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Tetrahedron 62 (2006) 5632–5640
Tetrahedron

Screening of ligands in the asymmetric metallocenethiolatocopper(I)-catalyzed allylic substitution with Grignard reagents

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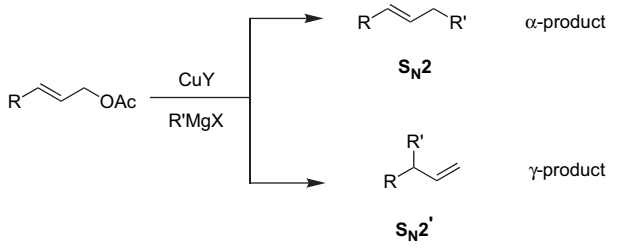
Received 17 January 2006; revised 14 March 2006; accepted 30 March 2006
Available online 2 May 2006

Abstract—Screening of metallocenethiolate ligands for copper(I)-catalyzed substitution of allylic acetates with Grignard reagents has been carried out. The previously used ligand, lithium (R,S_p)-2-(1-dimethylaminoethyl)ferrocenylthiolate (**4a**), possessing both central and planar chirality, was the starting point for the screening. It was found that the diastereomeric ligand lithium (R,R_p)-2-(1-dimethylaminoethyl)ferrocenylthiolate (**4b**) exhibiting reversed planar chirality gave increased enantioselectivity in the allylic substitution, at least when cinnamyl acetate was used as a substrate. The ruthenocene-based ligand lithium (R,S_p)-2-(1-dimethylaminoethyl)ruthenocenylthiolate (**4c**) gave an enhanced reaction rate, but lower chiral induction. The use of disulfide bis[(R,S_p)-2-(1-dimethylaminoethyl)ferrocenyl]disulfide (**7a**) as a ligand precursor worked well but resulted in lower enantioselectivity.

1. Introduction

Metal-mediated carbon–carbon bond formation has become a versatile synthetic method.[1] Organocopper(I) reactions are frequently used for carbon–carbon bond formation, and excellent results have been obtained in stoichiometric, as well as in catalytic reactions with zinc- or Grignard reagents.[2] The allylic substitution reaction has attracted considerable attention and several methods have been developed for the control of regio- and stereochemistry in these type of reactions. Copper-catalyzed reactions of allylic acetates with Grignard reagents were reported in 1977 by Schlosser,[3] and this reaction proceeds with high α-selectivity. Subsequently, Goering[4] and our group[5] showed that the regioselectivity of the copper-catalyzed Grignard reaction can be controlled toward either α- or γ-selectivity. In particular, our group showed that by careful choice of solvent, copper catalyst, and temperature, and by tuning the time of addition of the Grignard reagent, full control of regioselectivity can be obtained and the reaction of allylic acetates can be directed to give either an S_N2-type reaction (α-product) or an S_N2'-type reaction (γ-product), Scheme 1.[5] With dialkylcuprates only one alkyl group is transferred and often a large excess of the cuprate is required to obtain full conversion. By using non-transferable ligands, for example, alkoxy, aryloxy, alkylthio, or arylthio groups on copper, an efficient use of the alkyl group is achieved.[6] In a collaboration between our group and the group of van Koten, the allylic substitution of acetate with Grignard reagents was studied using catalytic amounts of copper(I)-arylthiolate (*rac*)-**1** (Scheme 2), where the arenethiolato group acts as a non-transferable group on copper. This reaction gave an even more pronounced γ-selectivity, than the previously used copper catalysts.[7]



Scheme 1. Allylic substitution of acetate with Grignard reagent performed either by an S_N2-type reaction to give the α-product or an S_N2'-type reaction to give the γ-product.

The need for efficient methods to prepare enantiomerically pure compounds has led to a continuously growing interest in asymmetric synthesis, especially asymmetric catalysis. In metal-catalyzed asymmetric synthesis the chirality can be introduced by the coordination of an enantiomerically pure ligand to the metal, assuming that the chirality is in near proximity to the reaction center. Ferrocene ligands have gained much interest in asymmetric catalysis, as numerous structural variations are possible.[8] Furthermore, ferrocenes may possess two kinds of chirality: (i) the central chirality of substituents and (ii) the element of planar chirality in

Keywords: Asymmetric induction; Copper catalysis; Allylic substitution; Cross-coupling; Ferrocene ligands.
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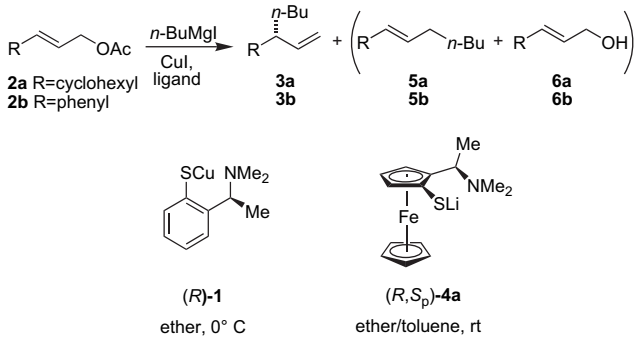
doi:10.1016/j.tet.2006.03.100



Scheme 2. Enantioselective substitution of allylic acetates with Grignard reagents and copper thiolate complexes.

unsymmetrical 1,2- and 1,3-substituted ferrocenes. Ferrocene is, by far, the metallocene most frequently used for chiral ligands. However, some examples of ruthenocene ligands have also been reported.[9]

The scope of the allylic substitution of acetate using Grignard reagents was extended to asymmetric catalysis, by using enantiomerically pure non-transferable ligands on copper; in this way the chiral ligand is in close proximity to the metal. Indeed, the use of copper(I)-arylthiolate **1** in the allylic substitution of **2a** with Grignard reagent gave the γ-product **3a** with an enantiomeric excess of 42%, Scheme 2.[10] Using the corresponding ferrocenylthiolate ligand **4a** gave the highest enantioselectivity obtained thus far with allylic acetates (64% ee).[11] Only traces of the α-product **5a** were formed and no alcohol **6a** could be detected. Substrate **2b** gave a lower enantiomeric excess (42%) with ligand **4a**.

Other groups have reported on asymmetric allylic substitution using external ligands.[12] Knochel, for example, has obtained an excellent result with 1-ferrocenylethylamines in reactions of allylic chlorides with dialkylzinc reagents, and Hoveyda has recently with success employed heterocyclic carbene ligands with allylic phosphates.[12g]

Arenethiols are susceptible to oxidation, forming the disulfide in the presence of oxygen.[13] This tendency is more pronounced for the electron-rich ferrocenylthiols.[14] Hence, protonation of lithium thiolate **4a** led to disulfide formation. Therefore, the copper(I) complex was generated in situ, by mixing lithium thiolate **4a** and a copper salt.[11]

A systematic screening of ligands was pursued in order to gain an insight into the factors governing the copper-catalyzed substitution of allylic acetates. We also investigated plausible background reactions that may lead to a less enantioselective formation of product. In order to obtain more robust reaction conditions, disulfide **7a** was tested as a ligand precursor.

2. Results and discussion

2.1. Ligand selection

Since a change of the steric and electronic properties of the ligand affected the enantioselectivity of the allylic substitution, by exchanging ligand **1** for ligand **4a**, ligand screening

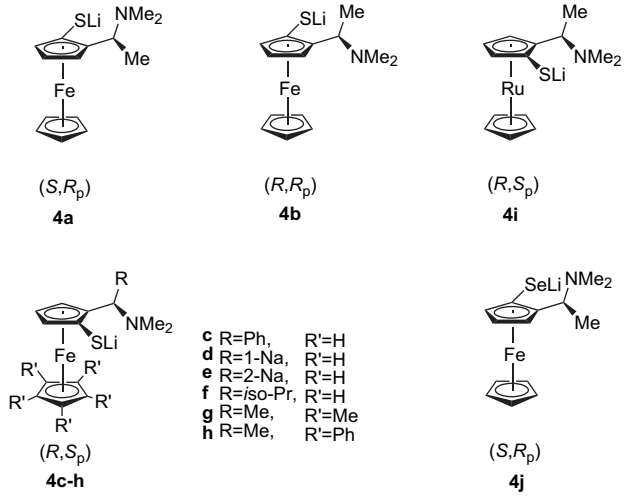


Figure 1. Ligands for the copper(I)-catalyzed allylic substitution.

based on the ferrocene structure was pursued, Figure 1. Due to the choice of method of preparation the ligands depicted in Figure 1 are of different absolute configuration. In one case also the relative stereochemistry is different (**4b**).

We wanted to study the effect of changing the substituent R and chose aliphatic, as well as, aromatic substituents in target compounds **4c–f**. Knochel and co-workers have shown that increased bulk of the R-group, led to higher enantioselectivity in the asymmetric copper-catalyzed reaction of allylic chloride with diorganozinc compounds.[12a,b]

The increase in enantioselectivity when changing from copper(I) complex **1** to the corresponding ferrocene ligand **4a** might be explained by a shielding effect of the lower cyclopentadienyl (Cp) ring. By introducing substituents on the lower Cp-ring the shielding effect would be even more pronounced. Furthermore, introducing substituents on the lower Cp-ring provides ligands that are assumed to exhibit different electronic properties, which in turn might affect the stability of the ligand. Hence, target compounds **4g** and **4h** were selected, possessing different steric and electronic properties.

Ruthenocene ligands have recently gained some interest. Fu reported on an accelerated reaction rate with ruthenocene over ferrocene but less chiral induction in most cases.[9a] According to Fu the lower enantioselectivity could be explained by the ruthenocene being less chiral than the corresponding ferrocene, due to the greater distance between the Cp-rings and thereby enhanced flexibility. Togni and co-workers reported on a slight decrease in enantioselectivity with ruthenocene over ferrocene ligands in palladium-catalyzed alkylation and rhodium-catalyzed hydroboration reactions.[9b] On the other hand, Hayashi and co-workers showed that in the case of bidentate ligands with coordination sites on both Cp-rings, the bite angle of the ligand changed, due to the difference in distance between the Cp-rings in ferrocene and ruthenocene. This did in fact have a positive effect on the enantioselectivity.[9c] Bolm reported that a very small difference in selectivity was observed between C_2-symmetric 1,1′-bis(oxazolinyl)metallocenes of Fe and Ru in asymmetric phenyl transfer from organozincs to aldehydes.[9d]

In our case, a change of the metal might have an impact on the stability of the copper complex, and therefore target compound **4i** was selected.

Arylthiolates are known to be excellent non-transferable ligands on copper due to the strong copper–sulfur bond. One approach to further increase the stability of the copper complex would be to make the ligand bind even more strongly to copper. This effect might be achieved by employing selenium instead of sulfur. Target compound **4j** was therefore selected.

As there might be a matched or mismatched situation in terms of chiral induction, ligand **4b** with reversed relative stereochemistry, in comparison to ligand **4a**, was prepared.

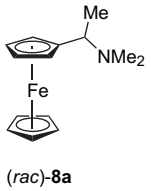
2.2. Ligand synthesis

The thiolate ligand **4a** has previously been prepared by stereoselective *ortho*-lithiation of enantiopure amine (*S*)-**8a**, followed by addition of elemental sulfur.[11] Amine (*S*)-**8a** was prepared according to a literature procedure, where resolution of (*rac*)-**8a**, which is known as Ugi's amine, with tartaric acid afforded enantiomerically pure (*S*)-amine, Figure 2.[15] The same procedure was used for the preparation of ligands **4c–g** and **4i**, except that the intermediate alcohol was obtained via enantioselective CBS-reduction, omitting the resolution step.[16,17] In these cases, the products with (*R*)-configuration were formed. Ligand **4b** was prepared from (*R*)-**8a** obtained from the mother liquor in the resolution step.

The chirality of the ligands was created in two key steps, enantioselective reduction to the alcohol and stereoselective *ortho*-lithiation of the amine (vide infra). The enantiomeric purity of the ligands was governed by the outcome of both these two reactions.

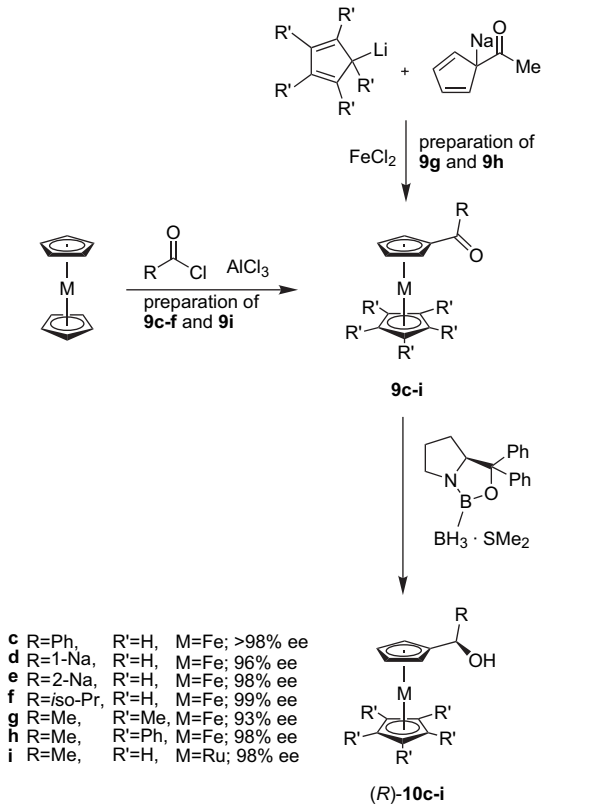
Ferrocene and ruthenocene were subjected to standard Friedel–Craft acylation conditions to give acylmetallocenes **9c–f** and **9i**, Scheme 3. Acylation of the pentasubstituted ferrocenes was not straightforward and an alternative method for the preparation of acetyl ferrocenes **9g** and **9h** was developed by mixing $FeCl_2$, sodium acetylcyclopentadienide and pentasubstituted lithium cyclopentadienide in good yields, which we have reported elsewhere.[18]

Enantioselective CBS-reduction of the ferrocenyl ketones has been performed previously.[17] We had problems in reproducing the published results and tried both commercially available methyl-oxazaborolidine and in situ prepared oxazaborolidine catalyst.[19] The difficulties encountered with the CBS-reduction may be ascribed to the purity of the catalyst and solvents used. Alcohols **10c** and **10f–h** were obtained in high enantiomeric excess, Scheme 3. Naphthyl



(*rac*)-**8a**

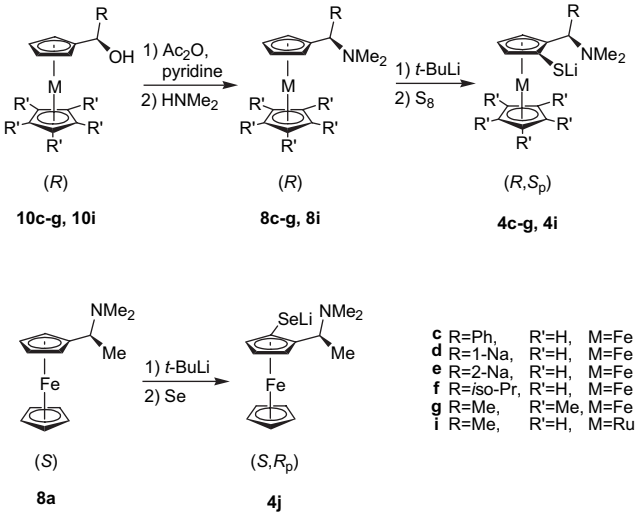
Figure 2. Ugi's amine.



Scheme 3. Preparation of chiral alcohols **10c–i**.

alcohols **10d** and **10e**, on the other hand, had to be recrystallized to give satisfactory enantiomeric excess. Hayashi has prepared the enantiomerically pure alcohol **10i** by treating ruthenocenecarboxaldehyde with dimethylzinc in the presence of a chiral ligand for an extensive period of time.[9c] As we had experience of CBS-reduction, this method was used instead and yielded alcohol **10i** in 45 min with excellent results.

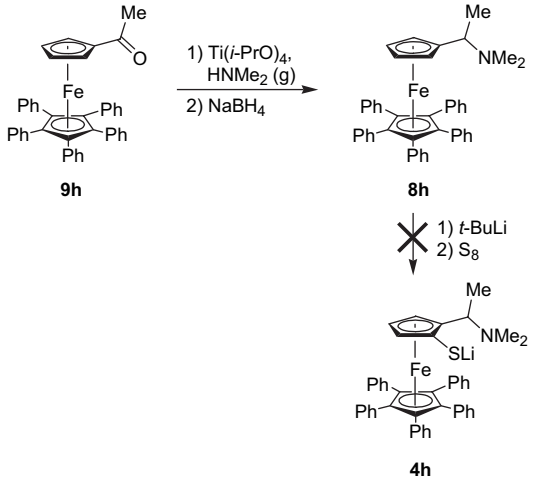
Alcohols **10c–i** were transformed to the corresponding acetates, which were substituted by dimethylamine to give amines **8c–g** and **8i**, in high yields (Scheme 4). Substitution



Scheme 4. Preparation of ligands **4c–g**, **4i**, and **4j**.

of an acetate group, at the α-carbon to ferrocene, proceeds via an S_N1-type of reaction, by anchimeric assistance from the metal with retention of the configuration at the carbon.[20] Hence, the enantiomeric excess of the alcohols is transferred to the amines.

The phenyl groups on the pentaphenyl-substituted ferrocene affected the reactivity of the ferrocene structure to a large extent. Alcohol **10h** was transformed into the corresponding acetate. No substitution of acetate by amine was observed when the acetate was treated with dimethylamine. This might be a consequence of the steric properties of the lower Cp-ring, but it may also be due to electronic effects. The racemic amine **8h** was instead prepared by reductive amination of the ketone **9h** employing a modified Ti(*i*-PrO)$_4$/HNMe$_2$/NaBH$_4$-system, Scheme 5.[21]

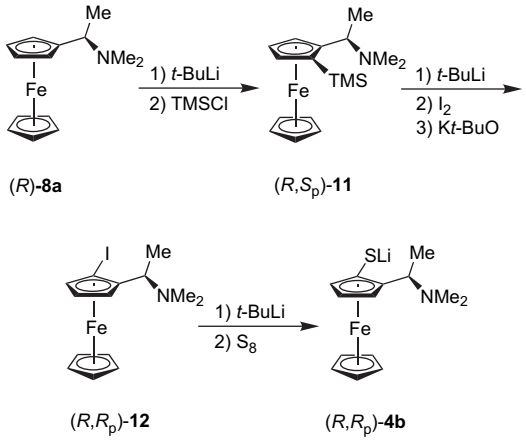


Scheme 5. Attempted preparation of ligand **4h**.

The amines **8c–g** and **8i** were *ortho*-lithiated by *t*-BuLi in ether and treated with elemental sulfur, Scheme 4.[11] Ligand **4j** was obtained by treating Ugi's amine with *t*-BuLi and selenium. For ligands **4b–e**, **4g**, and **4j** the lithium salts precipitated. Depending on the solubility of the product the precipitate was washed either with diethyl ether or hexane. In the case for ligand **4f** no material was precipitated and the solvent was removed by evaporation. The crude ligand was used in the allylic substitution without further purification. The purity of the ligands depended in this step on the selectivity of the *ortho*-lithiation, which was governed by the steric properties of the amine,[22] and the purification obtained in the precipitation of the lithium salts.

Attempts to *ortho*-lithiate the pentaphenyl-substituted amine **8h** by a variety of lithium sources in different solvents and at different temperatures were unsuccessful, Scheme 5. Unsuccessful lithiation of pentaphenyl-substituted ferrocenes has also been reported by others.[23]

The diastereomer with reversed planar chirality **4b** was obtained by treating (*R*)-**8a** with *t*-BuLi and TMS–Cl, blocking the *ortho*-position, which is preferably lithiated, Scheme 6.[24] The resulting compound **11** was subjected to an additional lithiation in the remaining *ortho*-position, followed by treatment with iodine as electrophile and removal of the TMS-group by base,[25] acquiring the diastereomer with reversed planar chirality, compound **12**. The lithium thiolate **4b** was subsequently obtained by halogen–metal exchange employing *t*-BuLi[26] and treatment with elemental sulfur. The bulky *t*-BuLi was used to prevent alkylation of the ferrocene by attack on the alkyl iodide formed during the reaction.



Scheme 6. Preparation of the diastereomeric ligand **4b** with reversed planar chirality.

2.3. The stereochemical purity of the ligands

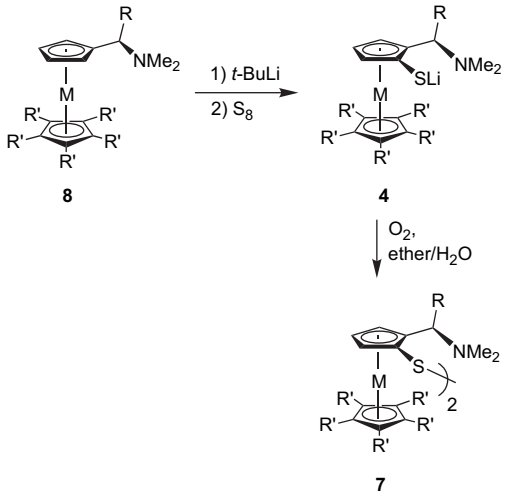
The enantiomeric and diastereomeric purity of the ligands is essential for the enantioselectivity of the allylic substitution reaction. As the copper complexes often are trimers or tetramers the relationship between the purity of the ligand and the enantiomeric excess obtained in the allylic substitution might be nonlinear.[27] Both van Koten and Pfaltz report on negative nonlinear effects when using copper(I)thiolates in conjugate addition of Grignard reagents to cyclic enones.[28] In theory even small amounts of a fast reacting isomer, yielding racemic product might hamper the reaction and give low enantiomeric excess. When using a ligand contaminated with stereoisomers, low enantiomeric excess may be caused by the contamination. Hence, to be able to compare the results obtained with different ligands the purity has to be considered.

The alcohols **10c–i**, obtained in the enantioselective CBS-reduction, had very high enantiomeric excess. Since the conversion to the amines, via the acetate, proceeds with retention of configuration, it can be assumed that no racemization took place.

It is well established that the *ortho*-lithiation of amine **8a** is selective, with a diastereoselectivity of around 95%.[24a,29] The diastereoselectivity of the *ortho*-lithiation of similar amines is not so well studied, but can be assumed to be highly affected by the structure of the amine. However, the selectivity could only be measured by indirect methods as the lithium chalcogenides **4a–g**, **4i**, and **4j** degrade in the presence of oxygen. As the *ortho*-protons for amines **8d**, **8e**, and **8i** were separated in the ^{1}H NMR spectra the selectivity of the *ortho*-lithiation could easily be determined by treating the lithiated amines with methanol-d_4. This revealed that *ortho*-lithiation of naphthylamines **8d** and **8e** was highly selective and none of the diastereomer with reversed planar chirality could be detected, probably due to the bulky naphthyl-substituent. *Ortho*-lithiation of ruthenocene-derived amine **8i** on the other hand, gave a diastereomeric ratio of 80:20.

The lower selectivity for **8i** can be a result of the larger distance between the Cp-rings, thus allowing for a nitrogen-assisted lithiation on both sides of the substituent.

To determine the selectivity of the *ortho*-lithiation in the cases when the *ortho*-protons overlap and to determine the purity of the lithium thiolates, the lithium thiolates **4** were transformed to disulfide **7** by treatment with oxygen according to a known procedure, Scheme 7.[13] In those cases where the thiolates **4** obtained according to Scheme 4 would consist of diastereomeric mixtures, disulfide formation would lead to a diastereomeric mixture of disulfides, hence the ratio between the stereoisomeric disulfides **7** should be possible to analyze by ^{1}H NMR.



Scheme 7. Disulfide formation.

Disulfide and diselenide formation worked well for Ugi's amine-derived ligands **4a** and **4j** and showed that the crystallization of the lithium salts improved the diastereomeric purity, as only one diastereomer could be detected. In the case of **4c**, **4f**, and **4g** disulfide formation was sluggish and the diastereomeric purity could not be determined. For ligands **4d** and **4e** there was no need for disulfide formation as the *ortho*-lithiation was highly selective. Disulfide formation with ruthenocene-derived **4i** showed an 80:20 relationship between the two major disulfide diastereoisomers, which shows that the diastereomeric ratio of the monomeric sulfide **4i** was 89:11.

Despite the fact that some of the ligands had unsatisfactory stereochemical purity we intended to try them as ligands in the allylic substitution reaction.

2.4. Allylic substitution

The allylic substitution reactions were performed in diethyl ether with ligands **4b–g**, **4i**, and **4j** (0.3 equiv), CuI (0.15 equiv), and substrates **2a** or **2b**. Higher temperatures and a slow addition of the Grignard reagents are required for high regio- and stereoselectivities.[5,7,30] Thus the reactions were performed at either 0 °C or rt and *n*-BuMgI (1.5 equiv) was added over 2 h. The results were compared with those previously published of ligand **4a** (entries 1 and 3, Table 1).[11] Although somewhat higher enantioselectivity had been obtained in ether/toluene 3:1 than in ether, we decided to use ether as solvent, since the product is volatile and hence difficult to isolate from toluene.

Increasing the bulk of the R-group, as in ligands **4c–f** gave very low enantioselectivity in the allylic substitution reaction (entries 5–9, Table 1). In the case of ligand **4f**, purification of the lithium thiolate by crystallization was not possible. The allylic substitution was performed using the crude ligand prepared in situ, which may have affected the outcome of the reaction. It can anyhow be concluded that other groups than methyl on the α-carbon are detrimental to the chiral induction.

With the pentamethyl substituted ligand **4g** 33% ee was obtained (entry 8, Table 1). The ruthenocene ligand **4i** also

Table 1. Reactions between allylic acetates and *n*-BuMgl catalyzed by Cul and ligands **4a–g**, **4i**, and **4j**[a]

Entry	Substrate	Ligand	Product	ee (%)[b]	γ:α Ratio	**6** (%)	Conversion (%)	Isolated yield (%)
1[c]	**2a**	(S,R_p)-**4a**	**3a**	64 (*S*)-(+)	98:2	—	100	88
2	**2a**	(S,R_p)-**4a**	**3a**	62 (*S*)-(+)	97:3	0	100	88
3[d]	**2b**	(S,R_p)-**4a**	**3b**	42 (+)	94:6	—	100	78
4	**2b**	(S,R_p)-**4a**	**3b**	40 (+)	96:4	5	100	82
5	**2a**	(R,S_p)-**4c**	**3a**	14 (*R*)-(−)	95:5	8	100	52
6[e]	**2a**	(R,S_p)-**4d**	**3a**	6 (*R*)-(−)	95:5	3	100	65
7[e]	**2b**	(R,S_p)-**4e**	**3b**	0	92:8	2	100	64
8	**2b**	(R,S_p)-**4e**	**3b**	14 (−)	89:11	0	100	60
9	**2b**	(R,S_p)-**4f**	**3b**	2 (−)	100:0	60	85	25
10	**2a**	(R,S_p)-**4g**	**3a**	33 (*R*)-(−)	94:6	6	99	80
11	**2b**	(R,S_p)-**4i**	**3b**	20 (−)	92:8	2	100	89
12[f]	**2b**	(R,S_p)-**4i**	**3b**	20 (−)	93:7	0	100	83
13[f]	**2b**	(S,R_p)-**4a**	**3b**	31 (+)	86:14	2	100	90
14	**2a**	(S,R_p)-**4j**	**3a**	42 (*S*)-(+)	93:7	2	98	67
15	**2b**	(S,R_p)-**4j**	**3b**	41 (+)	94:6	3	100	78
16	**2b**	(R,R_p)-**4b**	**3b**	52 (+)	94:6	38	100	60

[a] Reaction conditions: The allylic acetate **2**, ligand **4** (0.30 equiv), and CuI (0.15 equiv) were mixed in diethyl ether at rt for 30 min. *n*-BuMgI (1.5 equiv) was added via a syringe pump over 2 h to maintain a low concentration. The reaction mixture was kept at rt for 1 h.
[b] Enantioselectivity was measured by chiral GC, except for entries 2 and 6, which were measured by optical rotation.
[c] The reaction was performed in diethyl ether/toluene 3:1, with 13% CuI, and a ligand/CuI ratio of 2.7:1.
[d] The reaction was performed at 0 °C, with 13% CuI, and a ligand/Cu ratio of 1.3:1.
[e] The reaction was performed at 0 °C.
[f] *n*-BuMgI was added over 3 min.

gave lower enantioselectivity (20%) than ligand **4a** (entries 11 and 12, Table 1). However, the reaction was considerably faster. The same γ:α selectivity and enantioselectivity were obtained when the Grignard reagent was added over 2 h (standard conditions) or over 3 min. In the case of ligand **4a** the γ:α selectivity and the enantioselectivity dropped considerably when adding the Grignard reagent over 3 min (entry 13, Table 1). The faster reaction rate can be explained by the stronger coordinating ability of the ruthenocene ligand, compared to the ferrocene equivalent. The lower chiral induction can be a consequence of the lower diastereomeric purity (78% de) of **4i**, but it is more likely caused by the fact that the planar chirality is less pronounced, due to the greater distance between the Cp-rings in ruthenocene and therefore enhanced flexibility compared to ferrocene.[9a]

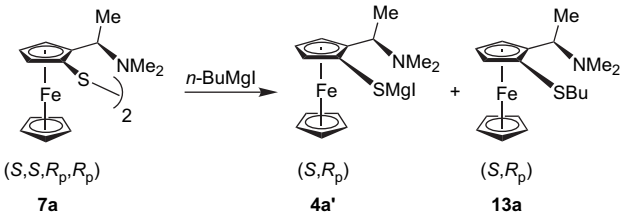
The lithium selenide **4j** gave the same enantioselectivity with cinnamyl acetate **2b** as ligand **4a**. However, for substrate **2a** ligand **4j** gave lower enantioselectivity in the allylic substitution than ligand **4a** (entries 14 and 15, Table 1), which is not the case for ligand **4a**.

Allylic substitution with the diastereomer of reversed planar chirality **4b**, compared to ligand **4a**, gave 52% ee with substrate **2b** (entry 16, Table 1). This is higher than the chiral induction obtained with ligand **4a**. It may therefore be that the chiral induction obtained with ligand **4a** is a mismatched situation, while a matched situation exists for ligand **4b**. It is interesting to note that the absolute configuration in the allylic substitution is governed by the planar chirality.

2.5. The disulfide as a ligand precursor

The difficulty in purifying the lithium thiolate and the susceptibility toward degradation prompted us to investigate the possibility of preparing a ligand precursor that would generate the ligand in situ. Disulfide formation worked cleanly for ligand **4a** resulting in disulfide **7a**, Scheme 7. It is known that disulfide bridges can be cleaved reductively.[31] Uemura showed that $LiAlH_4$ in THF could cleave the corresponding diselenide.[13] For the copper(I)-catalyzed substitution of allylic acetates, the cleavage of the disulfide in situ requires a reagent that does not affect the allylic substitution reaction. Alkali metal hydrides were therefore ruled out. Cleavage with alkali metal was attempted but so far this has been without success.

Dichalcogenides have previously been reported as ligand precursors, heterolytically cleaved in situ.[32] We decided to cleave the disulfide with the Grignard reagent employed in the allylic substitution reaction. Addition of 1 equiv of *n*-BuMgI to the disulfide resulted in heterolytic cleavage generating 1 equiv of magnesium thiolate **4a′** and 1 equiv of the corresponding butyl thioether **13a** in situ, Scheme 8. If the butyl thioether **13a** does not affect the allylic substitution negatively the disulfide **7a** can be used as a ligand precursor, generating the desired ligand with the Grignard reagent.



Scheme 8. Disulfide **7a** used as a ligand precursor, generating the desired ligand **4a′** in situ.

Allylic substitution with substrate **2a** under standard conditions gave 62% ee (entry 1, Table 2). Performing the allylic substitution on substrate **2a** without any ligand present gave almost only the alcohol by-product **7** (entry 2, Table 2). Employing the disulfide **7a** as a ligand afforded the desired product in high yield with 50% ee (entry 3, Table 2). The decrease in enantioselectivity can be explained by the presence of 1 equiv of butyl thioether **13a**. In a control experiment it was shown that the latter compound, when used as ligand in the same reaction afforded the product, though with a very low yield and in an almost racemic form (entry 4, Table 2). When the free amine **8a** was used as ligand in the allylic substitution with substrate **2b** racemic material was obtained (entry 5, Table 2). Employing substrate **2b** showed an even larger difference between the reactions using the thiolate ligand **4a** and the disulfide **7a**, 38 versus 18% ee (entries 6 and 7, Table 2). This can be explained by a higher reaction rate observed for the butyl thioether **13a** with substrate **2b**, compared to substrate **2a** (entry 8, Table 2). Furthermore, the butyl thioether **13a** gave the opposite enantiomer in the allylic substitution.

In conclusion, when using the disulfide **7a** as a ligand precursor the reaction catalyzed by the butyl thioether **13a** has to

Table 2. Reactions between allylic acetates and *n*-BuMgI catalyzed by CuI in the presence of ligand **4a**, ligand precursor **7a**, or **13a**[a]

Entry	Substrate	Ligand	Product	ee (%)[b]	γ:α Ratio	**7** (%)[c]	Conv (%)[c]	Yield (%) (**3**+**5**)[c]
1	**2a**	(S,R_p)-**4a**	**3a**	62 (*S*)-(+)	97:3	0	100	98
2	**2a**	—	**3a**	Not det.	Not det.	91	94	3
3[d]	**2a**	(S,S,R_p,R_p)-**7a**	**3a**	50 (*S*)-(+)	96:4	0	97	94
4	**2a**	(S,R_p)-**13a**	**3a**	3 (*R*)-(−)	80:20	25	32	6
5	**2b**	(*S*)-**8a**	**3b**	2 (+)	96:4	14	93	55
6	**2b**	(S,R_p)-**4a**	**3b**	38 (+)	96:4	5	100	90
7[d]	**2b**	(S,S,R_p,R_p)-**7a**	**3b**	18 (+)	96:4	10	100	84
8	**2b**	(S,R_p)-**13a**	**3b**	11 (−)	97:3	14	92	61

[a] Reaction conditions: The allylic acetate **2**, ligands (0.30 equiv) and CuI (0.15 equiv) were mixed in diethyl ether at rt for 30 min. *n*-BuMgI (1.5 equiv) was added via a syringe pump over 2 h to maintain a low concentration. The reaction mixture was kept at rt for 1 h.
[b] Enantioselectivity was measured by chiral GC, except for entry 1, which was measured by optical rotation.
[c] Determined by GC with 2-decanol as internal standard, for entries 1–3 and by ^{1}H NMR with 2-decanol as internal standard, for entries 4–8.
[d] The ligand/metal ratio was 1.2.

be suppressed, otherwise a decrease in enantioselectivity compared to the lithium thiolate catalyzed reaction will be observed. For substrate **2a** this might be possible, as the reaction catalyzed by the butyl thioether is slow, but not for substrate **2b**.

3. Conclusions

A systematic variation of the structure of thiolate ligands for the copper(I)-catalyzed substitution of allylic acetates was conducted. Eight different ligands (**4b–g**, **4i**, and **4j**) were prepared and employed in the allylic substitution reaction. Ligands **4c–g**, **4i**, and **4j** gave lower enantioselectivity than ligand **4a**. In agreement with Fu's observations, ruthenocene ligand **4i** gave a lower chiral induction than the corresponding ferrocene ligand, but an enhanced reaction rate. Ligand **4b** with reversed planar chirality (in comparison to ligand **4a**) gave a slightly better enantioselectivity than diastereomer **4a**.

A more robust system was investigated, employing disulfide **7a** as a ligand precursor. Generating the ligand **4a′** in situ by the reaction with the Grignard reagent would be useful if the butyl thioether **13a** did not catalyze the reaction. In the case of substrate **2a** this might be possible as only a small decrease of the enantioselectivity was observed with **7a** as a ligand precursor, compared to **4a** (64 versus 50% ee). Indeed, for substrate **2a** the butyl thioether did not catalyze the reaction. On the other hand, for substrate **2b** the butyl thioether did catalyze the racemic reaction and a substantial decrease of enantioselectivity was observed (38 versus 18% ee).

4. Experimental

4.1. General

^{1}H (400 or 300 MHz) and ^{13}C (100 or 75 MHz) NMR spectra were recorded on a Varian Mercury spectrometer. Chemical shifts (δ) are reported in parts per million, using residual solvent proton resonance or tetramethylsilane as internal standard. IR-spectra were obtained using a Perkin–Elmer 1600 FTIR instrument and the samples were examined on NaBr plates. Only the strongest/structurally most important peaks (cm^{-1}) are listed. Optical rotation was obtained on a Perkin–Elmer 241 Polarimeter. Merck silica gel 60 (240–400 mesh) was used for flash chromatography and analytical thin-layer chromatography was performed on Merck precoated silica gel 60-F_{254} plates. Unless otherwise noted, all the materials were obtained from commercial suppliers and used without further purification. All the reactions were performed under argon, using freshly distilled solvents. Ether was distilled from sodium benzophenone ketyl radical, hexane was distilled from sodium, and pentane was distilled from calcium hydride prior to use. Ruthenocene was prepared according to a published procedure.[33] Compounds **2a**,[5c] **7a**,[13] **8a**,[15] **8f**,[34] **8g**,[17] **8i**,[9c] **10c**,[35] and **12**,[25] were prepared according to published procedures and analytical data were in agreement with the literature. The enantiomeric excess of the intermediate alcohol **10f** was analyzed by chiral HPLC, using an ODH-column with 0.5 ml/min of hexane/isopropanol 95:5; rt_{major}=11.5 min, rt_{minor}=12.3 min. Compound **13a** was prepared by treating **4a** with *n*-BuI and analytical data were in agreement with the literature.[36]

The allylic substitution reactions were performed as previously reported, unless stated in Tables 1 or 2.[10b,11] Analytical and spectroscopic data for products **3a** and **5a**,[5c] **3b** and **5b**[37] were in agreement with those in the literature. The absolute configuration of **3a** was assigned from the optical rotation, accordingly to previously reported data.[10b,38]

4.1.1. (*R*)-*N*,*N*-Dimethyl-ferrocenyl-phenylmethylamine 8c.[39] The preparation was performed according to known procedures.[15,17] The enantiomeric excess of the intermediate alcohol **10c** was determined to be 98% by chiral HPLC, using an AD-column with 0.5 ml/min of hexane/isopropanol 95:5; rt_{major}=37.5 min, rt_{minor}=48.8 min. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, J=7.4 Hz, 2H), 7.40 (t, J=7.4 Hz, 2H), 7.30 (t, J=7.4 Hz, 1H), 4.22–4.17 (m, 2H), 4.16–4.12 (m, 1H), 4.12–4.05 (m, 1H), 3.78 (s, 1H), 3.73 (s, 3H), 2.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 128.6, 128.0, 127.1, 90.5, 72.4, 70.6, 68.8, 68.6, 67.3, 66.5, 44.6; $[\alpha]_D^{21}$ +108 (*c* 1.88, $CHCl_3$).

4.1.2. (*R*)-*N*,*N*-Dimethyl-ferrocenyl-1-naphthylmethylamine 8d. The preparation was performed according to known procedures.[15,17] The enantiomeric excess of the intermediate alcohol **10d** was analyzed by chiral HPLC, using an ODH-column with 0.5 ml/min of hexane/isopropanol 90:10; rt_{major}=29.2 min, rt_{minor}=41.1 min. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.67 (d, J=8.7 Hz, 1H), 7.91 (dd, J=7.8, 1.5 Hz, 1H), 7.85–7.80 (m, 2H), 7.61–7.48 (m, 3H), 4.57 (s, 1H), 4.28 (m, 1H), 4.24 (m, 1H), 4.12 (m, 1H), 4.10 (m, 1H), 3.45 (s, 5H), 2.15 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.4, 134.0, 132.2, 129.1, 127.5, 125.7, 125.6, 125.5, 125.4, 124.5, 91.2, 70.8 (2C), 68.6, 68.5, 67.5, 66.4, 45.1; $[\alpha]_D^{21}$ −96.6 (*c* 0.550, $CHCl_3$).

4.1.3. (*R*)-*N*,*N*-Dimethyl-ferrocenyl-2-naphthylmethylamine 8e. The preparation was performed according to known procedures.[15,17] The enantiomeric excess of the intermediate alcohol **10e** was analyzed by chiral HPLC, using an ODH-column with 0.5 ml/min of hexane/isopropanol 90:10; rt_{major}=30.1 min, rt_{minor}=48.6 min. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.92–7.88 (m, 3H), 7.86 (d, J=2.1 Hz, 1H), 7.69 (dd, J=8.7, 1.8 Hz, 1H), 7.53–7.44 (m, 2H), 4.26 (m, 1H), 4.23 (m, 1H), 4.15 (m, 1H), 4.12 (m, 1H), 3.97 (s, 1H), 3.68 (s, 5H), 2.12 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.1, 133.3, 132.9, 128.0, 127.8, 127.7, 127.11, 127.06, 126.10, 125.7, 90.5, 72.5, 70.5, 68.8, 68.6, 67.5, 66.6, 44.7; $[\alpha]_D^{21}$ +73.6 (*c* 0.635, $CHCl_3$).

4.1.4. (*rac*)-*N*,*N*-Dimethyl-1-pentaphenylferrocenylethylamine 8h. Titanium isopropoxide (0.469 ml, 1.59 mmol) was added to acetyl-pentaphenylferrocene (0.483 g, 0.794 mmol) dissolved in dichloromethane (5 ml). The solution was cooled to −15 °C and dimethylamine gas (1.27 g, 57 mmol) was condensed into the solution. The cooling bath was removed and the reaction mixture was kept at rt over night. An additional 5 ml of dichloromethane was added. The imine-solution was added dropwise to a suspension of sodium borohydride (126 mg, 3.32 mmol) in 10 ml of ethanol at rt. After 3 h the reaction had gone to completion. Saturated ammonium chloride was added and material

was extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$ and evaporated. The material was purified by chromatography dichloromethane/MeOH 95:5 and 0.384 g of **8h** (76%) was obtained as an orange colored solid. ^1H NMR ($CDCl_3$) δ 7.03–7.14 (m, 25H), 4.62 (m, 1H), 4.12 (dt, J=2.4, 1.5 Hz, 1H), 4.08 (dt, J=2.4, 1.2 Hz, 1H), 4.04 (m, 1H), 3.55 (q, J=6.6 Hz, 1H), 2.04 (s, 6H), 0.93 (d, J=6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 Hz) δ 135.9, 132.4, 127.1, 126.0, 95.1, 87.3, 75.0, 74.8, 74.4, 72.0, 54.7, 39.8, 10.8; IR (neat): 3056, 2933, 2821, 1601, 1502, 1443, 1089, 1074, 1028, 908, 739, 700 cm^{-1}. HRMS (m/z) calculated for $C_{44}H_{39}FeN$ (M^+), 637.2432; found, 637.2488.

4.1.5. General procedure for the preparation of thiolates 4a, 4c–g, 4i, and selenoate 4j. Amine **8** was added to a dry Schlenk tube, dissolved in ether and cooled to −15 °C. *t*-BuLi (1.05 equiv, 1.7 M in pentane) was added. The reaction mixture was stirred at −15 °C for 15 min and thereafter for 1 h at rt. In another Schlenk tube, sulfur or selenium (0.97 equiv) was suspended in ether and cooled to −15 °C. The lithiated amine was transferred to the sulfur or selenium suspension. The resulting mixture was stirred at −15 °C for 15 min and thereafter at rt for 1 h and worked up as described below for each case.

4.1.5.1. Thiolate 4a. Amine **8a** (532 mg, 2.07 mmol in 7 ml ether) was lithiated with *t*-BuLi (2.28 mmol), followed by treatment with S_8 (63 mg, 1.97 mmol), according to the general procedure. About half of the solvent was evaporated from the precipitate formed. The residing mother liquor was withdrawn from the product, which was subsequently washed with ether (3×3 ml). Ligand **4a** was isolated in 482 mg (79%) as an orange colored solid.

4.1.5.2. Thiolate 4c. Amine **8c** (159 mg, 0.498 mmol in 2 ml ether) was lithiated with *t*-BuLi (0.525 mmol), followed by treatment with S_8 (16.0 mg, 0.499 mmol in 2 ml of ether), according to the general procedure. The product precipitated after the addition of 1.5 ml pentane. After removal of the mother liquor, the product was washed with pentane (3×1.5 ml). Ligand **4c** was isolated in 143 mg (80%) as an orange colored solid.

4.1.5.3. Thiolate 4d. Amine **8d** (190 mg, 0.520 mmol in 2 ml ether) was lithiated with *t*-BuLi (0.566 mmol), followed by treatment with S_8 (16.0 mg, 0.499 mmol in 2 ml of ether), according to the general procedure. The product precipitated. After removal of the mother liquor, the product was washed with ether (2×1 ml). Ligand **4d** was isolated in 29 mg (14%) as an orange colored solid.

4.1.5.4. Thiolate 4e. Amine **8e** (200 mg, 0.542 mmol in 2 ml ether) was lithiated with *t*-BuLi (0.704 mmol), followed by treatment with S_8 (17.3 mg, 0.542 mmol in 2 ml of ether), according to the general procedure. The product precipitated after the addition of 3.0 ml pentane. After removal of the mother liquor, the product was washed with pentane (2×1.5 ml). Ligand **4e** was isolated in 126 mg (57%) as an orange colored solid.

4.1.5.5. Thiolate 4f. Amine **8f** (255 mg, 0.895 mmol in 3 ml ether) was lithiated with *t*-BuLi (1.164 mmol), followed by treatment with S_8 (28.7 mg, 0.895 mmol in 2 ml of ether), according to the general procedure. The product did not precipitate; instead the solvent was removed in vacuo obtaining **4f** as an orange colored solid.

4.1.5.6. Thiolate 4g. Amine **8g** (345 mg, 1.05 mmol in 4 ml ether) was lithiated with *t*-BuLi (1.10 mmol), followed by treatment with S_8 (32.7 mg, 1.02 mmol in 3 ml of ether), according to the general procedure. All the solvent was evaporated and hexane (3 ml) was added. The precipitate, which then formed, was washed with hexane (3×3 ml). Ligand **4g** was isolated in 258 mg (67%) as an orange colored solid.

4.1.5.7. Thiolate 4i. Amine **8i** (262 mg, 0.868 mmol in 3 ml ether) was lithiated with *n*-BuLi (1.128 mmol), followed by treatment with S_8 (27.9 mg, 0.868 mmol in 3 ml of ether), according to the general procedure. The product precipitated after the addition of 1.5 ml pentane. After removal of the mother liquor, the product was washed with pentane (3×1.5 ml). Ligand **4i** was isolated in 133 mg (45%) as white solid.

4.1.5.8. Selenoate 4j. Amine **8a** (545 mg, 2.12 mmol in 7 ml ether) was lithiated with *t*-BuLi (2.23 mmol), followed by treatment with Se (159 mg, 2.01 mmol in 5 ml ether), according to the general procedure. About half of the solvent was evaporated from the precipitate formed. The residing mother liquor was withdrawn and the product was subsequently washed with ether (3×3 ml). Ligand **4j** was isolated in 361 mg (50%) as an orange colored solid.

4.1.5.9. Thiolate 4b. (R,R_p)-1-iodo-2-(1-*N*,*N*-dimethylaminoethyl) ferrocene (**12**) (331 mg, 0.864 mmol in 3 ml ether) was treated with *t*-BuLi (0.907 mmol) at −78 °C. The reaction mixture was stirred at this temperature for 30 min, followed by 30 min at rt. The reaction mixture was transferred to another Schlenk tube containing S_8 (27 mg, 0.838 mmol in 3 ml ether). The product precipitated after evaporation of half the ether, followed by addition of 2 ml of hexane. The crude product was washed with hexane (3×3 ml). Ligand **4b** was isolated in 84 mg (33%) as an orange colored solid.

Acknowledgements

Financial support from the Swedish Research Council is gratefully acknowledged.

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