno = different, foreign; halo = halogen; phobia = intense fear of the situation; xenohalophobia= intense fear of situations (reaction mixtures) containing different halides (HvdW).

and, of major importance, chemical activators. In theory, it is relatively easy to scale up (compared to some other activation methods like eg. sublimation).

We have modified this excellent method to speed up the grinding of magnesium turnings. It is obvious that the Teflon stirring bar used for pulverization is relatively light, its surface is very smooth and therefore barely scores the magnesium turnings. We added glass splinters from one or two fragmented Pasteur pipettes to the turnings before stirring, and made use of a round bottomed flask and a stirring egg. The latter has a larger surface area and is heavier than a stirring bar of the same length. The stirring speed should be adjusted to preclude serious vortex formation, which lowers the contact areas of turnings, glass splinters and stirring egg. Instead of 2 days, stirring overnight is satisfactory to give a charcoal-coloured mixture of powder and turnings of reduced size.[j]

From the moment we have used this improved magnesium preparation, the formation of **4.2** was no longer a problem. The yield of **4.2** is moderate to good (60%) and the undesired homo coupled product is scarcely formed. In addition to these advantages, the Grignard solution is free from chemical additives (Section 4.4), which are often used for Mg surface preparation.

A remarkable feature of the improved Grignard solution is related to the **'Cross**-mixture'.[k] As previous mentioned in Section 2.3-IV Influence of zinc halide, Cross et al. reported that a mixture of RMgX and zinc halide must be used freshly, since no cross coupling reaction takes place any more when the mixture is allowed to stand for one hour. Based on literature,[32] they supposed that "R_2Zn was formed after this time" and, as a consequence, "the dialkyl species, if allowed to form, is apparently not very reactive". As probable intermediate the monoexchanged species RZnX was proposed, in which "the appropriate balance of reactivity may be reached".[15a] We disagree with this assumption, based on the fact that the

[j] For details see Section 4.9-Experimental section.

[k] The bold typed 'Cross' refers to Graham Cross, who discovered the in Chapter 2 described phenomenon of reversal of the enantioselection, on addition of zinc halide to RMgX solution prior to cross coupling.

organozinc species is in a Schlenk equilibrium that is instantaneously established - instead of after one hour, as suggested. Further, this assumption cannot be based on the reference cited.[32]

When the improved Grignard reagent was stirred with zinc halide for several hours, the resulting mixture was still reactive in contrast to the '**Cross**-mixture'. The single difference between this mixture and the '**Cross**-mixture' is the procedure by which the Grignard reagents are prepared. We performed several $NiCl_2$-DPPE[l] catalysed cross coupling experiments, where we made use of $ZnBr_2$-**4.2** mixtures that have been stirred for 3 to 4 hours. Although in Et_2O the reproducibility and yields were low (up to 40%, as determined by GC), with THF as (co)solvent the experiments were reproducible and yield raised to 80–90% (GC). This suggests that the nature of the alkylating agent is related to the Schlenk equilibrium. In theory, the Schlenk equilibrium is in THF more easily shifted towards the R_2Zn species than in Et_2O. These findings emphasize the complexity of starting material that is involved in the catalysed cross couplings. The R_2Zn species must be re-evaluated[m] as a possible alkylating agent that may be responsible for reversal of the enantioselection in cross coupling. The nature of the active species has become even more unclear.

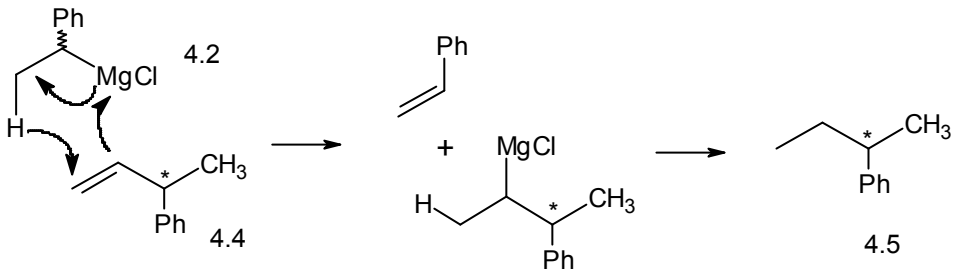
Determination of enantiomeric excess of 4.4

We found that the improved Grignard solution has a small drawback for it is able to reduce the cross coupling product **4.4** to **4.5** (Scheme 4.6). The reduction takes place without racemization, whereby the asymmetrically prepared alkene **4.4** and its corresponding alkane **4.5** have the same ee. In order to determine the ratio between the R and S enantiomer of **4.4**, the optical rotation was initially used as measure. Since the optical rotation of **4.4** has to be measured on neat material, it must be purified by a time-consuming method like preparative GC. The purified material, however, may still be

[l] DPPE is an acronym for diphenylphosphino ethane, a succesful achiral ligand in cross coupling reactions.

[m] The question whether R_2Zn was ever beyond evaluation is plausible, namely, the assumption that R_2Zn is formed not before RMgX and ZnX_2 are stirred for one hour, is obscure.

contaminated with aforementioned **4.5**, since **4.4** and **4.5** do not give complete base-line separation with preparative GC. The optical rotations of alkene **4.4** and alkane **4.5** differ dramatically[n] in value, but not in sign. In mixtures, this results in the measurement of a higher optical rotation. Where optical rotation was used as a measure for the ee, the observed rotation was undoubtedly the sum of these two different compounds. To our knowledge, the occurrence (or the possibility) of this feature in the present cross coupling reaction with improved Grignard reagent has never been reported before with conventially prepared Grignard solutions. The ratio of **4.4** and **4.5** can be determined by ^{1}H NMR and consequently their common optical yield[o].



Scheme 4.6

The time-consuming technique of preparative GC, the possibility of determining the o.p. of a mixture,[p] the remarkably temperature-dependency of the optical rotation[q] and the determination of optical purity rather than enantiomeric excess, prompted us to find a better and more reliable method for ee determination. Fortunately, we were able to find an acceptable chiral GC column[r] to determine the ee of **4.4**. Especially in the case of **4.4**, comparison of ee values (GC) with optical purities remains highly questionable.

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[n] 4.4: $[\alpha]_D^{20} = \pm 5.91°$; 4.5: $[\alpha]_D^{20} = \pm 24.30°$.

[o] Calculated $[\alpha]_{calc}^{20}(A + B) = \%A([\alpha]_{max}^{20}A) + \%B([\alpha]_{max}^{20}B)$.
Optical yield A = $[\alpha]_{obs}^{20}$ / calculated $[\alpha]_{calc}^{20}(A + B)$ = optical yield B.

[p] 4.4 and 4.5 do not give complete base-line separation with preparative GC.

[q] $[\alpha]_D^{20} = \pm 5.91° \pm 0.18°/°C$, in the temperature range from 16-29 °C.

[r] Lipodex C, see Section 4.9 - Experimental section.

4.7 Asymmetric cross couplings with improved Grignard solution

New type of asymmetric ligands

Consiglio reported an improvement of optical yield with more rigid diphosphines as ligand.[33] Since aminophosphines display higher enantioselectivity than diphosphines, introduction of rigidity in aminophosphines may improve this selectivity.

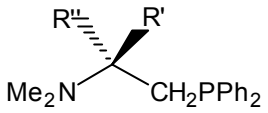
We expected that by introduction of a methyl substituent at the α-position of (natural) α-amino acids the rigidity in the backbone will be increased. In how far these amino acid derived ligands can influence the enantioselection of the reaction at hand, is described in the following sections. The syntheses of these ligands are described in Chapter 3.

Ligands with a β-aminophospine structure

In view of the high enantioselecting ability of chiral, non-racemic aminophosphines in asymmetric couplings, we decided to convert these α-methyl amino acids into such type of ligand (Figure 4.1). We have access to this kind of compound by readily available synthetic routes, as already described in Section 3.2. The results of the cross coupling reactions, as depicted in Scheme 4.5, with these ligands are summarized in Table 4.2. As these type of ligands proved to be extremely air sensitive, they were purified by distillation and passed through a short Al_2O_3 column to remove oxidized material, prior to any cross coupling experiment.

To establish the effect of the 'dry-stir' Grignard, we compared our results to data of Cross et al.[15a,b] In the case of entry 1, the optical yield was identical to literature data (69%). The noticeable difference in optical yield between entry 2 (56%) and the literature data, (41%), we attribute to the different nature of the Grignard reagents. Whereas Cross used elementary iodine to prepare the magnesium surface for Grignard, we used the 'dry-stir method' in case of entry 3. This emphasizes the importance of which magnesium pretreatment is used, in relation to the enantioselection in cross couplings. In case of α-methylated aminophosphines as ligand

(entries 4, 5 and 6), the optical yields obtained are moderate to low, demonstrating a low enantioselective catalyst. The sense of enantioselection in entries 1–4 is identical to the sense of catalysts that are chelated by aminophosphines derived from natural amino acids, suggesting that both α-Me and α-H aminophosphines chelate in similar fashion.



2.4: R' = ^{i}Pr, R'' = H
2.4a: R' = $PhCH_2$, R'' = H
3.9a: R' = CH_3, R'' = $PhCH_2$
3.9b: R' = Ph, R'' = CH_3

Figure 4.1

Table 4.2 Cross coupling reaction of **4.2** (X = Cl) with vinyl chloride catalysed by [$NiCl_2$, - ligand] to give **4.4** (optical rotation, optical puritiy, and configuration) (cf. Scheme 4.5); effect of addition of zinc bromide on enantioselection.

entry	ligand	additive	$[\alpha]_D^{22}$ (°)	% o.p. (config)[1]
1	**2.4**	–	+ 4.10	69(S)[2]
2	**2.4**	$ZnBr_2$	– 3.29	56(R)[3]
3	**2.4a**	–	+ 4.14	70(S)
4	**3.9a**	–	– 3.42	58(R)
5	**3.9a**	$ZnBr_2$	– 0.73	12(R)
6	**3.9b**	–	0.00[4]	0

[1] Determined optical rotation. [2] Literature value: 69(S) (ref. 15a,b). [3] Literature value: 41(R) (ref. 15a,b). [4] Ligand unstable (see Chapter 3).

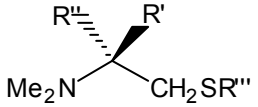
The result of entry 5 is remarkable. Although zinc halide is added to the Grignard solution, no reversal of the absolute configuration occurs in cross coupling product. The optical purity is low. A possible explanation for the lack of reversal of the absolute configuration is that it is the result of two competing reactions (the zinc halide assisted and the unaffected, classic cross coupling with RMgX) with opposite stereochemical outcomes. The existence of two mechanisms is in agreement with results found by Cross and Vriesema, who examined the effect of the ratio zinc halide/vinyl halide on optical yield.[15a] Under these assumptions, the 'classic

coupling' seems to govern the 'zinc halide assisted route' in the case of entry 5. Another explanation may be the different nature of the catalytic complex. This can include more than one scenario. As suggested by Consiglio, chelation of the metal centre by ligands in a monodentate fashion may occur in couplings.[10,34] The presence of aminophosphine **3.9a** derived impurities, probably chiral, may give rise to chelation as well.

The ^{31}P NMR spectrum of ligand **3.9b** shows a mixture of phosphor compounds, despite the purification procedure. We hoped, inspired by the aforementioned suggestions about monodentate chelation, that this ligand - mixture may induce enantioselectivity in a coupling, however, no optical rotation was established and the chemical yield was low (12%).

Ligands with a β-aminosulphide structure

The air-sensitivity and/or instability of the α-methyl aminophosphines prompted us to derive another ligand from the α-methyl amino acids, likely less air-sensitive. As a substitute for phosphines we selected a sulphide sulphur as a good chelating atom, because of the good results of ligands containing sulphur hetero atoms developed in our group by Vriesema et al.[8c,d] The presence of a bulky diphenylphosphine group in the catalytic ligand seems to be of major importance in successful asymmetric cross couplings, not only because of the chelating properties of phosphorus, but also because of the steric hindrance of the two aryl groups. The bivalent sulphur can connect only one aryl group to the chiral backbone, likely less bulky than the two aryl groups on the trivalent phosphorus. Sharpless et al. noted, in a different context, in a study of ligands in asymmetric dihydroxylation of olefins that large, plate-like aromatic substituents in ligands display high ee.[35]



3.10: R' = $PhCH_2$, R'' = H, R''' = 1-naphthyl
3.11: R' = $PhCH_2$, R'' = H, R''' = 2-naphthyl
3.11a: R' = CH_3, R'' = $PhCH_2$, R''' = 2-naphthyl

Figure 4.2

Table 4.3 Cross coupling reaction of **4.2** (X = Cl) with

vinyl chloride catalysed by [$NiCl_2$, - ligand] to give **4.4** (yield (%), optical puritiy or ee and configuration) (cf. Scheme 4.5).

entry	ligand	yield (%)	%o.p. / **ee**[1)] (config)
1	**3.11a**	27	n/a[2)]
2	**3.11**	64	12 (S)
3	**3.11**	64	**23** (S)
4	**3.10**	91	**11** (S)

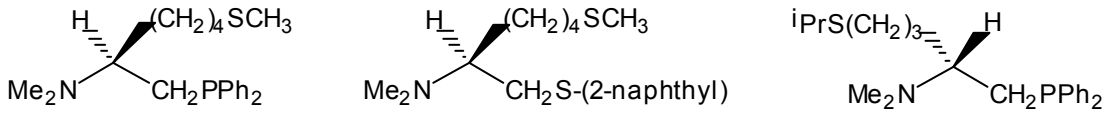
[1)] Ee determined by chiral GC column are printed in bold type. [2)] Insufficient material to determine optical rotation.

We studied the influence on enantioselectivity in cross couplings with aminosulphide ligands bearing on sulphur a large plate-like aromatic group like naphthyl. We expected that the steric hindrance of a naphthylsulphide-group would resemble that of the diphenylphosphine moiety in the aminophosphine ligands. We investigated the influence on enantioselectivity on replacing the 2-naphthyl by a 1-naphthyl group. The syntheses of **3.10**, **3.11** and **3.11a** are given in Chapter 3. The results of cross couplings with these ligands are given in Table 4.3.

It is evident that these types of β-aminosulphide ligands are not a promising class of asymmetric ligands for cross couplings. This may be due to the lack of a ligating phosphorus moiety. Owing to the low chemical yield in the case of entry 1, we could not isolate sufficient material by preparative GC to determine the optical yield. Entries 2 and 3 represent two different experiments under similar conditions, except the determination methods for enantioefficacy. Although the chemical yields are the same, the optical yield and enantiomeric excess differ by a factor 2. This may illustrate a low reproducibility of enantioselectivity, though different determination methods may contribute to this difference, too.

Ligands with β-aminophosphine structure bearing a sulphur appendage

Vriesema et al. discovered that a terminal hetero atom like sulphur in a linear side chain $-(CH_2)_n-$ of an aminophosphine ligand of type **3.12** (Section 3.4, Figure 3.3) is beneficial to the ee, which increases along the series n = 1,2, and 3, furnishing 38, 65 and 70% ee, respectively.[15a,c,d] A tendency for the sulphur to fold back towards the metal centre and participate in the reductive elimination step was proposed. This would lead to an intramolecular variation of an extra ligand, though no ligation of sulphur was observed for the Pd complexes.[15a,c,d] Alternative, it was proposed that the lone pairs on sulphur may provide an additional coordinating site for the organometallic reagent, prior to coupling. When the cross coupling was carried out at higher temperatures (–5°C instead of –50°C), an increase in ee was observed only for **3.12** (n = 3) as ligand, whereas ligands with shorter sulphur-containing side chains **3.12** (n < 3) showed a decrease in ee. We assumed that this tendency of higher enantioselectivity depends on chain length. Homologation of **3.12** (n = 3) by another methylene group to **3.12** (n = 4), would be interesting. An isopropyl- instead of a methyl- group on the side chain terminal sulphur, compound **3.24**, could give more information on the function of this third 'dentate', as well. We also applied amino sulphide **3.19** to study the need for a phosphorus moiety in a ligand for Ni and Pd catalysed asymmetric cross coupling reactions. In Section 3.4 the preparation of **3.12** (n = 4), **3.19**, and **3.24** is described. In Table 4.4 the ee's of **4.4** obtained with these compounds as ligands in asymmetric cross coupling reactions (Scheme 4.5), are given.



3.12 (n = 4) 3.19 3.24

Figure 4.3

Table 4.4 Cross coupling reaction of **4.2** (X = Cl) with vinyl bromide catalysed by ligand - (Pd, Ni) to give **4.4** (% ee, configuration) (cf. Scheme 4.5).

entry	[ligand- **M**][1)]	% ee[2)] (config)
1	[**3.19** - Ni]	15 (S)[3)]
2	[**3.19** - Pd]	13 (S)[3)]
3	[**3.12** (n = 4) - Ni]	68 (S)[3)]
4	[**3.24** - Ni]	70 (R)

[1)] **M** = Ni, Pd. [2)]Determined by chiral GC. [3)] Corrected for 71% ee of the ligand.

We found that the enantioefficacy with **3.12** (n = 4) as ligand (entry 3) is comparable with literature values for homomethphos (**3.12** (n = 3), 70% o.p.), but higher than for methphos (**3.12** (n = 2), 65% o.p.),[15a] though the differences are small at –50°C. Homologation of homomethphos (n = 3) does not lead to a significant increase in ee. An optimum length for a sulphur containing side chain is not clear.

Since the differences in ee are small at –50°C, it seems that the length of the chain is of importance at higher reaction temperatures, indicating it is a subtle effect. When the methyl group on sulphur in homomethphos is replaced by a 2-propyl group (**3.24**, entry 4), the effect on ee is not significant. This suggests that the feature of the sulphur moiety (to fold back towards the metal centre) is not sterically hindered by a bulkier group like 2-propyl. The effect of a sulphur in the side chain remains unclear.

Further investigations might be useful, especially about the effect of temperature, observed by Cross and Vriesema.[15] Homologation of the ligand by another CH_2 group and application of **3.12** (n = 4, or higher, $n \geq 4$) in cross couplings at higher temperatures will give deeper insight in the theory about the chain-length effect.

4.8 Summary, conclusions and perspectives

In this chapter the activation of magnesium turnings by prolonged stirring under inert atmosphere is described. The reproducibility of the Grignard reagent formation is improved, compared to conventional methods, as well as the purity of the resulting RMgX solution. The latter feature is indispensable in asymmetric cross coupling reactions. Grignard solutions, prepared from organo halides and magnesium turnings that are activated by chemicals, such as elementary iodine, definitely should not be used in asymmetric cross coupling reactions. These solutions contain different halides, which may have a significant effect on enantioselectivity in the asymmetric cross coupling reactions. The extent of the influence on enantioselection is unpredictable and has to be determined for every single catalyst.

The new class of β-aminophosphine ligands derived from synthetic α-methylamino acids (cf. Chapter 3), did lead to moderate ee's (up to 58%) in asymmetric cross coupling reactions. The effect of the enhanced rigidity of the ligand by the introduction of an α-methyl group is not beneficial. With the more stable β-aminosulphides as ligands, low optical yields were obtained, in variable chemical yield. In the homologous series of methphos, the new developed **3.12** (n = 4), bis(homo)methphos, displayed a high enantioefficacy as ligand in cross couplings. In comparison with homomethphos **3.12** (n = 3), the differences in ee are small and do not suggest an optimum in chain length. A more sterically hindered terminal sulphur group by 2-propyl group provided similar ee's. The effect of a terminal sulphur group in the side chain remains unclear.

We found that the reactivity in cross couplings of improved Grignard reagent - zinc halide mixture conflicts with the reported reactivity of the **Cross**-mixture; it is not easy to rationalize this discrepancy. A simple explanation is that two or more reaction pathways compete, with different stereochemical outcomes. The nature of the alkylating species in the Grignard reagent - zinc halide mixture in cross couplings, remains unclear. The directly prepared organozinc reagent, without intermediacy of the organomagnesium reagent, will be discussed in the next chapter.

4.9 Experimental section

General remarks: see Section 3.6. 1-Phenylethyl chloride (**4.1**) was prepared from D,L-1-phenyl ethanol, purchased from Fluka and Janssen) by reaction with 1.5 eq. $SOCl_2$ ($CHCl_3$, T < 20°C, overnight stirring; purification by bulb to bulb distillation, 75°C, 12 mm Hg). Magnesium turnings were purchased from Fluka and from Janssen (now Acros Chimica). The magnesium turnings obtained from Janssen were nearly flat pieces,[s] and were activated more readily than the more wrinkled magnesium turnings that were purchased from Fluka. Et_2O was dried over sodium, with benzophenone as indicator. For preparative GC was used a Hewlett-Packard F&M 700 gas chromatograph equipped with a TC detector and a 6 ft., 1/4 inch S.S. column, filled with 10% SE 30 on chromosorb W/AW DMCS 60-80 mesh. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at the sodium D line (589 nm). The yield of the coupling was determined on a Hewlett-Packard 5890A gas chromatograph, equipped with a 15 m, 0.53 mm, df = 2.65 μm, HP1 column, using undecane as reference. The ee of 3-phenyl-1-butene (**1.19**, (Ar = Ph) = **2.2** = **4.4** = **5.6** = **6.1**) was determined by GC on a similar gas chromatograph, equipped with a Macherey Nagel 50 m Lipodex C capillary column under the following conditions: oven temperature: 45°C; injection and detection temperature: 180°C; retention times (min): 69 (R - **4.4**), 70 (S - **4.4**).

1-Phenylethylmagnesium chloride in Et_2O solution (4.2)

Magnesium turnings (16 g, 660 mmol) were transferred to a 250-mL roundbottomed three necked B24 flask, equipped with a 250 mL pressure-equalized dropping funnel. Glass splinters, 1 cm in size approximately (1-2 Pasteur pipettes, carefully granulated by gloved hand), and a Teflon stirring egg (40 mm) were added. The system was purged by N_2. The stirring speed was adjusted in such a manner that excessive vortex formation was avoided, which could have led to less interaction between the Teflon stirring egg and the mixture of glass splinters and magnesium turnings. This mechanical activation was carried out overnight. After this time, the magnesium particle size was

[s] Probably offcuts of a magnesium ribbon instead of turnings.

reduced and a charcoal-grey powder covered the Mg-particles, glass splinters and the wall of the flask. A small amount of Et_2O was added, sufficient to moisten the magnesium. The mixture was cooled to 0°C and a solution of **4.1** (13.2 g, 100 mmol) in 150 mL Et_2O was added slowly (~1 drop s^{-1}). It should be emphasized that no additional activation or initiation is performed. After addition, the solution was stirred for another 3 hours. The Grignard reagent solution was titrated against 0.1 M 2-butanol solution in xylene, with 2,2'-bipyridine as indicator. The solution can be stored under N_2 at room temperature for several weeks without decomposition.

Zinc bromide - 4.2 mixture

A zinc bromide - 4.2 mixture, used in entries 2 and 5 in Table 4.2, was obtained by the following procedure. An equimolar amount of **4.2** solution was added to zinc bromide under magnetic stirring at ambient temperature. After addition, the mixture was allowed to stir for 15 min., after which the supernatant was transferred by syringe to a dropping funnel and used in cross coupling reactions described below. Nota bene, the composition of this mixture differs from the '**Cross**-mixture' in the absence of extraneous chemicals (such as I_2 or MgI_2) in the Grignard solutions.

General procedure for cross coupling reactions

The organometallic reagent **4.2** (10 mmol), or equimolar zinc bromide - **4.2** mixture, was added slowly to a magnetically stirred suspension of $NiCl_2$ (0.04 mmol), ligand (0.04 mmol), and vinyl bromide (8 mmol) in Et_2O (2 mL) at –40°C. The solution was allowed to reach 0°C over a period of 16 h. The reaction mixture was hydrolysed with 1 N HCl (50 mL) at 0°C. The crude reaction mixture was dissolved in Et_2O (50 mL), washed with 1 N HCl (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), concentrated under reduced pressure and purified by bulb to bulb distillation (90°C, 11 mm Hg) to give **4.4**. In case of ee determination by optical rotation, the sample was purified by preparative GC. Unless stated otherwise, the chemical yield was >95%.

Attempted synthesis of a solution of vinyl iodide in Et_2O

Via vinyl magnesium bromide in Et_2O: To magnesium (7.5 g, 0.3 mol), previously prepared by heating thoroughly with 0.7 mL of 1,2-dibromoethane in Et_2O, a solution of vinyl bromide (16 g, 0.15 mol) in Et_2O (100 mL) was added dropwise at 0°C. The resulting reaction mixture was cooled to –50°C and a solution of iodide (38.07 g, 0.15 mol) in dry Et_2O (100 mL) was added. After stirring for 16 h, $P(OEt)_3$ (12.4 mL, 60 mmol) was added dropwise at –30°C. The mixture was hydrolysed at 0°C with 4N HCL (50 mL). Et_2O (100 mL) was added and the organic layer was washed with 4 N HCl (50 mL), saturated $NaHCO_3$ solution (50 mL), water (50 mL), dried ($MgSO_4$) and Et_2O was concentrated for a major part under reduced pressure. Analysis of NMR data showed no vinylic proton signals.

Via vinyl magnesiumbromide in n-Bu_2O: Magnesium turnings (6.5 g, 0.27 mol) were prepared by addition of ethane dibromide (0.7 mL, 8 mmol) and local heating by means of a heat gun. The turnings were covered with n-Bu_2O (20 mL, freshly distilled from Na) and a solution of vinyl bromide (14 mL, 0.2 mol) in n-Bu_2O (35 mL) was added dropwise. The reaction mixture was stirred for 20 h at room temperature. The mixture was cooled to –5°C and a solution of I_2 (50 g, 0.2 mol) in n-Bu_2O (150 mL). After stirring for 1 h, the reaction mixture was quenched with 1 N HCl (50 mL). The organic layer was washed with water (50 mL), brine (50 mL) and dried ($MgSO_4$). No material could be isolated from the reaction mixture by careful distillation. The residue showed no trace of vinylic protons by ^1H NMR analysis.

Via vinyllithium: A solution of vinyl bromide (14.5 mL, 136 mmol) in Et_2O (60 mL) was added to KO^tBu (16.83 g, 150 mmol) at 0°C. The reaction mixture was added to -100°C and n-BuLi in hexane (93.8 mL, 1.6 M in hexane, 0.15 mol) was added by syringe. To this mixture, elementary iodine (41.3 g, 163 mmol) in Et_2O (160 mL) was added at –40°C. Fractional distillation, by aid of a 30 cm Vigreux column, provided no fractions containing vinylic compounds.

Via vinylcuprate: To a suspension of $Cu^{(I)}Br$ (31.6 g, 0.22 mol) in Et_2O (20 mL) was added a vinyl magnesium bromide solution (200 mL, 1 M, 0.2 mol) at –40°C, and stirred for 30 min. At –15°C, a solution of elementary iodine (50.8 g, 0.2 mol) in

Et_2O (200 mL) was added. After stirring for 1h, the reaction mixture was quenched with 1 N HCl (50 mL). The organic layer was washed with water (50 mL), brine (50 mL) and dried ($MgSO_4$). After partly concentration of the solvent, no trace of vinylic protons could be detected by ^1H NMR.

Via potassium iodide - nickel catalyst: A mixture of vinyl bromide (0.7 mL, 10 mmol), potassium iodide (4.2 g, 25 mmol), $NiBr_2$ in DMF (1.2 mL, 0.17 M, 0.2 mmol), zinc dust (50.8 mg, 0.77 mmol) in HMPA (8.8 mL) was stirred for 20 h at ambient temperature, after which the reaction mixture was quenched with 2N HCl solution (50 mL), extracted with Et_2O (3x 50 mL) and dried (Na_2SO_4). The organic layer was partly concentrated by the aid of a 30 cm Vigreux column, and a trace of vinylic proton signals could be detected by ^1H NMR . ^1H NMR ($CDCl_3$, 60 MHz): δ 6.15-6.63 (m, 3H). Attempts to isolate the vinylic compound by further fractional distillation, were unsuccessful.

Attempted synthesis of 1-phenylethyl iodide

To a cooled (–5°C) solution of PPh_3 (3.15 g, 12.0 mmol) in dry Et_2O (40 mL) was added elementary iodine (3.05 g, 12.0 mmol) followed by HMPA (38 mL, 20 mmol). The resulting mixture was cooled to –10°C and 1-phenylethanol (1.2 mL, 10 mmol) was added dropwise. After 16h stirring at –10°C the cooling bath was removed and the bright yellow slurry was diluted with Et_2O (40 mL) and stirred for 30 min. at ambient temperature. The resulting bright orange solution, with yellow solid material on the bottom, was quenched with an ice-cold saturated Na_2CO_3 solution (50 mL). The organic layer was washed with a saturated Na_2SO_3 solution (50 mL), 1 N H_2SO_4 (50 mL) and a saturated Na_2CO_3 solution (50 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was identified by ^1H NMR as a 75:25 mixture of starting material and product. We characterized 1-phenylethyl iodide from this spectrum as: ^1H NMR ($CDCl_3$, 60 MHz): δ 2.17 (d, J=7.2 Hz, 3H), 5.37 (q, 1H) 7.07-7.81 (m, 5H). Attempts to purify the product by distillation (120°C, 15mm Hg) failed, yielding a mixture of starting material and product in a 60:40 ratio and a styrene residue.

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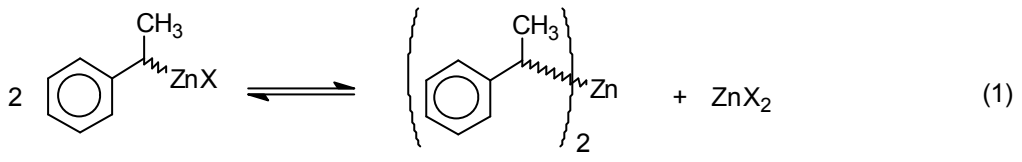
Chapter 5

Organozinc Reagents And Asymmetric Cross Coupling Reactions

5.1 Introduction

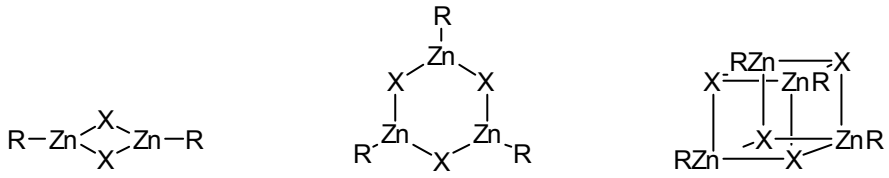
The preparation of the first organozinc compound by Frankland[1] in 1848 led in the second half of the nineteenth century to the use of these compounds in reactions, and in the synthesis of other organometallic compounds. From 1900 onwards, however, the Grignard reagent, owing to the ease of preparation and reactivity, became more popular.[2] Organozinc species are well-known as monosubstituted derivatives RZnX (X= halogen, OR, NR_2, SR, etc.) and disubstituted compounds R_2Zn. Higher coordinated anions, eg. $[R_3Zn]^-$, $R_4Zn]^{2-}$, can be formed by reaction of alkali metal organometallics with disubstituted zinc derivatives. In a typical organozinc compound the two C–Zn bonds can be regarded as occupying two equivalent *sp*-hybridized molecular orbitals, resulting in a linear geometry of the molecule. In case of symmetrical diorganozinc compounds therefore, the dipole moment should be zero.[3] The zinc atom has in this situation four low-energy orbitals available for bonding, but only two pairs of bonding electrons. On that account it is to be expected that formation of coordinative bonds with ligands containing non-bonding electrons is possible. Further, zinc is a rather electropositive element, the Pauling electronegativity being 1.6. In diorganozinc compounds covalent but rather polar zinc-carbon bonds will be present and the zinc will be electron deficient. The zinc atom can make use of its available p-orbitals to form weak complexes by accepting lone electron pairs from donor molecules. Cyclic ethers and chelating diethers, such as THF or 1,4-dioxane and 1,2-dimethoxyethane, form stable complexes with Me_2Zn. There is convincing evidence for the presence of Schlenk-type equilibria in ethereal solvents as depicted in Scheme 5.1, for R = 1-phenylethyl.[4] The equilibrium lies to the left, but is easily shifted to the right in solvents such as THF.[5a]



5.1a 5.1b

Scheme 5.1

When one of the R groups in R_2Zn is replaced by an electronegative atom, such as a halide X, the acceptor character of the zinc and donor character of the zinc-bound electronegative atom are enhanced. Therefore, RZnX compounds readily associate into dimers (**5.2**), or higher aggregates (**5.3**, **5.4**) (Figure 5.1).[6] Dialkylzinc compounds (R_2Zn, R = alkyl or aryl), on the contrary, are monomeric with linear structures and are unable to attain coordination saturation through formation of alkyl or aryl bridges. The reader is referred to the contributions of Boersma[5a] and O'Brien[5b] in the series *"Comprehensive Organometallic Chemistry"*, that give a good entry to physical properties and general preparative methods of organozinc species and a survey of zinc chemistry up to 1995.



5.2 5.3 5.4

Figure 5.1

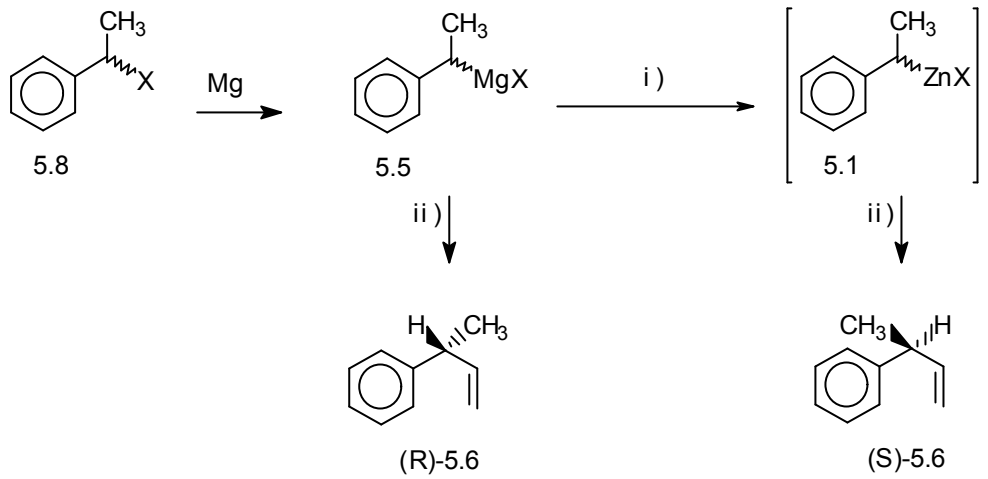
In 1977, Neghishi *et al.* first used organozinc compounds in cross coupling reactions.[7] Kumada *et al.* applied organozinc compounds successfully in an asymmetric cross coupling system.[8] In this system, which involves the use of $PdCl_2$[(*R*)-(*S*)-PPFA][a] as catalyst, the organozinc reagents gave better results than

[a]Diastereomer of 2.5, Chapter 2.

Grignard reagents with regard to the optical yield.[8a] The organozinc species were prepared *via* transmetallation of the corresponding Grignard reagent with zinc halide.

Influence of zinc halide on enantioselection in asymmetric cross coupling reactions

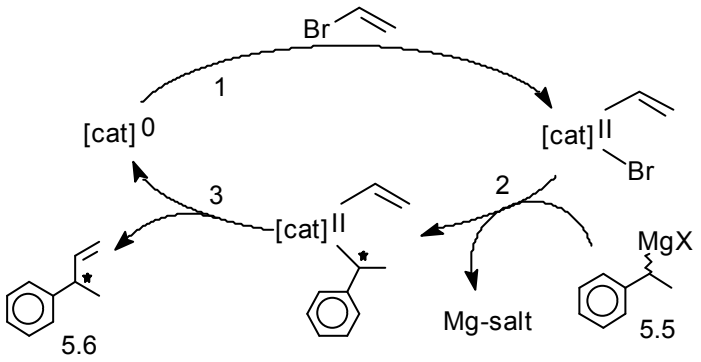
In our research group, the organozinc species **5.1** was applied in asymmetric cross coupling systems that involve the use of nickel or palladium catalysts that bear a β-aminophosphine ligand (cf. Chapter 2 and 4). For the preparation of **5.1**, the corresponding Grignard reagent solution (**5.5**) was added to a stoichiometric amount of anhydrous zinc halide and stirred for 15 minutes. When this mixture was applied in asymmetric cross couplings under the same conditions as the couplings with **5.5**, a remarkable phenomenon was observed by Cross *et al.* The sense of enantioselection in cross coupling reactions with **5.1** *inverted*, with regard to the reaction with **5.5**, although the same asymmetric catalyst was used.[9] The opposite enantiomer ((*S*)-**5.6**, Scheme 5.2) was obtained under these '**Cross**-conditions'. In other words, *both* enantiomers of **5.6** can be prepared separately with only *one* asymmetric catalyst. The sign of the optical rotation of **5.6** can be inverted on addition of ZnX_2 to the Grignard reagent. Zinc bromide increases the rate of coupling, whereas zinc chloride showed inhibitory effects. Addition of other salts (e.g. magnesium halide) neither inverted nor influenced the optical rotation of **5.6**.



i) $ZnBr_2$; ii) $BrCH{=}CH_2$, $Ni^{(0)}$ or $Pd^{(0)}$ - Valphos complex.

Scheme 5.2

The alkylation of the transition metal catalyst (Scheme 5.3, step **2**), is thought to be responsible for asymmetric induction. The final step (**3**), in which the carbon-carbon bond is formed by reductive elimination, is probably stereospecific.[10]



[cat] = ligand - Pd or Ni complex; $[cat]^{index}$ = oxidation state (0 or II)

Scheme 5.3

Consiglio *et al*. observed that all factors that are known

to influence the structure of the Grignard reagent in solution also may affect the asymmetric induction in cross coupling reactions, at least for systems containing asymmetric diphosphine ligands.[11] This would explain the sensitivity of enantioselectivity for alterations in the composition of the reaction mixture before and in the course of the reaction.

Under the assumption that addition of zinc halide affects the alkylating agent **5.5**, two possible intermediates were proposed by Cross *et al*. It was found that no cross coupling occurred after prolonged stirring (>1h) of the $RMgX–ZnX_2$ mixture. On basis of this result and in combination with results of Negishi,[7] Cross *et al*. supposed **5.1b** to be a less likely alkylating agent, wherefore **5.1a** was proposed as possible intermediate. The other proposed intermediate involved a zincate complex $RMg\text{-}ZnX_3$.[9b]

Incentive to this research

We were interested in the nature of the alkylating species responsible for the reversal of enantioselection. Is it an organozinc reagent? And if so, in which form: RZnX or R_2Zn? Or is it a zincate complex?

We have investigated the preparation of organozinc compounds for application in the asymmetric cross coupling reaction (Scheme 5.2), under magnesium salt-free conditions. The solution of **5.1** should meet the prerequisites for Grignard reagents, that is as far as possible exclusion of extraneous compounds that potentially influence the *ee* of the coupling product. In brief, these prerequisites apply to the type of solvent, type of halide and other extraneous factors such as certain activating agents.[b] Preferentially, RZnX should be formed directly from the halide RX and zinc metal, in Et_2O.

Our perspective for the development of the organozinc reagent was influenced by experimental results. As these are treated in other chapters, occasionally cross referencing must be made to understand the strategy.

5.2 Synthesis of organozinc compounds

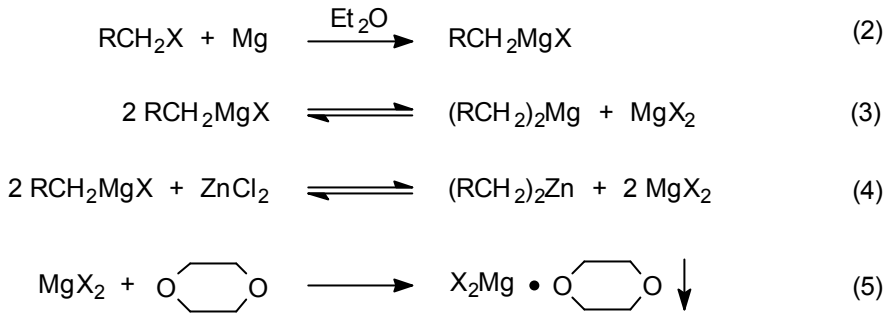
See Chapter 2 and 4.

The catalytic asymmetric additions of dialkylzinc species to aldehydes[12] for the preparation of optically active secondary alcohols, has attracted much attention. Extension to the use of dialkyls other than Et_2Zn has been limited,[13] although, at the time of this research, Knochel *et al*. have made the organozinc species more accessible *via* a general route.[14] There are three general methods to prepare organozinc compounds: *i*) direct formation by organohalide RX and activated Zn, *ii*) alkylation or arylation of Zn-salt by RMX (M = Mg, Li, Al), or *iii*) metathesis.

In the asymmetric cross coupling chemistry, the main prerequisite for the alkylating organometallic solutions is the absence of the so-called 'extraneous compounds', since they may influence enantioselection in the asymmetric couplings (cf. Section 2.3 and Section 4.4). The preparative methods *ii*) and *iii*) are less attractive for our purposes, since these methods make use of or furnish such extraneous compounds. At first sight, 'direct formation' (method *i*) seems to give a solution that is free of such extraneous compounds. The activation of zinc metal, however, is usually performed by dispersion or alloying with another metals, for instance Cu or Na. Other approaches involve the reduction of zinc salts with an alkali metal in hydrocarbon or ethereal solvents, for instance potassium metal in diglyme, yielding finely divided powders, which are far more reactive than the corresponding commercial metal.[15]

Three promising methods (*vide infra)* were selected for further research on cross coupling reactions by organozinc species. The methods had to be adapted owing to the reactivity or reproducibility of the resulting organozinc solutions. The composition of the solutions, however, may not fulfil all the conditions we made beforehand.

Each separate organozinc solution is represented by a code connected to **5.1** by * (eg. **5.1***[dioxan]). The * represents: 'originating from', followed by the specific preparative method in square brackets. When necessary, this code is followed by type of halide in parentheses, eg. (X = Br). Default is equivalent to X = Cl.



Scheme 5.4

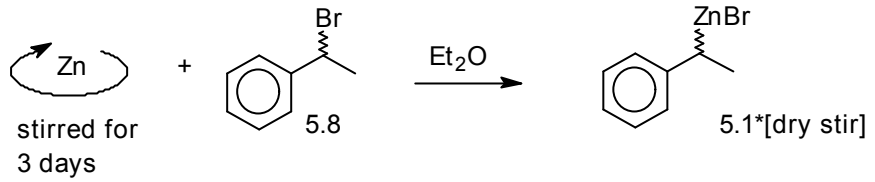
Transmetallation and magnesium-salt removal with 1,4 dioxane

Seebach *et al.* used a strategy devised by Sheverdina *et al.* to furnish magnesium salt-free solutions of dialkylzinc compounds.[13a,d] These are prepared from Grignard reagents (Scheme 5.4, Eq. 2 and 3) by transmetallation with zinc halide (Eq. 4), analogous to the '**Cross**-mixture'. The resulting magnesium halide is subsequently precipitated as a dioxane complex on addition of 1,4-dioxane (Eq. 5). The Schlenk equilibrium (Eq. 4) shifts towards the dialkylzinc species. After separation of the magnesium dioxanate, a clear solution of R_2Zn remains. This method is well-suited for the synthesis of R_2Zn compounds. However, it has a serious drawback, namely, the presence of strongly coordinative 1,4-dioxane in the organozinc solution. This may influence the enantioselectivity in the subsequent asymmetric cross coupling.

We have applied this procedure successfully to the synthesis of **5.5**. To generate **5.1a**, we took advantage of the Schlenk equilibrium another time, since **5.1b** was reported to be not very reactive in the cross coupling reaction (*vide supra*).[9] On addition of an extra 0.5 equivalent of zinc halide to the isolated R_2Zn solution, the Schlenk equilibrium supposedly shifts to the left, in favour of **5.1a** (see Eq. 1). ^{1}H NMR spectrum analysis of a hydrolysed sample showed ethylbenzene, as a proof of the organometal in solution. The solution was subjected to cross coupling, as described in Section 5.3.

Activation of granular zinc by 'dry stirring'

As described in Chapter 4, the 'dry-stirring method' is an excellent procedure to prepare a reactive magnesium surface. Organohalide react smoothly to form a RMgX solution in high yield, which is suitable for asymmetric cross couplings.

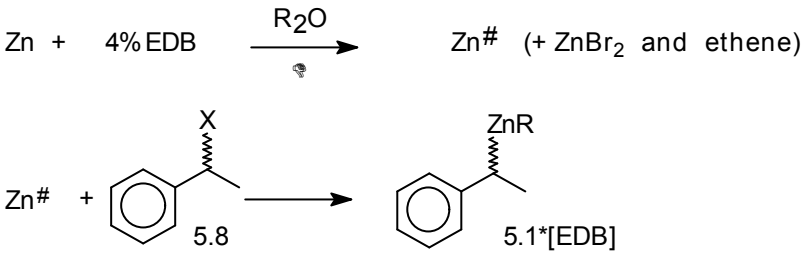


Scheme 5.5

In an extrapolation of this procedure, we stirred zinc granules with glass splinters under an inert atmosphere for three days prior to addition of **5.8**. We then were able to prepare **5.1** (X = Br) in Et_2O by using this zinc (Scheme 5.5). However, we did not succeed in the synthesis of **5.1** (X = Cl) in Et_2O. The yield of **5.1***[dry stir] is low (<20%), as is the reproducibility. A solution of **5.1***[dry stir] (X = Br) was subjected to standard cross coupling, as defined in Section 5.3.

Activation of metallic zinc with 1,2 dibromoethane

A mild and general synthesis of benzylic organozinc species has been developed by Knochel *et al.*; their method involves another direct formation from an organo halide and zinc. Zinc foil or dust has been activated sufficiently by ethylene dibromide (EDB) in THF to allow direct reaction with RX, leading to RZnX (Scheme 5.6). It has been shown that use of organo chlorides, instead of bromides, leads to reduced formation of homocoupled product R–R.[14b,e] It is evident, however, that undesirable reagents are applied in this method, namely THF and EDB. Both potentially influence the optical yield of succeeding asymmetric cross coupling reactions.



EDB = 1,2-dibromoethane
Zn# = zinc, with chemically activated surface
X = halide
R = halide or 1-phenylethyl

Scheme 5.6

We successfully have adapted the method of Knochel *et al.* from THF to Et_2O as solvent. A slurry of zinc dust and Et_2O with 4% EDB was thoroughly heated. At 0°C, the resulting mixture was treated with a solution of **5.8** (X = Cl) in Et_2O. ^1H NMR analysis of a hydrolysed sample showed ethylbenzene, as a proof of organozinc formation. Further analysis of the ^1H NMR spectrum showed styrene formation along with ethylbenzene. In a similar experiment, except for a small amount of THF used during activation of zinc,[c] no styrene was detected. This suggests that THF possibly stabilizes the organozinc species. In other experiments with THF as co-solvent, however, styrene was detected as well (GC). The formation of styrene suggests that ß-hydride elimination of the organozinc species takes place in Et_2O, indicating the instability of **5.1** (during the formation) in this solvent. Another possible source of styrene is the decomposition of the organozinc species **5.1**. The decomposition may involve disproportionation of RZnX, yielding styrene and ethylbenzene. Besides disproportionation, homo-coupling of the organozinc compound can occur, yielding 2,3-diphenylbutane. Kochi states that these two competitive processes, disproportionation and homo-coupling, are not strongly dependent on the solvent.[16] In our investigations, the

[c] The reproducibility of the RZnX formation is still in favour of THF. Since the indicative studies did not deal with asymmetric couplings, we applied THF during activation of zinc with EDB, as stated.

ratio of styrene to ethylbenzene differed in every separate experiment. We did not find a logical trend in formation of styrene. These qualitative findings are not decisive proof that the organozinc species is unstable in diethyl ether, merely a demonstration of the moderate reproducibility of the formation of RZnX *via* this method. The organozinc reagent was prepared several times this way and subjected to cross coupling, as described in Section 5.3.

5.3 Organozinc solutions and asymmetric cross couplings

Introduction

The three preparative methods, discussed in Section 5.2, yield organozinc solutions that differ in composition. On that account, we will discuss their reactivity in cross coupling experiments separately. We have used an efficient achiral ligand, diphenylphosphinoethane (DPPE) for the catalyst. In the following text this is referred to as 'standard conditions' which involve the general cross coupling experiment described in Section 4.9, using $NiCl_2$/DPPE as catalyst, vinyl bromide, and Et_2O as solvent (see Scheme 4.5). Slight modifications (as using THF instead of Et_2O during activation) are documented within text.

1-Phenylethylzinc solution [dioxan method] in cross couplings

Attempts to perform cross coupling reactions with **5.1***[dioxan] under standard conditions did not give **5.6**. After work up, the major product appears to be ethylbenzene, together with a minor amount of **5.8** (X = Cl), based on ^{1}H NMR and GC data. This indicates that no reaction has taken place with the organometallic compound. It is remarkable that the otherwise productive '**Cross**-mixture' is not reactive any more on addition of a small amount of 1,4-dioxane. Several interpretations can be made. The cross coupling reaction may have been inhibited by complexation of 1,4-dioxane to a catalytic intermediate or to the alkylating species - whatever their nature may be. The Schlenk equilibrium may have been shifted to the right (R_2Zn) on addition of 1,4-dioxane. Whatever the explanation, we did not proceed with **5.1***[dioxane], since we did not aim at more factors that influence the enantioselectivity of cross coupling reactions.

1-Phenylethylzinc solution [dry stirring method] in cross couplings

When we subjected **5.1***[dry stir][d] to a standard cross coupling reaction, we found no trace of **5.6** (GC). We have performed only a few cross coupling experiments with **5.1***[dry stir], because of the low reproducibility and low yield of this method of preparation. We decided to continue cross coupling experiments with **5.1** obtained by the EDB-method, even though the formation of zinc bromide is a major drawback. Since we did not investigate *asymmetric* couplings, the potential influence of zinc bromide on enantioselection could be overlooked.

1-Phenylethylzinc solution [EDB method] in cross couplings

Attempted cross coupling under standard conditions with **5.1***[EDB] did not give **5.6**. The major product was ethylbenzene, besides a minor amount of **5.8**, based on NMR and GC analysis. This lack of reactivity of the directly formed organozinc species in cross couplings, prompted us to modify the solution of the alkylating agent.

Addition of $MgBr_2$ - diethyl etherate

A significant difference between **5.1***[EDB] and the **Cross**-mixture involves the presence of magnesium salts. We considered a possible magnesium-salt dependency of the cross coupling.[17] We therefore mimicked the **Cross**-mixture closely on addition of a stoichiometric amount of anhydrous $MgBr_2$-diethyl etherate to **5.1***[EDB]. No cross coupling was observed (GC).

Addition of $ZnBr_2$

Cross *et al.* assumed, without experimental verification, RZnX (**5.1a**) to be reactive in couplings and not R_2Zn (**5.1b**).[9] Based on this assumption, we added a stoichiometric amount of $ZnBr_2$ to **5.1***[EDB], in order to shift the Schlenk equilibrium further to the left, generating **5.1a**. This mixture was subjected to cross coupling, but did not give **5.6**.

Use of 1-phenylethyl bromide

[d]Prepared from 5.8 (X = Br) and dry-stirred zinc granules.

Cross *et al.* found that a RMgX–$ZnCl_2$ mixture inhibits cross coupling reactions. Remarkably, mixtures of RMgX and $ZnBr_2$ or ZnI_2 not only furnish asymmetric cross couplings, but also reversal of the absolute configuration of the product. They suggested the rate of some exchange reactions on Zn^{II} to be halide dependent, chloride exchanging more slowly.[9a] Although in the synthesis of the **5.1***[EDB] solution no such exchange reactions take place, the use of **5.8** (X = Br), instead of (X = Cl), could provide a deeper insight in the role of chloride in the reaction at hand. We considered the possibility that chloride may inhibit the reaction by acting as a 'sponge' to zinc, since $ZnCl_4^{2-}$ could be formed. We have applied a **5.1***[EDB] solution prepared from **5.8** (X = Br) in a 'chloride-free' cross coupling system.[e] In the cross coupling reaction, no **5.6** was found (^{1}H NMR, GC), although ethylbenzene and styrene were observed.

Addition of alkoxide

The modifications discussed above embrace the mimicking of the '**Cross**-mixture', in attempts to furnish cross coupling reactions. Since these modifications failed, we have looked for general methods to activate **5.1***[EDB]. In the field of diorganomagnesium species it was found that addition of alkali-metal alkoxides furnish solutions that are generally more reactive than conventional organomagnesium compounds.[18] It has been demonstrated that dialkylzinc species can be activated by (amino)alcohols.[19] Replacement of the alkyl group by such electronegative substituents increases the polarity of the R–Zn to a great extent (Figure 5.2). Consequently, this results in enhancement of the donor property of the alkyl group and the acceptor character of the zinc atom. Solutions prepared from dialkylzinc and alkali-metal alkoxides form zincate species,[20] probably similar to the magnesiate analogues.[21]

[e] This experiment is, except for 5.8 (X = Br), identical to the standard cross coupling reaction and not described in the Experimental section.

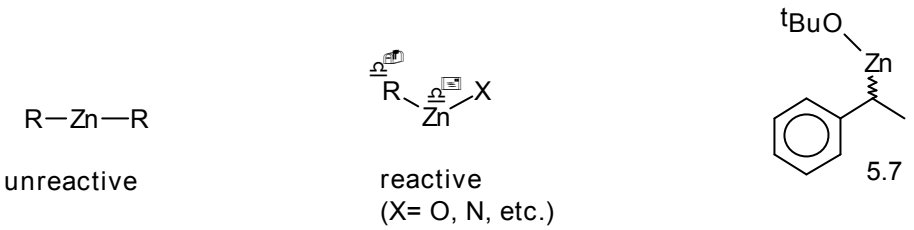


Figure 5.2

We were interested whether the reactivity of **5.1***[EDB] could be increased on addition of alkoxides, furnishing **5.7** (Figure 5.2). On addition of KO^{t}Bu to the solution of **5.1***[EDB] in a 1:1 ratio, prior to cross coupling, no **5.6** was detected (GC, ^{1}H NMR).

A promising improvement to this modification may lay in the variation of the ratio between KO^{t}Bu and RZnX, comparable to findings of Jansen and Feringa. They reported that organozinc species, prepared on addition of 2 eq. RMgX to a mixture of KO^{t}Bu and $ZnCl_2$, show a strong tendency to undergo 1,4-addition to α,β-unsaturated ketones.[22]

Use of preformed catalysts

In the so-called 'standard cross coupling reaction' (Scheme 4.5), the actual catalytic centre Ni^0 is prepared on reduction of the Ni^{II}-salt. The reduction is generally performed by the first drops of the solution containing the organometallic. The possibility that **5.1***[EDB] was incapable to reduce $NiCl_2$, would be circumvented by using preformed catalysts. We chose diisobutylaluminium hydride (DIBAL-H) to reduce $NiCl_2$, prior to cross coupling. A yield of **5.6** (~1%) was detected by GC.

Neghishi has reported that cross coupling with zinc reagents proceeded successfully only in THF and that Ni^0-complexes proved to be inactive[f] in their system.[8a] We therefore carried out experiments in THF with $[Pd^0(dba)_2]$-PPh_3 as

[f] This is not in agreement with couplings that are performed under Cross-conditions, where Ni-complexes successfully catalyse the reaction in Et_2O. This suggests that under Cross-conditions an organometallic species other than organozinc is involved.

catalyst,[g] according to a procedure of Knochel.[23] Under further standard conditions, **5.6** was formed in 1.6 % after overnight stirring at ambient temperature (GC). On heating this mixture at 35°C for a further 3 days, the yield raised to 10.9%. This very low yield, obtained under relative drastic conditions, did not encourage us to proceed with this method.

5.4 Summary, conclusions and perspectives

In this chapter the preparation of magnesium salt-free **5.1** solutions in Et_2O is described. Three different methods of preparation were used. Transmetallation of Grignard reagent with zinc halide and subsequent removal of magnesium salts by use of 1,4-dioxane to obtain **5.1** (X = Cl) were accomplished. Activation of granular zinc by the 'dry-stirring' method to yield **5.1** (X = Br) in Et_2O was accomplished only with a low reproducibility. A promising improvement to this method may be the use of THF as solvent for purposes other than asymmetric cross couplings since THF is reported to be detrimental to the optical yield of the asymmetric couplings. The method where zinc is activated by ethylene dibromide in Et_2O has proven to be a moderately reproducible procedure for the synthesis of **5.1** (X = Cl). An effective, highly reproducible method to form an organozinc species, that meets all the prerequisites we defined for asymmetric couplings, was not found.[h]

All methods failed to provide a diethyl ether solution of **5.1** that is active in cross coupling reactions. With THF as (co)solvent, very low yield of **5.6** could be obtained, using **5.1** from ethylene dibromide activation. The lack of reactivity of the magnesium salt-free **5.1** solutions, described in this chapter, implies that these are not identical to the alkylating agent in the **Cross**-mixture. This underscores the complexity of the whole catalytic process under investigation, and suggests more than one possible reaction pathway.

5.5 Experimental section

General remarks: see also Sections 3.6 and 4.9. As evidence

[g] Palladium bis-(dibenzylideneacetone).

[h] No further efforts were made after mid 1993 when we changed the course of this research.

for formation of organometallic species, hydrolysed samples of the reaction mixtures were checked for ethylbenzene by GC. The standard cross coupling reactions were performed as described for Grignard reagents in Section 4.9 and defined in Section 5.3, unless other stated.

1-Phenylethylzinc chloride solution from transmetallation of Grignard reagent and magnesium-salt removal with 1,4 dioxane (5.1*[dioxane])

To a suspension of anhydrous $ZnCl_2$ (0.82 g, 6 mmol) in Et_2O (9 mL) in a double Schlenk-vessel (P4) under N_2 at room temperature under stirring **5.5** (52 mL 0.23M, 12 mmol) was added dropwise. After stirring for 2 h, 1,4-dioxane (2.25 mL) was added under formation of a white precipitate. The reaction mixture was stirred for 45 min and filtered. To the clear solution was added anhydrous $ZnCl_2$ (0.82 g, 6 mmol) and the reaction mixture was stirred for a further 45 min. The resulting solution was transferred to a dropping funnel under N_2 and subjected to standard cross coupling reaction, defined in Section 5.3.

1-Phenylethylzinc chloride solution from mechanical activated zinc (5.1*[dry stir])

Granular zinc (4.02 g, 61 mmol) was stirred for 3 days with glass splinters under conditions similar to the procedure for magnesium, described in Section 4.9. After mechanical activation, a small amount of Et_2O was added, sufficient to moisten the zinc. The mixture was cooled to 0°C and a solution of 1-phenylethyl bromide (3.7 g, 20 mmol) in Et_2O (100 mL) was added slowly (~1 drop s^{-1}) and stirred for another 2 h. The solution was transferred to a dropping funnel and subjected to standard cross coupling reaction, as defined in Section 5.3.

1-Phenylethylzinc chloride solution from EDB activated zinc (5.1*[EDB])

Typical procedure: Zinc dust (1.7 g, 26 mmol) and 1,2-dibromoethane (200 mg, 1.1 mmol) in Et_2O (sufficient to cover the zinc) were heated thoroughly with a heat gun for 2 min. After cooling to ambient temperature, Et_2O (5 mL) was added. To this mixture, a solution of **5.8** (X = Cl) (3.02 g, 21.5

mmol) in Et_2O (12 mL) was added slowly (1 drop/5 sec) at 0°C, followed by stirring for 1-2 h at ambient temperature to give a pale yellow solution. The solution was transferred to a dropping funnel and subjected to standard cross coupling reaction, as defined in Section 5.3. No **5.6** was obtained (GC). Slight modifications to the above procedure (as using THF instead of Et_2O during activation) were carried out and are documented within text.

Modification: addition of magnesium bromide diethyl etherate. A solution of **5.1***[EDB] was prepared analogous to the standard method in a double Schlenk vessel (P4), filtered and added to a stoichiometric amount $MgBr_2 \bullet Et_2O$ (5.55 g, 21.5 mmol) and stirred for a 15 min. The supernatant was transferred to a dropping funnel and subjected to standard cross coupling reaction, as defined in Section 5.3. No **5.6** was obtained (GC).

Modification: addition of zinc bromide To activated zinc dust (*vide supra*), were added at room temperature anhydrous $ZnBr_2$ (5.85 g, 26 mmol) and Et_2O (5 mL). After cooling down to 0°C a solution of **5.8** (X=Cl) (3.02 g, 21.5 mmol) in Et_2O (12 mL) was added slowly (1 drop/5 sec), followed by stirring for 1.5 h at ambient temperature. The resulting mixture was filtered, transferred to a dropping funnel and subjected to standard cross coupling reaction, as defined in Section 5.3. No **5.6** was obtained (GC).

Modification: addition of t-BuOK. To a stirred solution **5.1***[EDB] (25 mL, 0.25 M in Et_2O) a solution of KO^tBu (0.70 g, 6.25 mmol) in Et_2O (25 mL) was added. After stirring for 1 h at 0°C, the resulting mixture was transferred to a dropping funnel and subjected to standard cross coupling reaction, as defined in Section 5.3. No **5.6** was obtained (GC).

Modification: use of preformed Ni^0 catalyst

To an orange solution of $NiCl_2$ (5.2 mg, 0.04 mmol) and DPPE (16 mg, 0.04 mmol) in THF (3 mL) at ambient temperature was added diisobutylaluminium hydride (1.0 M in THF, 0.05 mL, 0.05 mmol). After stirring the mixture for 30 min, the colour of the solution was changed to yellow and vinyl bromide (5.0 M in Et_2O, 1.6 mL, 8 mmol) was added. This solution was subjected to standard cross coupling, as defined in Section 5.3, using a solution of **5.1***[EDB] (typical procedure) at standard temperature (–40°C), yielding no **5.6** (GC). Another experiment,

with an identical solutions, was performed at higher temperature (40°C). A negligible yield (<1%) was obtained.

Modification: use of Pd^0 catalyst

A red solution of $Pd(dba)_2$ (27 mg, 0.05 mmol) and PPh_3 (52 mg, 0.2 mmol) in THF (10 mL) was stirred for 10 min at ambient temperature. To the resulting orange solution was added vinyl bromide (5.0 M in Et_2O, 1.6 mL, 8 mmol). This solution was subjected to standard cross coupling, as defined in Section 5.3, using a solution of **5.1***[EDB] (typical procedure) at ambient temperature. A sample was taken after stirring for 18 h at ambient temperature and analysed (1.6%, GC). A further heating of the reaction mixture (35°C) yielded 3.6%, 10.5%, and 10.9% of **5.6**, after respectively 2 h, 24 h, and 96 h.

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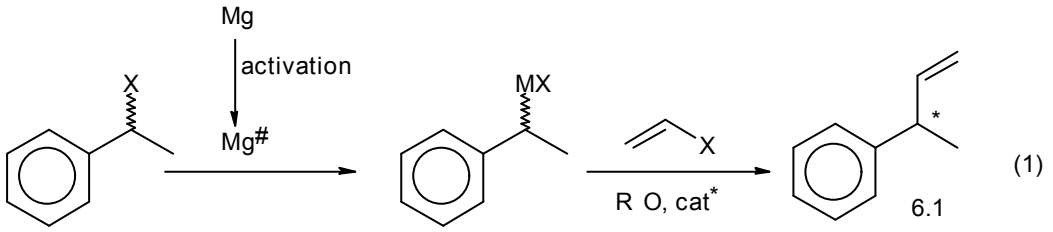
Chapter 6

Towards Enantioselective S_N2' Reactions

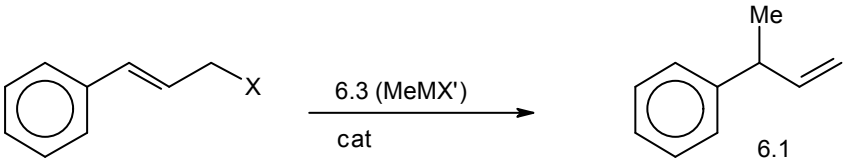
6.1 Introduction

In the first part of this thesis, we have described the asymmetric synthesis of profen precursor **6.1** by asymmetric catalysed cross coupling reactions (Chapters 2, 4, and 5). In brief, this reaction involves a stereoselective carbon–carbon bond formation between a vinylic- and a benzylic moiety, and the reaction is catalysed by a chiral, non racemic catalyst (Scheme 6.1, Eq. 1). The benzylic magnesium halide reagent is a chiral, racemic compound that appears to racemize on the same time scale as the cross coupling reaction. Therefore, the asymmetric cross coupling reaction is a dynamic kinetic resolution. We concluded from our work, as well as that of others, that the *ee* of the product depends on too many variables, some of which are beyond control. We are inclined to believe that the degree of reproducibility of the *ee* of **6.1** is a function of the specific research group and researcher. As a consequence, the asymmetric cross coupling reaction at hand is an unreliable measure to rank ligands with regard to their enantioefficacy, unless the conditions used are specified very precisely.



(1)

(Some of the factors that potentially influence the enantioselection are printed in italics)



(2)

6.2a: X = OAc
6.2b: X = Br
6.2c: X = Cl

M = Mg, Li, Zn, Cu, Ti, etcetera
X' = halide, alkyl, etcetera
cat = $Cu^{(I)}$- salt (complex)

Scheme 6.1

Further, the above mentioned complications are unacceptable for a reaction that is intended for a larger scale process. For these reasons, we looked for an alternative asymmetric catalytic process to prepare **6.1**.

Recapitulating, this research was set up within the framework of asymmetric catalysis, leading to a precursor of profen compounds like **6.1**. This has been discussed in Chapter 1. Therefore, the alternative approach we searched for had to fit in this framework as well. The alternative approach must involve asymmetric catalysis and formation of profen precursor **6.1** in enantiomeric excess.

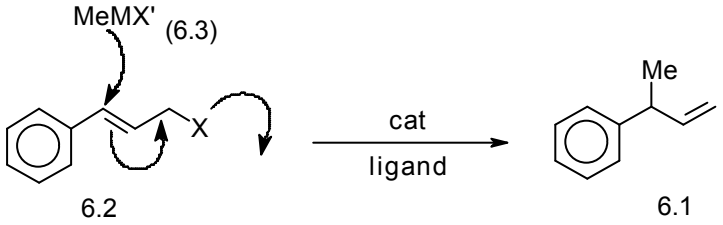
We saw an appropriate alternative reaction for the preparation of **6.1** in the nucleophilic substitution of an allylic species by a methylmetallic reagent in a S_N2' fashion (Scheme 6.1, Eq. 2). In the following section, mechanisms together with theoretical and practical findings will be discussed. In Section 6.3, the strategy towards enantioselective S_N2' reactions is discussed, based on some inspiring reports. S_N2' reactions in practical sense are discussed in Section 6.4, followed by an epilogue (Section 6.5) and conclusions in Section 6.6.

6.2 An alternative route to compound 6.1: the S_N2' reaction

It is evident that from methylmetallic species **6.3** and cinnamyl compounds **6.2**, the profen precursor **6.1** can be prepared by the γ–selective S_N2' reaction. The methyl group then must attack at the benzylic position of the allylic cinnamyl compound and, concomitant with movement of the double bond, the leaving group X eliminates under formation of **6.1** (Scheme 6.2). On closer examination, the carbon-carbon bond formation in S_N2' fashion also can be considered as a cross coupling reaction. In order to avoid confusion, we will refer to the present reaction as a *S_N2' reaction* or *γ-selective (substitution) reaction*. The S_N2' reaction is an essentially different approach to **6.1**, compared with the cross coupling reaction described in the Chapters 2, 4, and 5. Instead of the vinyl group, the methyl group is coupled to the benzylic position. When we compare both reactions with regard to stereochemistry, the asymmetric cross coupling reaction is a

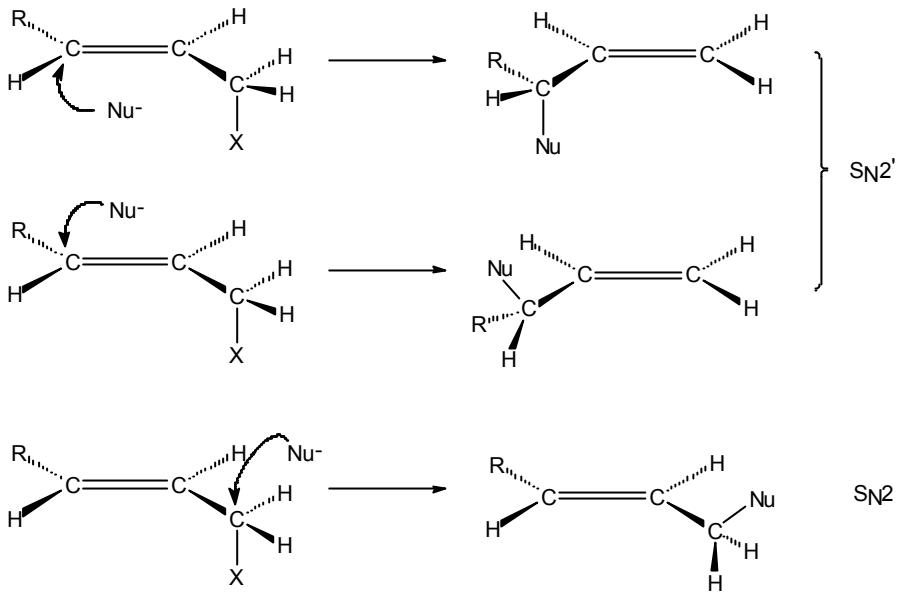
dynamic kinetic resolution of a racemic 1-phenylethyl metallic species, and **6.1** can be obtained in high optical yield. On the other hand, the S_N2' reaction involves the attachment of a methyl group to an allylic, prochiral[a] position by a nucleophilic substitution.

Three pathways are possible for nucleophilic substitution of allylic substrates. The nucleophile may attack the π-bond at the γ-position in either a (1) syn or (2) anti fashion relative to the leaving group, the S_N2' mechanism, or (3) may substitute at the saturated α-position by an S_N2 mechanism. The S_N2' reaction is a bimolecular nucleophilic displacement of a nucleofuge by a nucleophile, accompanied by an allylic rearrangement. The regiochemistry (α- *versus* γ-attack) has been an important problem of this reaction, and often mixtures of S_N2' and S_N2 products are obtained.[1] In addition to the stereochemistry of the reaction, the question remains whether the S_N2' displacement proceeds in a stepwise manner through a stable intermediate or in a concerted fashion. This topic has been a subject of controversy.[2,3]



Scheme 6.2

[a]Prochiral is the term used for an achiral compound which can be converted into a chiral compound after one chemical step.

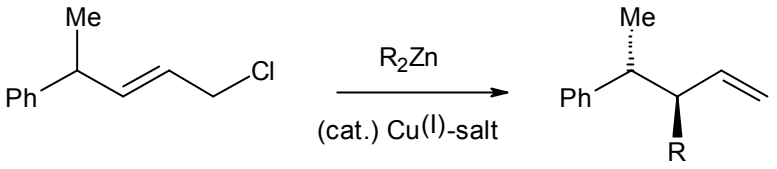


Scheme 6.3

Recent theoretical studies on the identity of S_N2' reactions propose that the gas phase degenerate nucleophilic reactions of an allylic system with nucleophiles X^- = H^-, F^-, Cl^- (which in these studies are leaving groups simultaneously) proceed by different mechanisms depending on X (Scheme 6.3). The stepwise pathway, with the rate-limiting breakdown of the intermediate, is favoured for nucleophile (and leaving group) X = H, which has a relatively low electronegativity. For the highly electronegative X = Cl, the direct S_N2 displacement mechanism is favoured. In the case of X = F, the intermediate of the syn form is less stable and all three mechanisms (*vide supra*) can compete. In this case the rotational barrier of the CH_2F group prevents the anti-S_N2' path from going through the syn-S_N2' intermediate, as found for X = H. The anti-S_N2' reaction provides the lowest energy path, which is found to proceed concertedly.[3]

In a practical sense, standard Gilman reagents (R_2CuLi) have been successfully applied in S_N2' reactions, though their γ-regioselectivity is unreliable. The scope has been extended

to reagents based on combinations[b] of copper(I) and Lewis acidic metals as Mg-Cu,[4] Zn-Cu[5,10] and Ti-Cu.[5,6] These combinations have been found to give consistently high γ-regioselectivity. Stereoselective S_N2' reactions have been extensively reported on the prochiral position of chiral, racemic substrates, affording diastereomers as depicted in Scheme 6.4. [6,7,8,13]



Scheme 6.4

At the time of these investigations, asymmetric catalysed enantioselective S_N2' reactions on achiral allylic species had no precedent, to our knowledge.

6.3 Strategy towards asymmetric catalysed S_N2' reactions

Introduction

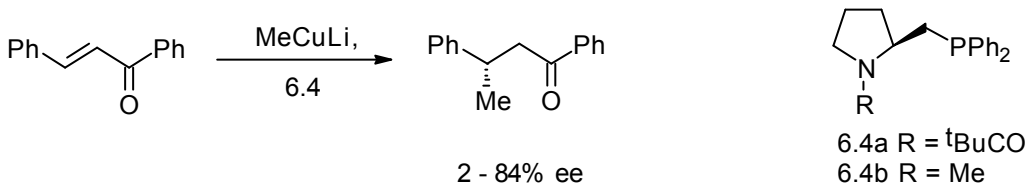
We expected that an S_N2' reaction in an asymmetric catalysed version has the potential to serve our purposes very well, affording **6.1** in enantiomeric excess. The combination of ligand, catalyst and methyl-metal compound has to meet the following conditions: First, the S_N2' substitution must take place highly γ-selectively, without competing formation of the S_N2 product. Second, in the absence of catalyst, no reaction must occur. In this way, the blank reaction without chiral induction is prevented. Third, the methyl transfer in the S_N2' substitution must occur in an enantioselective manner.

The scope of S_N2' reactions is broad,[8] even for the synthesis of a closely defined compound as **6.1**. The outlines we have drawn were inspired by reports from the literature (*vide infra)*. For a better understanding of the selection we made of catalysts and ligands, we will review some papers concerning copper chemistry and S_N2' chemistry. One of the papers deals with enantioselective conjugate addition reactions with organocopper species, the others relate to S_N2' chemistry.

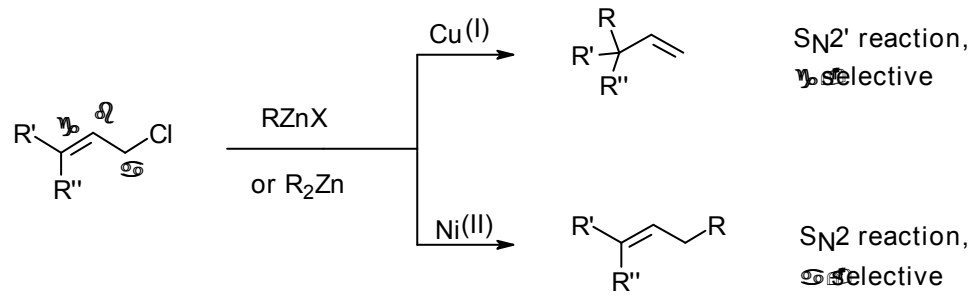
[b] In stoichiometric and, more recently, in catalytic amounts.

Recent developments

In the area of organocopper chemistry, enantioselective conjugate addition is a rapidly developing area. Chiral modification of heterocuprates has been the prototype of these approaches, wherein chiral amides, alkoxides and thiolates are employed as chiral components of the cuprates.[9] In this section we focus on another, scarcely used, approach where chiral external ligands have been used as asymmetric controllers. In 1992, Tomioka *et al*. derived some ligands from proline.[9] In enantioselective conjugate additions of lithium dimethylcuprate to chalcone in the presence of these ligands (Scheme 6.5), remarkable differences in stereoselective behaviour were observed. Conjugate Me_2CuLi additions in the presence of aminophosphine **6.4b** gave only 2% *ee*, whereas amidophosphine **6.4a** afforded 84% *ee*. This effect is attributed to a selective metal differentiating coordination of the carbonyl oxygen to the lithium atom, and of the phosphorus to the copper atom.



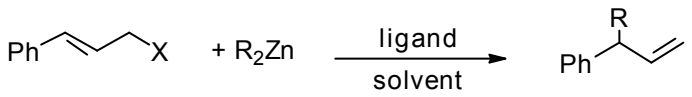
Scheme 6.5



Scheme 6.6

In 1988, Nakamura *et al*. showed that organozinc species undergo highly S_N2'-regioselective $Cu^{(I)}$ catalysed allylation reactions.[10] They found that the mode of regioselection shifted

from S_N2' (γ) to S_N2 (α), simply by switching from $Cu^{(I)}$-based to $Ni^{(II)}$-based catalysts (Scheme 6.6). γ–Regioselectivity (S_N2' reaction) of 98% was obtained with $CuBr{\bullet}SMe_2$ as catalyst. In contrast to copper reagents based on RLi or RMgX, the [RZnX – $Cu^{(I)}$-catalyst] reagent shows high chemoselectivity and neither reacts with allylic acetates nor with alkyl halides. In 1993, Nakamura *et al*. reported that a regio- and stereoselective allylation of organozinc reagents was not completely limited to Cu-based reactions.[11] Dialkylzinc reagents could undergo highly regio- (Scheme 6.7) and diastereoselective (Scheme 6.8) S_N2' allylation reactions in the presence of coordinating additives such as HMPA, TMEDA, or DMF. A monodentate amine, Et_3N, proved to be ineffective. Regio- and diastereoselectivity as well as reaction rate depended on the nature of the solvent. For instance, the reaction in pure hexane in comparison with THF is much less selective (50% *versus* 97%) and much slower (9% *versus* 87% yield).

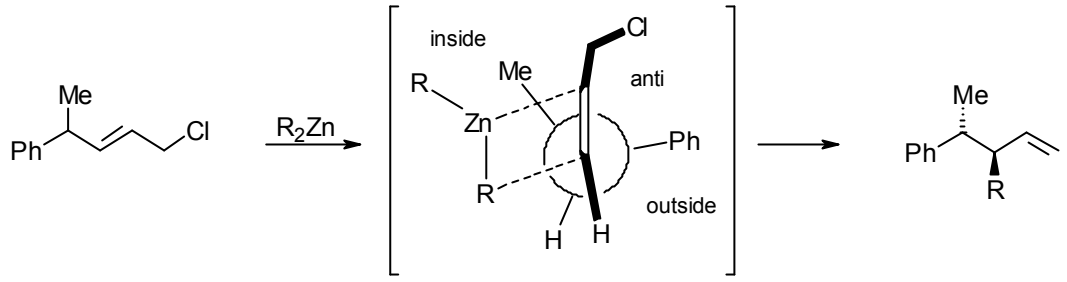


X = Cl, Br, $OP(O)(OEt)_2$; ligand: DMF, HMPA, TMEDA; solvent: THF, hexane

Scheme 6.7

For the allylation of organocopper reagents, two mechanisms have been proposed. (1) The copper mediated reactions are presumed to proceed through a $Cu^{(III)}$-allyl intermediate, on attack of the copper atom to the olefinic carbon. The mechanism through $Cu^{(III)}$, however, cannot be applied to the organozinc mediated reactions, since such a hypervalent zinc species is improbable. Another proposed mechanism involves a nucleophilic attack of the alkyl group on the copper atom, leading directly to the allylation product. (2) Nakamura *et al.* observed that for organocopper and organozinc reagents the sense and level of the diastereoselectivity were surprisingly similar.[12] It is probable that the second mechanism is also applicable to the organocopper reactions. The observed stereoselectivity conforms to Cram's rule proposed for carbonyl additions. Though the mechanisms of the

present allylation reaction and the carbonyl addition may seem different from each other, similarity may become rational if the allylation reaction is viewed as a carbometalation-like reaction (Scheme 6.8).[11]



Scheme 6.8

From the above reports we conclude that a highly γ–selective allylation reaction of the organometallic species depends on appropriate choice of the organometallic compound or intermediate, the allylic reagent and the solvent. In our search to obtain catalytic enantioselective S_N2' reactions we were interested in the following: *i*) which reagents provide high γ-regioselectivity in S_N2' substitution reactions, and: *ii*) which asymmetric catalyst would potentially induce enantioselectivity, as well as high γ-regioselectivity.

i) Reagents and regioselectivity

We have seen in the above reports that the organometallic reagent in S_N2' reactions is not only limited to organocuprates. Organozinc reagents in the presence of a copper catalyst can be applied successfully in γ-selective allylation reactions. Also, on addition of appropriate coordinating additives to the organozinc species, even the Cu-based catalyst can be omitted. Among the reagents that have been applied successfully in the alkyl transfer were organometallic compounds or intermediates based on Mg, Li, Zn, and Ti. Levisalles *et al*. reported that the regioselectivity in substitution reactions on terpene acetates, reversed from α to γ on changing $CH_3(X)CuLi$ from X = CH_3 to X = CN. With organocuprate X = SPh, mixed behaviour was observed.[13] The possibility of two geometric isomers around Cu in the

$CH_3(CN)CuLi$ π-allyl intermediate is given as explanation for this behaviour. In the case of $(CH_3)_2CuLi$, it seems reasonable that the proposed π-allyl copper complex retains stereochemistry and is sterically disposed to transfer the CH_3 group to the less hindered carbon. So far, adequate rationalization has not been given for the behaviour in all experiments.[8]

For the allylic reagent, an appropriate leaving group is required in order to realize **6.1**. This condition is easily fulfilled since, for instance, cinnamyl acetates and halides (Scheme 6.1, Eq. 2, **6.2a-c**) are commercially available, and are easy to handle. Significant effects of the leaving group on regioselectivity have been found.[14] Which type of leaving group is to be chosen depends on the choice of organometallic compound or catalytic intermediate. In Cu-catalysed reactions with organozinc reagents, we expected **6.2a-c** (Scheme 6.1, Eq. 2) to be proper reaction partners. Further, it is probable that the enantioefficacy in the reaction is solvent dependent, like the asymmetric cross coupling reactions described in Chapter 2, 4 and 5.

ii) Asymmetric ligands in S_N2' reactions

We speculated that appropriate asymmetric ligands for the organometallic intermediate might induce chirality at the γ-position. In organocuprate or $Cu^{(I)}$-catalysed reactions, asymmetric ligands may chelate to the Cu centre, and/or to the organometallic species. In S_N2' allylation reactions with organozinc reagents, asymmetric ligands may perform the function of polar additives. We expected that these asymmetric complexes may approach the allylic moiety in a syn- or anti-selective fashion and transfer the methyl group in this way. Chelation of an asymmetric organometallic intermediate to the leaving group, prior to alkyl transfer, may also play a role in the enantioselectivity.

The above reports inspired us in the design of an appropriate ligand. In both the conjugate addition of organocuprates[9] (Scheme 6.5), and the γ-selective allylation of organozinc species[11] (Scheme 6.6), superior ligands contain nitrogen, phosphorus and oxygen. Further, a sulphur based ligand, dimethylsulphide, was used by Nakamura to stabilize

the $Cu^{(I)}$-catalyst in Scheme 6.6.[10] We considered that α-amino acid derived ligands that contain nitrogen, phosphorus or sulphur, as described in Chapter 3, may serve very well the purpose of asymmetric ligands for catalysts in regio- and enantioselective S_N2' reactions. In our group, and in the present research, homologues of methphos have been developed. These tridentate ligands are interesting ligands for this reaction. Another interesting ligand is the proline-derived amidophosphine **6.4a** (see Scheme 6.5), which is an effective ligand in the conjugate addition reaction. We expected that **6.4a** may give a proper chelation to a **6.2a** - methyl cuprate complex, when applied in the S_N2' reaction. This will be discussed under the heading *Organozinc reagents in S_N2' reactions*, in Section 6.4.

6.4 Substitution reactions in S_N2' fashion
Organozinc reagents in S_N2' reactions

The choice of methylzinc compounds as alkylating reagents gave us the opportunity to select two types of catalysed S_N2' reactions, namely, on the one hand [MeZnX - $Cu^{(I)}$] couples and on the other hand [RZnX - polar additive] combinations. In either case, asymmetric ligands can be applied as a ligand for $Cu^{(I)}$ or as a coordinating additive for RZnX.[15] Methylzinc halide (MeZnX•LiX, X = Cl, I) was prepared by a metathesis reaction of MeLi•LiX (X = I or Cl) with $ZnCl_2$ in THF.[c] The method used for the preparation of the organozinc reagent seems to play no pivotal role in regioselectivity. Organozinc reagents prepared by a metathesis reaction,[10,11] as well as through a direct reaction between zinc and organic halides,[16] provide highly S_N2'-selective organozinc reagents. The commercially available 2.0 M Me_2Zn solution in toluene proved less practical in the present investigation. We found that product **6.1** and the solvent, toluene, are difficult to separate by distillation, probably due to the formation of an azeotrope.

[c] Later on, we made use of MeLi•LiCl in EtO, kindly provided by R. Duchateau.

Asymmetric catalysts for S_N2' reactions with methylzinc reagents

We performed some pilot experiments with $Cu^{(I)}$-catalysed S_N2' reactions (Scheme 6.1, Eq. 2) using achiral ligands like dimethyl sulphide and 2,2'-bipyridine (entries 1 and 2). The MeZnX solution, in the presence of 5-10 mol% of [$Cu^{(I)}$ - ligand] combination, was treated with the cinnamyl compound. The chemical yields of the substitution product obtained with dimethyl sulphide and 2,2'-bipyridine were moderate: 40% and 30% respectively, but in fair S_N2' : S_N2 regioselectivity of 80 : 20 and 67 : 33, respectively (^{1}H NMR). Further, we employed asymmetric ligands derived from amino acids[d] in the above described S_N2' reaction. These experiments were inspired by literature analogues, based on considerable empirical research. With **3.11** (Section 3.3) as ligand (entry 3), the reaction proceeded with a moderate S_N2' : S_N2 regioselectivity (60 : 40, ^{1}H NMR), and **6.1** was obtained in 42% chemical yield. However, no chiral induction took place (no rotation observed). With tridentate compound **3.24**, (Section 3.4) containing phosphorus, nitrogen and sulphur as heteroatoms, **6.1** was obtained in low yield (13%) as a racemate (chiral GC column).

Table 6.1 S_N2' reactions on **6.2** with [Zn - CH_3] species (cf. Scheme 6.1, Eq. 2)

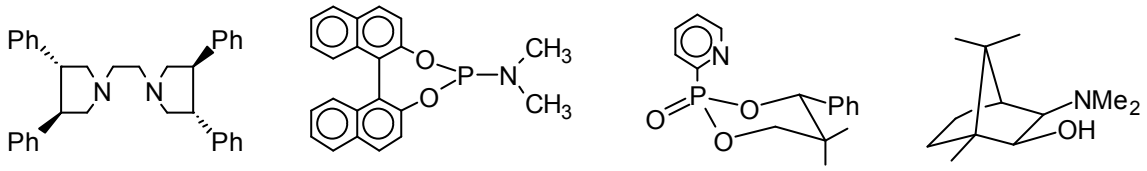
entry	ligand	$Cu^{(I)}$-salt	regioselectivity (γ : α)	% yield (γ)
1	Me_2S	CuBr	80 : 20	40
2	bipy[a)]	CuBr	67 : 33	30
3	**3.11**	CuBr	60 : 40	42
4	**3.24**	CuBr	n.d.[b)]	13
5	**6.5**	CuBr	n.d.[b)]	90
6	**6.6**	CuBr	n.d.[b)]	70
7	**6.7**	---	n.d.[b)]	30
8	**6.8**	CuBr	70 : 30	25

a) 2,2'-bipyridine b) n.d.: not determined

The next asymmetric ligands were selected on basis of their similarity to achiral analogues, as reported by Nakamura *et al.* (*vide supra*).[11] These ligands were kindly provided by

[d] See Chapter 3.

colleagues from the Chemistry Department (Figure 6.1).[e] In these empirical studies we determined the enantioselectivity due to the asymmetric ligand and not the regioselectivity. The chemical yields of **6.1** in these experiments were comparable to the experiments with achiral catalysts, being about 40%. We considered **6.5** as an asymmetric analogue of TMEDA. In entry 5, **6.1** was obtained in 90% chemical yield as a racemate. Further, we have used bis-β-naphthol derived compound **6.6**. This ligand furnished **6.1** in 70% yield, but without enantiomeric excess.[f] We fancied that with compound **6.7**, the P=O and the aromatic nitrogen in the pyridine appendage would give an appropriate chelation to the zinc reagent, like e.g. HMPA in [RZn-polar additive]-type S_N2' reactions.[g] Under reaction conditions similar those reported by Nakamura,[11] **6.1** was obtained in 30% chemical yield as a racemate.



6.5 6.6 6.7 6.8

Figure 6.1

Besides the S_N2' reactions with the above ligands, we performed several studies with **6.8**. In these studies, we used 5 mol% $Cu^{(I)}Br$ as catalyst.[10] We rationalized[h] that 10 mol% of **6.8** would chelate for a part to the copper catalyst and for another part to the methylzinc species. When we allowed the methylzinc reagent to react with **6.2b**, a dark brown, complex reaction mixture was obtained. Working under the assumption that this coloration was due to halide formation,[i] we then

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[e]Ton (T.R.) Vries, Ron (A.J.R.L.) Hulst, Bas (A.C) Dros and André (A.H.M) de Vries are thanked for the generous gift of compounds to be ligands in this reactions. These compounds are 6.5, 6.6, 6.7, and 6.8, respectively.

[f] This result was later supported by results of A.H.M. de Vries, using a similar ligand, where nitrogen was substituted by two isopropyl groups instead of two methyl groups. (A.H.M. de Vries, PhD thesis 1996).

[g]cf. ref. 11.

[h]Analogous to additions of dialkylzinc to RR'C=O bonds.

[i] From triiodide, bromine or another brown-coloured halide combination.

chose **6.2c** as allylic substrate. This combination provided also a brown coloured crude reaction mixture, containing **6.1** (NMR). Purification of this crude material by routine distillation furnished a dark brown, complex reaction mixture, similar to what we observed in the previous experiment. The coloration may be due to the presence of iodide salts in the reaction mixture, resulting from MeZnX•LiX, X = Cl, I. We expected no colouring of the reaction mixture with commercially available Me_2Zn solution in toluene, since this solution does not contain halides. The resulting reaction mixture was coloured brown after work up and turned rapidly into a darker coloured liquid on standing. In a following experiment, $Cu^{(I)}Br$ was omitted in order to trace the source of brown coloration. The S_N2' reaction was presumed to occur *via* an [MeZn, **6.8**] combination. No colouring occurred, but still a complex reaction mixture was obtained. We identified the formation of a small amount of **6.1** by GC and NMR (<5%). In a $Cu^{(I)}Br$ catalysed experiment with as ligand the alkoxide of **6.8**, entry 8, the brown coloured crude material was obtained with an S_N2' : S_N2 ratio of 70 : 30. The S_N2' product could be isolated in 25%. Attempts to prevent the continuing return of the brown colour failed.[j] Since the coloration of the reaction mixture probably stems from the $Cu^{(I)}Br$ catalyst, we changed to $Cu^{(I)}CN$ as catalyst.

Methylzinc reagents in S_N2' reactions: conclusions

From the above results, we concluded that the S_N2' reactions performed with methylzinc species are moderately γ-selective. In cases where asymmetric ligands have been applied, no chiral induction was observed. Moreover, we observed that S_N2' reactions may take place without a catalyst.[k] In the present research, however, the intermediacy

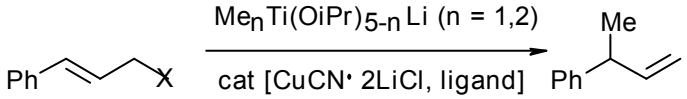
[j] The brown colour vanished periodically on washing the crude material extensively with sodium metabisulphite (4 times) and triethyl phosphite (1 time). The product, purified by distillation, was still slightly contaminated, according to the pale pink colour.

[k] We emphasize that the ensuing result was not investigated into detail, for which reason an extensive discussion is omitted. We know from the literature that saturated alkylzinc species do not react with alkenes or aldehydes. Addition of a ligand or auxiliary to the organozinc species distorts the linear geometry of the zinc-alkyl bond and accelerates the alkyl transfer reaction (ref. 15). Therefore, it is peculiar that we detected a trace of 6.1 in a qualitative experiment where Me_2Zn and 6.2c have been stirred without any additives as (polar) ligands or catalysts. Since the GC signal of 6.1 was superimposed upon the very broad tail of the toluene signal, the yield could not be determined;

of an asymmetric catalyst is a prerequisite for the intended chiral induction. On that account, we shifted our strategy and performed for this study some closing experiments with organotitanium reagents.

Organotitanium reagents in S_N2' reactions

We have selected organotitanium reagents as an alternative for methylzinc reagents in S_N2' reactions. $Cu^{(I)}$-catalysed S_N2' reactions with organotitanium reagents have been found to give high regioselectivity.[6] Analogously to successful γ-selective substitution reactions with *n*-butyltitanate complexes,[6b] we employed methyl-titanate complexes in the S_N2' reaction (Scheme 6.9). These ate-complexes, $[MeTi(OiPr)_4Li]$ and $[Me_2Ti(OiPr)_3Cl]$, are easily prepared from MeLi and $Ti(OiPr)_4$ or 2 MeLi and $ClTi(OiPr)_3$, respectively. Generally, 8 mol% of the ligand was stirred with CuCN•2LiCl at 0°C, prior to addition to the titanate complex (1.5 eq.). To the resulting mixture 1.0 equivalent of cinnamyl compound was added at -70°C. The mixture was stirred overnight, during which time it was allowed to warm to ambient temperature. After careful hydrolysis of the reaction mixture with moist hexane and subsequent distillation, the material was subjected to chiral GC analysis.



Scheme 6.9

With these [MeTi-Cu] combinations, the chemical yield and regioselectivity of **6.1** improved significantly, in comparison with the [MeZn-catalyst] combinations (*vide supra*). On the average, we obtained **6.1** in 70% yield using this method. In all cases, we did not observe the formation of S_N2 product (GC). We established that this reaction is highly Cu-catalyst

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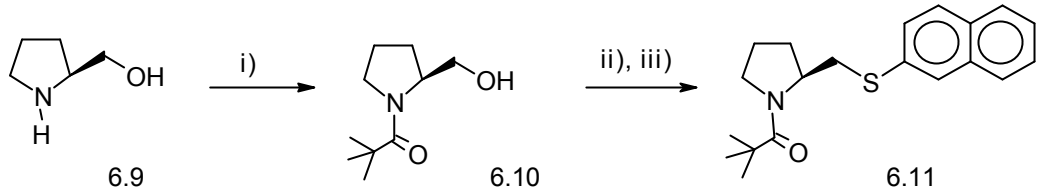
toluene and 6.1 are inadequately separated by distillation (see Section 6.4 Organozinc reagents in S_N2' reactions). We assume that the reaction may have taken place for a few percent without a ligand as accelerator, or that another mechanism is involved. It must be noted that we were not able to reproduce this experiment.

dependent. In a standard experiment where we treated **6.2a** with [$Me_2Ti(OiPr)_3Li$], no trace of **6.1** was detected in the case when the $Cu^{(I)}$-catalyst was omitted nor was formation of α-regioselective product observed. Since we have found that organozinc reagents perform S_N2' reactions without catalyst, *vide supra*, the Ti-Cu combination is promising for our purpose.



6.9 6.10 6.11

i) pivaloyl chloride; ii) methanesulphonyl chloride; iii) 2-naphthalenethiol.

Scheme 6.10

Synthesis of compound 6.11

One of our aims in the enantioselective S_N2' reaction (Scheme 6.1, Eq. 2) was to employ **6.4a**, since this compound has proven to be a successful ligand in enantioselective conjugate additions (*vide supra*).[9] For the method of preparation of **6.4a**, Tomioka *et al.* refer to a Japanese patent,[17] (abridged in Chemical Abstracts)[18], and to a report of Kagan *et al.*[19] The latter report describes a general procedure to convert alcohols into phosphines. Several attempts, however, to obtain **6.4a** from **6.9** by the above mentioned and other approaches were unsuccessful.[20] Whatever the explanation, this result prompted us to modify our strategy with regard to the ligand. We expected that an amidosulphide ligand (eg. **6.11**, Scheme 6.10) would be an appropriate substitute for the intended amidophosphine. In order to mimic partly the two aromatic moieties that are present in the diphenylphosphino group, we chose a 2-naphthyl group. Compound **6.9** was allowed to react with pivaloyl chloride, affording **6.10** in 96% yield. Analogously to the synthesis of aminosulphides described in Chapter 3, compound **6.10** was converted into the corresponding mesylate which reacted *in situ* with a mixture of KO^tBu and 2-naphthalenethiol in THF to give **6.11** in 53% yield.

Asymmetric catalysts for S_N2' reactions with methyltitanate reagents

In the S_N2' reaction (Scheme 6.9) we used **6.11** as ligand for the copper catalyst. Further, we selected **3.9b**. (see Section 3.2), which is an 'on shelf' ligand. The chemical yields of **6.1** in the S_N2' reactions catalysed by **6.11** and **3.9b** were comparable: 71% and 69%, respectively (Table 6.2, entries 1 and 2). These are fair yields, compared with experimental results of Nakamura, where a butyl group is introduced on the same allylic substrate. The chemical yields are at least higher than the yield obtained by Nakamura with the $CuBr{\bullet}SMe_2$ catalyst (57%). On basis of the above results, it is tempting to suggest that **6.11** and **3.9b** are better as ligands in this reaction than dimethylsulphide. Yet, this is not experimentally demonstrated by a $CuBr{\bullet}SMe_2$ catalysed $_NS2'$ reaction between methyl-titanate and **6.2a**. At least, we can conclude that **6.11** and **3.9b** are moderately successful ligands. In the S_N2' reaction with **3.9b** as ligand, the yield may be improved by using **6.2a** instead of **6.2c**. The regioselectivity of both experiments is, from GC measurements, absolutely γ-selective, in agreement with literature data (>99%).[6b] No trace of α-product, phenyl-1-butene, was detected by GC. To our disappointment, both experiments afforded **6.1** in racemic form on the basis of a chiral GC analysis.

Table 6.2 *S_N2' reactions on **6.2** with [Ti - CH_3] species (cf. Scheme 6.9).*

entry	ligand	regioselectivity (γ : α)	% yield (γ)
1	**6.11**	>99 : <1	71
2	**3.9b**	>99 : <1	69

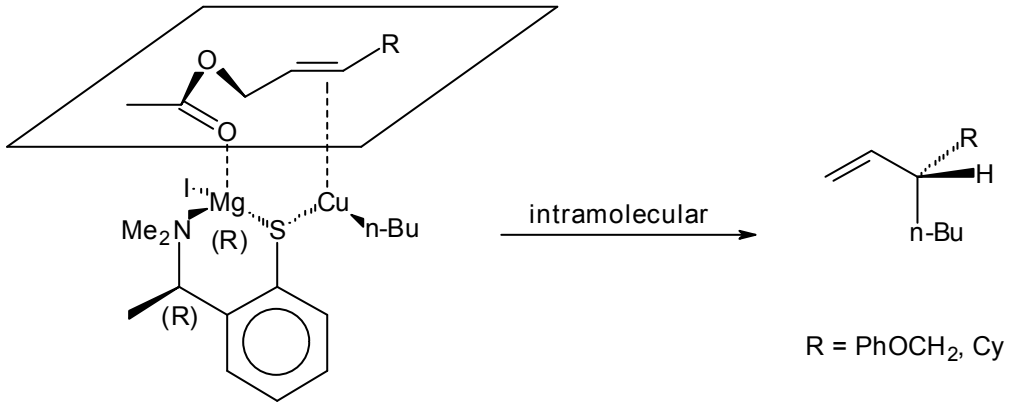
$CuCN{\bullet}2LiCl$ was used as catalyst.

Methyltitanate reagents in S_N2' reactions: conclusions

From the above results, we concluded that the S_N2' reactions performed with methyltitanate species are highly γ-selective. In cases where asymmetric ligands have been applied, no chiral induction was observed.

6.5 Epilogue

Recently, Van Koten *et al*. reported asymmetric catalysed enantioselective S_N2' reactions on two achiral allylic substrates, **6.12a** and **6.12b**.[21] Asymmetric arenethiolatocopper(I) complexes (Scheme 6.11) afforded an enantioselectivity of up to 42% between those allylic acetates and *n*–butylmagnesium halide. The rationale for the model proposed for enantioselectivity is interesting. The authors postulate the acetate and the alkene group of the allylic moiety to anchor to the magnesium and the copper moiety, respectively, of the catalytic intermediate. The enantioselectivity in the alkyl transfer was explained on the basis of coordination of the copper-alkyl group to the alkene moiety, in combination with the configuration of the (chiral) magnesium centre. They used an equilibrium between two possibilities derived from molecular modelling to explain the moderate *ee* of only 42% (underscoring the subtleness of this enantioselection). Although it is stated that there is little steric interaction between the allylic substrate and the alkyl group containing catalytic intermediate, the question remains what will happen to the moderate enantioselectivity if the *n*-butyl group is replaced by a smaller group like methyl. In other words: can a profen precursor like 3-phenyl-1-butene be realized by this method? An explanation for the non-enantioselectivity in the S_N2' reaction that we have performed with methylmetallic reagents, may be that the methyl group is too small compared to, for instance, the *n*-butyl group.



Scheme 6.11

Also, we have to bear in mind that the enantioselectivity in the above report is explained on basis of a mechanism that is applicable to organocuprates, namely *via* a $Cu^{(III)}$ intermediate, but not to organozinc species (cf. Section 6.3 - *Recent developments*). This emphasizes that possibly two or more mechanisms exist for the S_N2' reaction between organometallic reagents and allylic substrates.

6.6 Conclusions

In this chapter, the application of asymmetric ligands in catalysed S_N2' reactions of methylmetallics on allylic cinnamyl species towards enantiomeric enriched **6.1** is described. Attempts to make the methyl transfer enantioselective by addition of various asymmetric ligands to the [MeZn, $Cu^{(I)}$-catalyst] couple, failed. Also S_N2' reactions with [MeZn, chiral, polar additive] as methyl donating complex failed, regarding to enantioselectivity. The γ-selectivity of S_N2' reactions with [MeZn, chiral, polar additive] reagents was moderate (up to 70%). Methylzinc reagents in S_N2' reactions on cinnamyl species were not found to be absolutely catalyst dependent.

S_N2' reactions on cinnamyl species with [Me-titanate, $Cu^{(I)}$-catalyst] combinations furnished **6.1** in 70% yield, on the average. Attempts to make the methyl transfer enantioselective, on addition of asymmetric ligands to the [Me-titanate, $Cu^{(I)}$-catalyst] couple, failed. Substitution reactions on cinnamyl compounds with methyltitanates were highly γ-selective (> 99%).

Recent developments in enantioselective S_N2' reactions with organocuprates (Section 6.6) show that this is a promising area for asymmetric catalysis. The *ee*'s that have been reported are moderate (up to 45%), and the proposed intermediate responsible for enantioselection is based on cuprate chemistry, *via* $Cu^{(III)}$ intermediates. Since an alternative mechanism has been proposed for organozinc species,[11,12] which is also applicable to organocuprates, the mechanism of enantioselection becomes more unclear: a promising new area for further research.

6.7 Experimental section

General remarks: see Sections 3.6 and 4.9.

Synthesis of MeZnX•LiX (typical procedure)

To $ZnCl_2$ (2.73 g, 20.0 mmol) in THF (20 mL) was added by syringe MeLi•LiX (1.2 M, 17 mL, 20 mmol). The resulting solution of MeZnX•LiX is further denoted as MeZnX, where X = halide, dependent on the methyl halide used to prepare MeLi, and on zinc halide, being $ZnCl_2$ in the present investigations.

S_N2' reactions with methylzinc reagents on cinnamyl compounds (6.2)

[*ligand - catalyst combination*]:

[*Me_2S - CuBr*] *and standard work up*: To a mixture of [$CuBr•SMe_2$] (0.50 g, 2.43 mmol) in THF (5 mL) was added MeZnX (1.2 M, 17 mL, 20 mmol) at 0°C. The mixture was stirred for 15 min, after which **6.2b** (4.04 g, 20 mmol) in THF (5 mL) was added at 0°C. The reaction mixture was stirred for 18 h at ambient temperature. The mixture was poured in a saturated NH_4Cl solution (100 mL) extracted with Et_2O (2 x 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), concentrated under reduced pressure and distilled under standard conditions (cf. Chapter 4) to give **6.1** (56%).

[*2,2'-bipyridine - CuBr*]: The same procedure was followed as for [Me_2S - CuBr] as catalyst; **6.1** was obtained in 30% yield.

[L-*2-Dimethylamino-1-(2-naphthylthio)-3-phenylpropane (3.11) - CuBr*]*:* To a mixture of **3.11** (80 mg, 0.25 mmol) and CuBr (36 mg, 0.25 mmol) in Et_2O (5 mL) was added MeZnX (1.0 M in Et_2O, 5 mL). A solution of **6.2b** (985 mg, 5 mmol) in Et_2O (5 mL) was added dropwise at –40°C. After usual work up procedure, 465 mg of crude material was obtained, a mixture of S_N2' and S_N2 products in a ratio of 60 : 40, where **6.1** was obtained in 42% yield.

[D-*2-Dimethylamino-1-diphenylphosphino-5-(2-propylthio)-pentane (3.24) - CuCN*]: A previously prepared mixture of MeLi•LiCl (1.0 M in Et_2O, 10 mL, 10 mmol) and $ZnCl_2$ (1.126 g, 5 mmol), was added to a mixture of **3.24** (78 mg, 0.20 mmol), CuCN (22 mg, 0.25 mmol) and **6.2a** (0.84 mL, 5 mmol) in Et_2O (12

mL) and the reaction mixture was stirred for 18 h at ambient temperature. The standard work up procedure led to **6.1** (13%) as a racemate (GC, Lipodex C).

[*(All-R)-N,N-ethylene-bis-(3,4-diphenylpyrrolidine (6.5) - CuBr*]: To a mixture of **6.5** (354 mg, 0.75 mmol), and CuBr (100 mg, 0.70 mmol) in Et_2O (2 mL) was added MeZnX (1.0 M in Et_2O, 15 mL, 15 mmol) at –40°C. A solution of **6.2b** (2.96 g, 15 mmol) in Et_2O (20 mL) was added at –40°C, and the reaction mixture was stirred for 18 h at ambient temperature. The standard work up procedure led to **6.1** (90%) as a racemate (GC, Lipodex C).

[*O,O'-(1,1'-Dinaphthyl-2,2'-diyl)-N,N-dimethylphosphorus amidite (6.6) - CuCN*]: To a mixture of **6.6** (89 mg, 0.25 mmol), CuCN (22 mg, 0.25 mmol) and a solution of **6.2c** (763 mg, 5 mmol) in THF (20 mL) was added Me_2Zn (2.0 M in toluene, 3.75 mL, 7.5 mmol), at –60°C. The reaction mixture was stirred for 18 h at ambient temperature. The standard work up procedure led to **6.1** (ca. 70%) as a racemate (GC, Lipodex C).

[*(S)-2-(2-Pyridinyl)-2-oxo-4-(S)-phenyl-5,5-dimethyl-1,3,2-dioxaphosphorinane (6.7) - Me_2Zn*]: To a solution of **6.7** (303 mg, 1.0 mmol) was added Me_2Zn (2.0 M in toluene, 0.25 mL, 0.50 mmol) at –70°C, followed by **6.2c** (0.055 mL, 0.3 mmol). The reaction mixture was stirred for 18 h. The standard work up procedure led to **6.1** (ca. 30%) as a racemate (GC, Lipodex C).

[*(–)-Cis-exo-N,N-dimethyl-3-aminoisoborneol ((–)-DAIB), (6.8) - CuBr*]:

S_N2' on 6.2b: To a solution of **6.8** (296 mg, 1.5 mmol) and CuBr (108 mg, 0.75 mmol) in Et_2O (5 mL) was added MeZnX (1.0 M in Et_2O, 15 mL, 15 mmol). **6.2b** (2.95 g, 15 mmol) was added at 0°C, and the reaction mixture was stirred for 18 h at ambient temperature. The standard work up procedure led to a dark brown oil, that turned out to be a complex reaction mixture (^{1}H NMR). Optical rotation was not determined.

S_N2' on 6.2c: This experiment was repeated on a 10 mmol scale with **6.2c**. A similar brown coloured complex residue was obtained, and no optical rotation was determined.

S_N2' on 6.2b by Me_2Zn: To a solution of **6.8** (197 mg, 1.0 mmol)

and CuBr (72 mg, 0.50 mmol) in toluene (20 mL) was added Me_2Zn (2.0 M in toluene, 5,0 mL, 10 mmol). At 0°C **6.2c** (1.52 g, 10 mmol) in toluene (5 mL) was added. The reaction mixture was stirred for 18 h at ambient temperature. The standard work up procedure led to a dark brown oil that turned out to be a complex reaction mixture (^{1}H NMR). Optical rotation was not determined.

S_N2' on 6.2b without $Cu^{(I)}$-salt: To a solution of **6.8** (99 mg, 0.50 mmol) in toluene (5 mL) was added Me_2Zn (2.0 M in toluene, 6.0 mL, 12 mmol). The solution was stirred for 20 min. and cooled to –78°C and **6.2c** (1.53 g, 10 mmol) in toluene (5 mL) was added. The reaction mixture was stirred for 18 h at ambient temperature. The standard work up procedure led to crude material in which **6.1** among other compounds could be detected (GC). **6.1** could not be isolated from toluene. Optical rotation was not determined.

S_N2' on 6.2b with (6.8-alkoxide): To a solution of **6.8** (197 mg, 1.0 mmol) in THF (2 mL) was added *n*-BuLi (1.6 M in hexane, 0.625 mL, 1.0 mmol) followed by CuBr (72 mg, 0.5 mmol). To the resulting mixture was added MeZnX (1.0 M in Et_2O, 10 mL, 10 mmol) and **6.2c** (1.53 g, 10 mmol) in Et_2O (5 mL). To remove the repetitive return of the brown coloration, the brown residue was washed twice with $Na_2S_2O_5$ (aq), stirred with $Na_2S_2O_5$ for 3 h, and treated with $P(OEt)_3$. After careful acidic work up (2 N HCl) under cooling (0°C), the organic layer was washed with 2 N HCl (100 mL), careful washed with a saturated $NaHCO_3$ solution (gas evolution) and brine (100 ml), dried ($MgSO_4$), and concentrated under reduced pressure. Ratio S_N2' : S_N2 = 70 : 30 (^{1}H NMR). Distillation of the crude material under standard conditions afforded racemic **6.1** as a very pale pink oil (25%).

Synthesis of N-(trimethylacetyl)-2-pyrrolidinemethanol (6.10)

To a cooled (0°C) solution of **6.9** (1.53 g, 15 mmol), triethylamine, (2.34 mL, 16.5 mmol) and a micro spatula-tip full with DMAP[1] (ca. 20 mg), in CH_2Cl_2 (12 mL), was added dropwise a solution of pivaloyl chloride (1.83 g, 15.2 mmol) in CH_2Cl_2 (30 mL) over a period of 1h. The mixture was allowed to come to ambient temperature and stirred for 18 h. The reaction was quenched on dropwise addition of water (75 mL). The water layer was extracted with CH_2Cl_2 (2 x 75 mL) and the combined organic layers were washed with brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give **6.10** (96%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.24 (s, 9 H), 1.81 - 2.07 (m, 4 H), 3.36 - 3.85 (m, 4 H), 4.27 - 4.30 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 25.4 (t), 27.3 (t), 27.5 (q), 39.1 (s), 48.5 (t), 62.3 (d), 67.6 (t), 179.1 (s).

Synthesis of N-(trimethylacetyl)-2-(2-naphthylthio)-pyrrolidine (6.11)

Methanesulphonyl chloride (0.31 mL, 4.1 mmol) was added dropwise to a stirred solution of **6.10** (689 mg, 3.72 mmol) and triethylamine (0.6 mL, 4.1 mmol) in THF (30 mL) at 0°C. Stirring was continued at 0°C for 2 h, after which time the reaction was treated in one portion with a freshly prepared mixture of 2-naphthalenethiol (595 mg, 3.72 mmol) and KO^{t}Bu (1.04 g, 9.30 mmol) in THF (20 mL) at 0°C. The mixture was stirred for an additional 2 h at 0°C. The reaction mixture was concentrated and shaken with 15% NaOH and benzene (75 mL). The aqueous layer was extracted twice with benzene (50 mL) and the combined organic layers were washed with a saturated NH_4Cl solution, dried (Na_2SO_4) and concentrated under reduced pressure to give **6.11** (53%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.21 (s, 9 H), 1.72 - 2.19 (m, 6 H), 2.90 - 3.83 (m, 3 H), 7.25 - 7.97 (m, 7 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 25.2 (t), 27.5 (q), 28.1 (t), 35.1 (t), 48.5 (t), 58.2 (d), 125.3 (d), 125.8 (d), 126.3 (d), 126.6 (d), 127.1 (d), 127.6 (d), 128.3 (d), 131.5 (s), 133.8 (s), 133.9 (s).

Synthesis of $Me_2Ti(OiPr)_3Cl$ (typical procedure)

[1] DMAP is an acronym for 4-dimethylaminopyridine, which is used as a hypernucleophilic acylation catalyst.

To a cooled (–70°C) solution of $ClTi(OiPr)_3$ (1 M in hexane, 1.5 mL, 1.5 mmol) was added a solution of MeLi•LiCl (1.59 M in Et_2O, 1.9 mL, 3.0 mmol).

S_N2' reactions with methyltitanate reagents on cinnamyl compounds (6.2)
[*ligand - catalyst combination*]:

***Without $Cu^{(I)}$ catalyst*:** To a cooled (–70°C) solution of $Me_2Ti(OiPr)_3Cl$ (1.5 mmol, see *typical procedure*) was added **6.2a** (176 mg, 1.0 mmol).The reaction mixture was stirred for 18 h during which time the mixture was allowed to come to ambient temperature. The reaction mixture was hydrolysed by hexane, saturated with water and dried ($MgSO_4$). Standard work up afforded 430 mg crude material. ^1H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) data showed that the product was starting material together with unidentified impurities. No **6.1** could be detected (GC).

[L-*2-Dimethylamino-2-methyl-1-diphenylphosphino-2-phenylethane (3.9b) - CuCN•2LiCl*]: To a cooled (–30°C) solution of CuCN•2LiCl (1.0 M in THF, 0.08 mL, 0.08 mmol) was added **3.9b** (52 mg, 0.15 mmol) in THF (1 mL).The resulting mixture was stirred for 15 min. and transferred to the cooled (–70°C) solution of $Me_2Ti(OiPr)_3Cl$ (1.5 mmol, see *typical procedure*). The reaction mixture was allowed to come to ambient temperature, and cooled (–70°C) again. To the resulting clear bright yellow solution was added a solution of **6.2c** (1.53 mg, 1.0 mmol) in THF (1 mL). The reaction mixture was stirred for 18 h during which time the mixture was allowed to come to ambient temperature. The reaction mixture was hydrolysed by hexane, saturated with water and dried ($MgSO_4$). The standard work up led to **6.1** (71%) as a racemate (GC, Lipodex C).

[*N-(Trimethylacetyl)-2-(2-naphthylthio)-pyrrolidine (6.11) - CuCN•2LiCl*]: To a cooled (–70°C) solution of $Me_2Ti(OiPr)_3Cl$ (1.5 mmol, see *typical procedure*) was added a previously prepared mixture of CuCN•2LiCl (8 mol%) and **6.11** (16 mol%) in THF (1 mL). The resulting clear bright yellow solution was allowed to come to ambient temperature. After cooling (–70°C),

6.2a (176 mg, 1.0 mmol) was added. The reaction mixture was stirred for 18 h during which time the mixture was allowed to come to ambient temperature. The reaction mixture was hydrolysed by hexane, saturated with water and dried ($MgSO_4$). The standard work up led to **6.1** (70%) as a racemate (GC, Lipodex C).

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Samenvatting

Inleiding

"Als iemand in de spiegel kijkt dan ziet hij zichzelf", zo wordt aangenomen. Naast het feit dat slechts een afbeelding wordt waargenomen, is deze bewering verder ook onjuist: het is Het Spiegelbeeld dat wordt waargenomen. Zou Het Spiegelbeeld tot in detail (dus ook met gespiegelde ingewanden, cellen, DNA, stofwisselingsprocessen, enz.) in onze wereld kunnen stappen, in driedimensionale vorm, dan zou dat veel problemen met zich meebrengen. De overwegend linkshandige Spiegelbeelden zouden veel moeite hebben om routineus een schroefje in de muur te draaien. Op ijsbanen zullen ze geweerd moeten worden, tenzij ze linksom leren schaatsen. Dit voorbeeld is door te voeren op allerlei materie, processen enzovoorts, voor zolang het spiegelbeeld ervan niet volledig identiek is aan het orgineel. Ook allerlei biologische processen in het lichaam zijn afhankelijk van moleculen die ook wel een spiegelbeeld hebben, zoals aminozuren, maar waarvan het spielgelbeeld in de natuur niet (of bij hoge uitzondering) voorkomt. Een glaasje water, met de symmetrische watermoleculen, zou Het Spiegelbeeld zonder problemen kunnen drinken, maar appelsap zal waarschijnlijk als bitter worden ervaren. Wat het effect van allerlei voedingsmiddelen zal zijn op stofwisselingsprocessen in Het Spiegelbeeld is niet te overzien. Het Spiegelbeeld zou een wezen zijn dat niet tot 'mens' gerekend kan worden - en omgekeerd. Voortplanting tussen de beide wezens is zo goed als uitgesloten.

De ruimtelijke vorm van moleculen en de ruimtelijke vorm van de omgeving waar een bepaalde werking in het lichaam plaats moet vinden, bijvoorbeeld ruiken of proeven, kan van essentieel belang zijn voor het optreden van die werking. Dit kan ook van groot belang zijn voor een eventuele therapeutische werking van een medicijn in het lichaam. Het is ook zeer belangrijk dat er op enantiomeren of diastereomeren (spiegelbeeldisomeren op één of meer centra in het molecuul) van het medicijn wordt gelet. Spiegelbeeldmoleculen kunnen in het lichaam ook neveneffecten veroorzaken, omdat ze misschien elders in het lichaam wel 'passen' vanwege hun andere ruimtelijke vorm, met alle mogelijke gevolgen van dien. Zij kunnen zo de oorzaak zijn van ernstige bijwerkingen, zoals

bijvoorbeeld bij een medicijn als Softenon is gebleken. Andere medicijnen worden in een 1 op 1 verhouding van beeld en spiegelbeeld (racemaat) aangeboden als er geen schadelijke bijwerkingen van het spiegelbeeldisomeer zijn waargenomen.

Binnen de categorie pijnstillers die zonder recept verkrijgbaar zijn, nemen de profens een belangrijke plaats in. Een van de meest bekende profen-pijnstillers is ibuprofen, dat onder merknamen als (o.a.) Advil, Nerufen, Relian of Femapirin over de toonbank gaat, naast de generieke vormen van dit medicijn. Afgezien van het middel naproxen, dat in één ruimtelijke vorm wordt toegediend vanwege bijwerkingen van de andere spiegelbeeldvorm, worden de profens als een weliswaar zuivere verbinding, maar toch als een mengsel van de twee spiegelbeelden, enantiomeren, aangeboden. Aanvankelijk werd aangenomen dat van ibuprofen slechts één enantiomeer actief was in de pijnbestrijding. Er is echter gevonden dat het inaktieve enantiomeer, curieus genoeg, wordt omgezet in het lichaam tot het aktieve enantiomeer. Een mengsel van beide enantiomeren, een racemaat, werd dan ook niet als bezwaarlijk geacht. Er blijken echter wat esculaapjes onder het gras te schuilen.

Dit proefschrift

In hoofdstuk 1 wordt besproken welk voordeel het heeft om beide enantiomeren van een profen-pijnstiller afzonderlijk op de markt te brengen, als twee verschillende medicijnen, met verschillende toepassingen. Verder wordt in dit hoofdstuk ingegaan op synthesemethodes die leiden tot profens of voorlopers daarvan. Het doel van dit proefschrift is het verder ontwikkelen van een enantioselectieve synthese route die leidt tot verbindingen die voorlopers van profen-pijnstillers zijn. Een van de syntheseroutes is de enantioselectieve cross coupling-reactie.

In hoofdstuk 2 wordt nader ingegaan op het mechanisme van de enantioselectief gekatalyseerde cross coupling-reactie. Bij enantioselectieve ofwel asymmetrisch gekatalyseerde cross coupling-reacties wordt, in het meest gunstigste geval, selectief één van beide spiegelbeeldisomeren van de profen-voorloper gevormd. Om dit te bereiken wordt de ruimtelijke omgeving rond de katalysator aangepast door een asymmetrisch ligand. Deze asymmetrische liganden kunnen we vergelijken met een linker- of een rechterhand. Een dergelijk ligand schermt

als het ware een deel van de katalysator op asymmetrische wijze af. Ruimtelijk gezien zal de meest voor de specifieke 'hand' liggende binding tussen de uitgangsstoffen gevormd worden. In dat geval wordt een product verkregen in enantiomeer verrijkte vorm (enantiomeric excess, ee) of, in het meest gunstige geval, in enantiomeer zuivere vorm. In dit hoofdstuk worden ook de verwachte en onverwachte invloeden van verschillende factoren op de enantioselectiviteit besproken. Een niet onbelangrijke drijfveer voor dit onderzoek was het volgende fenomeen dat in onze researchgroep werd ontdekt. Door het toevoegen van een zinkzout aan een van de uitgangsstoffen, een organomagnesium-verbinding, voorafgaande aan de asymmetrische cross coupling-reactie, werd het andere enantiomeer gevormd. Dit, terwijl hetzelfde ligand met zijn chirale (specifiek ruimtelijke) omgeving was gebruikt. Deze omkering van enantioselectiviteit heeft als gevolg dat beide spiegelbeelden van profen-voorlopers afzonderlijk kunnen worden verkregen met één en hetzelfde asymmetrische ligand - afhankelijk van het wel of niet toevoegen van een zinkzout. De invloed van zinkzouten op de organomagnesiumverbinding en de natuur van de organometaalverbinding die de cross coupling ondergaat, was één van de onderzoeksdoelen.

Hoofdstuk 3 gaat nader in op een ander onderzoeksdoel, de ontwikkeling en synthese van asymmetrische liganden voor de Ni en Pd katalysatoren in de asymmetrische cross coupling. In onze researchgroep is veel expertise opgedaan met het gebruik van aminofosfine-liganden die zijn afgeleid van aminozuren. Dit betreft zowel liganden afgeleid van natuurlijke aminozuren als van synthetisch verkregen aminozuren. De asymmetrische katalysator wordt gevormd door de amino- en de fosfinogroep van een asymmetrisch aminofosfine met een metaal als nikkel of palladium te laten complexeren. Een nieuwe invalshoek vonden wij in de omzetting tot liganden van synthetisch verkregen asymmetrische α-methylaminozuren, waarbij het proton, dat zich bij natuurlijke aminozuren op het chirale centrum bevindt, vervangen is door een methylgroep. Van deze α-methylaminozuren hebben we zowel α-methylaminofosfines als α-methylaminosulfides afgeleid. Een ander type ligand betreft aminofosfines die naast een amino- en een fosfinegroep ook een sulfidegroep in een zijarm bezitten. Het is al eerder in onze researchgroep gevonden dat een dergelijk zwavel bevattende zijarm de enantioselectiviteit in de cross coupling verhoogt.

Verlenging van deze zij-arm met een één-koolstof-eenheid, en het dientengevolge het opschuiven van het zwavel atoom met één positie zou meer informatie over de optimale lengte van deze zijarm kunnen geven. Verder hebben we een ligand gesynthetiseerd waarbij de zwavelgroep in de zij-arm ruimtelijk minder toegankelijk is gemaakt door deze te voorzien een meer omvangrijk substituent.

In hoofdstuk 4 worden twee onderwerpen behandeld. Allereerst de synthese van een van de uitgangsstoffen, het organomagnesiumreagens of 'Grignard-reagens'. Verschillende methodes worden behandeld om het oppervlak van magnesium te aktiveren vóór de vorming van het Grignard-reagens. Chemische aktiveringsmethodes van magnesium, die tot nu toe gebruikt werden om dit Grignard-reagens te maken voor asymmetrische cross couplings, blijken niet zonder stereochemische gevolgen voor de volgende reactiestap, de cross coupling-reactie. Chemische toevoegingen zoals bijvoorbeeld een jodiumkristal om het oppervlak van magnesiumkrullen vooraf chemisch te aktiveren, blijkt nu van invloed te kunnen zijn op de ee van het uiteindelijke produkt van de cross coupling. Deze aktiveringsmethode werd veelvuldig gebruikt voor de synthese van het Grignard-reagens, dat weer gebruikt werd in asymmetrische cross coupling-reacties. De activeringsmethode verliep met wisselend succes. Echter, mechanische activering door het roeren van magnesiumkrullen met glassplinters zonder oplosmiddel blijkt in hoge reproduceerbaarheid een Grignard-reagens op te leveren. De reactie gaat in goede opbrengst en in de oplossing van het Grignard-reagens bevinden zich geen resten van aktiveringschemicalien: zeer geschikt voor asymmetrische cross coupling reacties.

Verder worden in hoofdstuk 4 asymmetrische cross coupling-reacties beschreven, waarbij chirale liganden uit hoofdstuk 3 zijn gebruikt voor nikkel- en palladiumkatalysatoren. De α-methylaminofosfines leiden, wanneer ze gebruikt worden als liganden van de katalystor in de cross coupling-reactie, niet tot hoge enantioselectiviteit. Van de α-methylaminosulfides als ligand moet helaas hetzelfde gezegd worden. Het aminofosfine dat in hoofdstuk 3 werd besproken, waarbij het zwavelatoom één positie werd opgeschoven door de zijarm met een één-koolstof-eenheid te verlengen, leverde nagenoeg hetzelfde stereochemische resultaat in de cross coupling-reactie als met het ligand

zonder deze verlenging. Een optimale positie voor zwavel in deze zijarm is niet duidelijk.

Door zinkzout aan een organomagnesiumverbinding toe te voegen wordt in het algemeen een organozinkverbinding gevormd en magnesiumzout. Om de oorzaak van het voornoemde fenomeen, de omkering van enantioselectiviteit, vast te stellen besloten we organozinkverbindingen direkt te maken, zonder tussenkomst van de organomagnesium-verbinding. In hoofdstuk 5 wordt uiteengezet welk drietal methoden zijn gebruikt om de organozinkverbinding direkt uit zink en organohalide te vormen. Echter, onder dezelfde omstandigheden als gebruikt voor de cross couplings met organomagnesium - zinkzout mengsels, bleek geen van de direkt gevormde organozinkverbindingen aktief te zijn in de cross coupling-reactie. Dit maakt de aard van de verbinding die verantwoordelijk is voor het fenomeen, de omkering van de enantioselectiviteit, niet duidelijker. Dit, en andere factoren heeft ons er toe doen besluiten om het onderzoek aan de asymmetrische cross coupling-reacties af te sluiten en om te kijken naar een alternatieve aanpak om profen-type verbindingen te maken via asymmetrische katalyse.

In hoofdstuk 6 wordt een katalytische reactie beschreven waarmee dezelfde profen-voorloper kan worden verkregen: de S_N2'-reactie. Deze reactie was bij de aanvang van ons onderzoek nog niet op een enantioselectief-gekatalyseerde manier uitgevoerd. Het verschil met de cross coupling-reactie zit in de aanpak: wordt bij de cross coupling een vinylgroep geintroduceerd op het benzylische centrum, bij de S_N2'-reactie is het de methylgroep, onder vorming van een eindstandige dubbele binding. De reactie wordt uitgevoerd met organocupraten of verloopt koper(I)-gekatalyseerd. Door deze koper(I)-katalystatoren te voorzien van een asymmetrische omgeving met chirale liganden moet, in beginsel, enantioselectiviteit mogelijk zijn. Koper(I)-gekatalyseerde S_N2'-reacties met methylzink-verbindingen op kaneelbromide, ~chloride en ~acetaat zijn uitgevoerd. Deze leidden met succes tot het gewenste product, dat in racemische vorm werd verkregen. Doordat de S_N2'-reacties met organozinkverbindingen niet volledig katalysator-afhankelijk bleken te zijn., werd overgegaan op organotitaniumverbindingen. Hoewel deze titaniumverbindingen wel katalysator-afhankelijk bleken te zijn, werd met asymmetrische liganden geen product in

enantiomere overmaat verkregen.

STELLINGENbehorend bij het proefschrift van Henk van der Worp

1 Ibuprofen veraangenaamt het leven van een promovendus.
Dit proefschrift.

2 Het getuigt van onzorgvuldigheid om landkaarten niet te voorzien van het jaar van registratie. Deze omissie op autokaarten leidt ongetwijfeld tot een hoger brandstofverbruik.
Onder andere: Falkplan autokaart 19??, ANWB kaarten 19?? en 19??.

3 Het plegen van plagiaat lijkt een vorm van kleptomanie te kunnen aannemen.

4 De zinspreuk "Meer blauw op straat" lijkt tot nu toe meer te slaan op de constatering van de toename van geweldsdelicten dan op de realisering van het streven naar meer uniformen op straat.

5 De eenvoud van iets dat "voor de hand ligt", kan mede afhankelijk zijn van welke hand bedoeld wordt.

6 Verkeerd gebruik van het woord "enigste" is meestal het enigst voor de oplettende toehoorder.

7 Het verschil tussen een flex-werknemer en een ex-werknemer is niet groot.

8 Vrouwen die tijdens de zwangerschap rookwaar blijven gebruiken, nemen de kwalificatie aanstaande moeder wel erg letterlijk op.

9 Zonder referentiekader impliceren "pH neutrale" lichaamsverzorgingsmiddelen een valse veiligheidsgarantie.
Oil of Olaz, Sanex, Unicura, Badedas, e.a.

10 De bewering dat Rietvelds "rood-blauwe stoel" verstoken zou zijn van zit-comfort is, door de bank genomen, gestoeld op gebrek aan zit-ervaring met deze stoel.

Groningen, 24 januari 1997