Ferrocenyl Thiolates as Ligands in the Enantioselective Copper-Catalyzed Substitution of Allylic Acetates with Grignard Reagents

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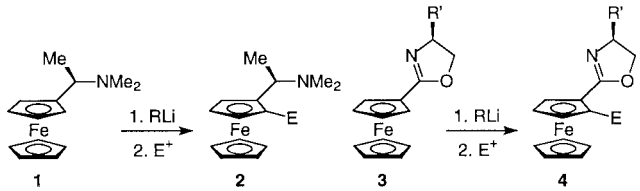
Abstract: The application of ferrocenyl thiolates as ligands in copper-catalyzed asymmetric substitution reactions of allylic acetates with Grignard reagents is reported. The catalyst formed from lithium thiolate **12** gave the γ-products in high selectivity and with up to 64% ee.

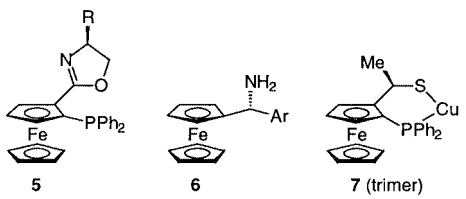
Keywords: asymmetric synthesis, copper, ferrocenyl ligands, sulfur, asymmetric catalysis

Chiral ferrocenes have received much attention as ligands in transition-metal-catalyzed asymmetric reactions.[1] Ligands based on the ferrocenyl amine **1**[2,3] and ferrocenyl oxazoline **3**[4,5] have become increasingly popular (Scheme 1). They are readily accessible in enantiomerically pure form, and they can be diastereoselectively *ortho*-lithiated (Scheme 1).[6,7] After this lithiation a number of electrophiles can be introduced, resulting in diastereomerically pure ferrocene derivatives **2** and **4** containing both central and planar chirality.[8]

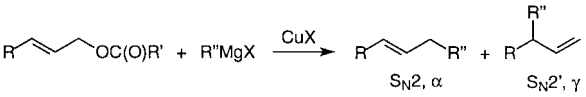


Scheme 1

Only a few reports on the use of ferrocene ligands in organocopper chemistry have been published. Stangeland and Sammakia[9] used the ferrocenyl oxazoline phosphine **5** as ligand for the copper-catalyzed conjugate addition of *n*-BuMgCl to enones with ee's up to 92%. Knochel et al.[10] developed chiral ferrocenyl amines **6** that were used as ligands in the copper-catalyzed allylic substitution reaction of allylic chlorides with diorganozinc reagents. With sterically hindered diorganozinc reagents high ee's were obtained. Togni et al.[11] synthesized the ferrocenyl thiolato copper(I)-complex **7**, which, however, yielded racemic product in conjugate addition of Grignard reagents to enones.

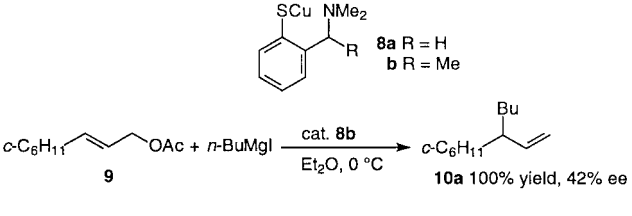


We have previously studied the copper-mediated allylic substitution reaction between allylic esters and Grignard reagents (eq 1) in order to develop conditions for regioselective reactions and to elucidate the mechanism of this process.[12]



Equation 1

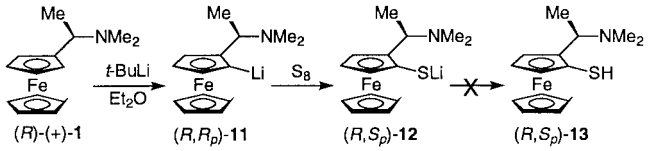
During these studies, it was observed that copper arenethiolate **8a** (Scheme 2), developed by van Koten et al.,[13] gave highly regioselective allylic substitution reactions.[14] By use of chiral complex **8b** as catalyst, allylic acetate **9** and *n*-BuMgI gave γ-product **10a** with 42% ee (Scheme 2).[15] The use of copper arenethiolates prepared in situ from the corresponding arenethiols has also been studied for the asymmetric version of this reaction.[16] Similar results were obtained as when preformed copper arenethiolates were used.



Scheme 2

We now report on the synthesis of a new ferrocene-derived ligand **12** and its use in copper-catalyzed reactions of allylic acetates with Grignard reagents.

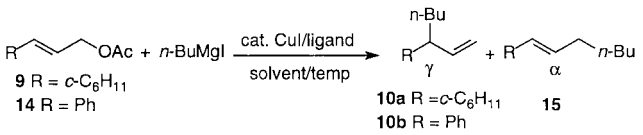
The synthesis of the ferrocene thiolate ligand **12** is depicted in Scheme 3. Lithiation of **1**[3] followed by treatment with elemental sulfur in Et_2O gave **12** as a pale orange precipitate. However, attempts to isolate the corresponding thiol **13** via hydrolytic workup led to oxidation of the thiol moiety, and decomposition of the ferrocene, resulting in



Scheme 3

complex mixtures of products. Complex **12**, when washed and dried in vacuo, seems to be stable for a long time in the solid state under argon, but undergoes fast oxidation in solution even in the presence of minor amounts of oxygen, resulting in conversion to the diferrocenyl disulfide.[17] The facile oxidation of ferrocene thiols has been discussed in the literature.[18,19]

Mixing of **12** and CuI in Et_2O or toluene at room temperature led to a clear yellow solution within 30 min. Addition of allylic ester **9** or **14** to this solution, followed by *n*-BuMgI, according to our previously reported S_N2'-selective reaction conditions,[15,16] gave the desired γ-substitution products **10**, together with small amounts of α-substitution product **15** (eq 2, Table 1).



Equation 2

The effects of the temperature, solvent and amount of ligand were studied. A slight excess of ligand to copper was always used to compensate for any ligand decomposition. A reaction at 0 °C gave a better result in a Et_2O/toluene mixture (53% ee, Table 1, entry 1) than in Et_2O alone (40% ee, Table 1, entry 2). Lowering the temperature to -20 °C led to a decrease in the enantiomeric excess to 28% in Et_2O (Table 1, entry 3). This result is in accordance with results for copper arenethiolate **8b**, where a lower temperature also led to a lower enantioselectivity.[15] Increasing the temperature to room temperature (Table 1, entries 4 and 6) or 10 °C (Table 1, entry 9) gave a better selectivity than at 0 °C. Changing the solvent to pure toluene (Table 1, entry 5) gave a much lower enantioselectivity than Et_2O or Et_2O/toluene. The highest enantioselectivity was obtained in Et_2O/toluene when the amount of ligand was doubled (64% ee, Table 1, entry 7). In this reaction a higher γ:α-ratio (98:2) was also observed. The higher selectivity obtained when a larger amount of ligand was used could be explained by the low stability towards oxidation of these ferrocenyl thiolate systems.

Cinnamyl acetate **14** as substrate at 0 °C in Et_2O gave **10b** with an enantiomeric excess of 42% (Table 1, entry 10). This result is better than the enantiomeric excess obtained with catalyst **8b** prepared in situ (30% ee).[16] With **14** as substrate no improvement was achieved at room temperature in Et_2O/toluene (Table 1, entry 11).

The scope of the reaction with respect to the Grignard reagent was also briefly examined according with Table 2. In all cases reasonable ee's were obtained for the γ-substitution products which were formed in high selectivity.

Table 1 Reactions between allylic esters and *n*-BuMgI catalyzed by CuI and ferrocenyl ligand **12**.[a]

Entry	Substrate	12	L/CuI	Temp (°C)	Solvent	Conversion (%)[c]	Yield (%)[d]	γ:α-ratio[c]	Ee (%)[e]
1	**9**	(R,S_p)	1.2:1	0	$Et_2O/PhCH_3$[b]	97	59	93:7	53[f]
2	**9**	(S,R_p)	1.3:1	0	Et_2O	98	76	93:7	40
3	**9**	(R,S_p)	1.2:1	-20	Et_2O	92	78	93:7	28
4	**9**	(R,S_p)	1.2:1	RT	Et_2O	100	84	93:7	62[f]
5	**9**	(R,S_p)	1.2:1	RT	$PhCH_3$	100	45	87:13	34
6	**9**	(S,R_p)	1.3:1	RT	$Et_2O/PhCH_3$[b]	100	75	95:5	58
7	**9**	(S,R_p)	2.7:1	RT	$Et_2O/PhCH_3$[b]	100	88	98:2	64
8[g]	**9**	(S,R_p)	5:1	RT	$Et_2O/PhCH_3$[b]	100	82	96:4	55
9	**9**	(S,R_p)	1.3:1	10	$Et_2O/PhCH_3$[b]	100	87	96:4	59
10	**14**	(S,R_p)	1.3:1	0	Et_2O	100	78	94:6	42
11	**14**	(S,R_p)	1.3:1	RT	$Et_2O/PhCH_3$[b]	100	68	95:5	38

[a] Unless otherwise noted ligand **12** and CuI (13 mol%) were stirred at r.t. for 30 min in the solvent indicated and then the allylic acetate (1 equiv, typically 0.5 mmol) was added. *n*-BuMgI (1.5 equiv in Et_2O) was added over 2 h via syringe pump. [b] $Et_2O/PhCH_3$ (3:1). [c] Determined by GC. [d] Isolated yield after column chromatography. [e] Determined by GC using a chiral stationary phase (CP-Chirasil-Dex CB). (R,S_p)-**12** gave (*R*)-**10a**, and (S,R_p)-**12** gave (*S*)-**10a** as the major enantiomer. [f] The average of two GC-runs. [g] 4 mol% of CuI.

However, the yields were in general lower than those obtained in the reaction with *n*-BuMgI. There is no general correlation between the steric bulk of the alkyl group in the Grignard reagent and the ee of the γ-product.

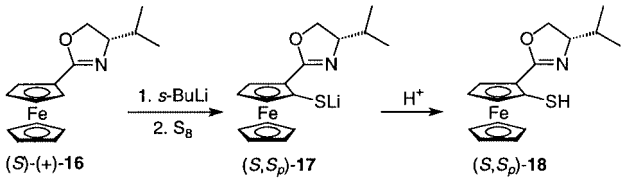
Table 2 Allylic substitution reactions between **9** and RMgX catalyzed by CuI and ferrocenyl ligand (S,R_p)-**12**.[a]

Entry	RMgX	L/CuI	Conversion (%)[b]	Yield (%)[c]	γ:α-ratio[b]	Ee (%)[d]
1	*n*-BuMgI	2.7:1	100	88	98:2	64
2	MeMgI	2.7.1	100	42[e]	93:7	44
3	EtMgI	2.6:1	100	55	98.2	62
4	PrMgI	2.5:1	100	77	96:4	54
5	*i*-PrMgBr	2.4:1	100	51	96:4	52

[a] The reactions were carried out as described in Table 1 in Et_2O/toluene 3:1 at r.t. [b] Determined by GC. [c] Isolated yield of α- and γ-substitution products. [d] Determined by GC using a chiral stationary phase (CP-Chirasil-Dex CB). [e] The alcohol, formed by direct attack of the Grignard reagent on the acetate moiety, was also observed.

To study the thiol anion effect we blocked the sulfur in ligand **12** with a *t*-butyl or a phenyl group. These ferrocenyl thioethers[20] gave essentially racemic product (0-2% ee) in the copper-catalyzed reaction of **9** with BuMgI, which shows the importance of anionic coordination to copper by sulfur.

We also prepared ferrocenyl oxazoline thiol **18** (Scheme 4) and studied it in the allylic substitution reactions. Pfaltz et al.[21] have previously used the corresponding oxazolidine phenylthiol in enantioselective conjugate additions with some success. Lithiation of oxazoline ferrocene **16** followed by reaction with elemental sulfur gave lithium salt **17**. Protonation of **17** afforded compound **18**, which was quite unstable and could only be isolated in low yields after purification by column chromatography. Treatment of **17** with CuI gave a catalyst that was used in the allylic substitution reaction of **9** with *n*-BuMgI. The S_N2'-product **10a** was isolated in 65% yield with an enantiomeric excess of 10%.



Scheme 4

In conclusion the results obtained with ferrocenyl thiolate **12** as ligand for the substitution of allylic acetates with Grignard reagents, clearly demonstrate the positive influence of the ferrocenyl backbone on the enantioselectivity in this reaction. Neutral thioether ligands were not suitable for this reaction, showing the importance of anionic coordination to copper. It is interesting to note that 64% ee obtained in the present study is the highest ee ever reported for allylic acetates (carboxylates) in the copper-catalyzed allylic substitution, and further investigations of ligands **12** and related ferrocenyl thiolate ligands in enantioselective allylic substitution reactions are in progress.

In the accompanying paper Alexakis et al[22] disloses a chiral phosphorous ligand for the Cu-catalyzed S_N2' substitution of cinnamyl chlorides by Grignard reagents.

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