Enantioselective Copper-Catalyzed S_N2' Substitution with Grignard Reagents

Alexandre Alexakis, Christophe Malan, Louise Lea, Cyril Benhaim, Xavier Fournioux

Chimie Organique, Sciences II, University of Geneva, Quai Ernest Ansermet, CH-1211, Geneva, Switzerland
Fax +41 22 3287396; E-mail: Alexandre.Alexakis@chiorg.unige.ch

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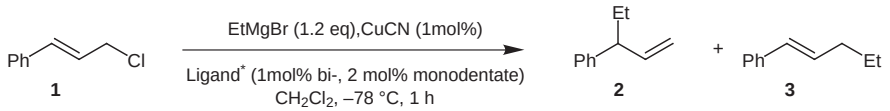
Abstract: Cinnamyl chlorides undergo selective S_N2'allylic substitution by Grignard reagents using catalytic amount (1 mol%) of CuCN and 1-2 mol% trivalent phosphorus ligand, in dichloromethane. With chiral phosphorus ligands derived from TADDOL ee's up to 73% could be obtained.

Key words: chiral phosphorus ligands, copper, asymmetric catalysis, S_N2', TADDOL

Allylic compounds have been of synthetic, mechanistic and biological importance for over 50 years. Catalytic asymmetric allylic substitutions are therefore potentially useful methods for the preparation of a wide range of chiral molecules. The copper(I)-catalyzed allylic substitution reaction has generated a great deal of interest in recent years and several methods have been developed for the control of both regio- and stereochemistry in this reaction. An advantage is that a broad range of organometallic compounds, organolithium, Grignard and organozinc reagents can be used in these allylic substitutions.[1-6] Copper(I)-promoted asymmetric γ-substitution (S_N2') of allylic substrates with a chiral leaving group has been reported,[7-13] but catalytic procedures employing chiral ligands on copper are scarce and only moderate ee's are obtained. Van Koten, Bäckvall et al. recently reported arenethiolatocopper(I) complexes which acheive ee's of up to 64% in the catalytic S_N2' reaction between allylic acetates and *n*-BuMgI.[14-16] Knochel et al. have developed chiral ferrocenyl amine ligands, reporting ee's of up to 98% in the catalytic S_N2' reaction between allylic chlorides and highly hindered diorganozinc reagents.[17,18]

Our efforts so far have focused on the enantioselective copper(I)-catalyzed conjugate addition reaction on enones[19] and other Michael acceptors,[20,21] during the course of which we have reported the use of several chiral phosphorus ligands.[22-25] We have recently turned our attention to the application of such ligands to asymmetric allylic substitution and report herein the results of our investigation.

To establish optimum conditions required for regioselectivity (Scheme 1) we first examined the reaction of cinnamyl chloride **1** with simple Grignard reagents in the presence of a copper(I)-catalyst and triethylphosphite. Various conditions were investigated (Table 1): EtMgBr



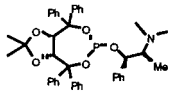
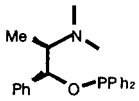
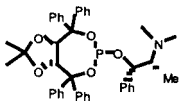
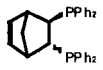
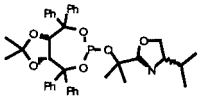
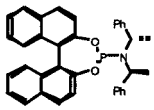
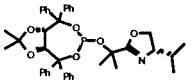
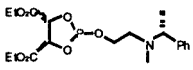
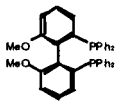
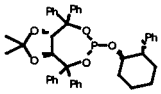
Scheme 1

Table 1 Copper-Catalyzed Substitution of Cinnamyl Chloride with Ethyl Grignard Reagents in the Presence of Triethylphosphite

Entry	Grignard	Mode of addition	Temperature (°C)	Solvent	Copper salt	S_N2' :S_N2
1	EtMgCl	inverse	–30	THF	$Cu(OTf)_2$	32 :68
2	EtMgCl	inverse	–30	Et_2O	$Cu(OTf)_2$	20 :80
3	EtMgCl	inverse	–30	CH_2Cl_2	$Cu(OTf)_2$	37 :63
4	EtMgCl	inverse	–30	toluene	$Cu(OTf)_2$	29 :71
5	EtMgBr	inverse	–30	CH_2Cl_2	CuI	60 :40
6	EtMgBr	normal	–30	CH_2Cl_2	$Cu(OTf)_2$	70 :30
7	EtMgBr	normal	–30	Et_2O	CuCN	67 :33
8	EtMgBr	normal	–30	CH_2Cl_2	CuCN	88 :12
9	EtMgBr	inverse	–80	CH_2Cl_2	CuCN	80 :20
10	EtMgBr	normal	–80	CH_2Cl_2	CuCN	**97 :3**
11	EtMgBr	normal	–80	CH_2Cl_2	CuCN	1 :4*

EtMgCl (2.8 M in THF). EtMgBr (3.0 M in Et_2O). Conversion >95% in all cases. *Cinnamyl acetate
Normal addition refers to slow addition of the Grignard reagent (over 20 min) to the reaction mixture at −78 °C. Inverse addition refers slow addition of cinnamyl chloride (over 20 min) to the reaction mixture at −78 °C.

Table 2 Some Chiral Phosphorus Ligands Screened; Reaction Conditions as Scheme 1

Ligand	%Conv.	$S_N2':S_N2$	%ee	Ligand	%Conv.	$S_N2':S_N2$	%ee
 **4**	100	>99 :1	61	 **9**	100	95 :5	17
 **5**	100 100 100	95 :5 63 :37 66 :34	34 39[a] 36[b]	 **10**	100	98 :2	12
 **6**	100	95 :5	32	 **11**	100	95 :5	6
 **7**	100	77 :23	11	 **12**	100	98 :2	2
 **8**	100	86 :14	18	 **13**	78	90 :10	0

[a]with CuBr, [b] with CuCl

Table 3 CuCN-Catalyzed Substitution of Cinnamyl Halides with EtMgBr in the Presence of Ligand **4**

Entry	Halide	Solvent (0.4M)	%CuCN	%Ligand	$S_N2':S_N2$	%ee
1	Cl	CH_2Cl_2	1 mol%	2 mol%	>99 :1	61
2	Cl	CH_2Cl_2	2.5 mol%	5 mol%	100 :0	67
3	Cl	CH_2Cl_2	1 mol%	1 mol%	100 :0	63
4	Cl	CH_2Cl_2	1 mol%	1 mol%	94 :6	**73**[*]
5	Br	CH_2Cl_2	2.5 mol%	5 mol%	55 :45	38

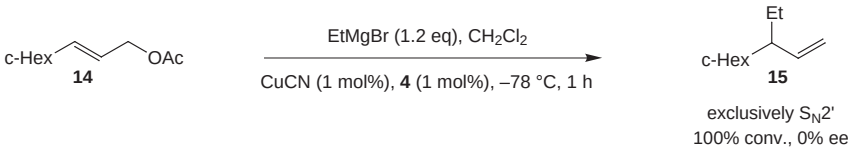
Reactions carried out at −78 °C. EtMgBr (3M in Et_2O) was added over 20 min unless otherwise stated.
[*]Grignard addition over 40 min

was shown to give a more favorable regioselectivity than EtMgCl; reaction temperature and the choice leaving group had a significant effect on product distribution with lower temperatures (−80 °C) favoring the S_N2' product **2** and cinnamyl chloride giving a favorable $S_N2' : S_N2$ ratio while cinnamyl acetate favored the S_N2 product **3**; solvent effects were shown to be of importance with CH_2Cl_2 being the favored solvent; and finally the choice of copper salt was critical to the product distribution, copper(I) cyanide giving the best results ($S_N2' : S_N2$ = 97:3).

A total of 29 chiral phosphorus ligands were screened, many of which gave little or no asymmetric induction. However some ligands, particularly: (i) those derived from (−)-TADDOL and (ii) those bearing two points of attachment on the lateral chain (e.g. an amino alcohol or oxazoline moiety) gave good results (Table 2). One ligand, PO_3-(−)-TADDOL-(−)-*N*-methylephedrine **4** showed a remarkably increased asymmetric induction over the other ligands achieving an ee of 61% in preliminary studies.

Optimization of reaction conditions afforded a maximum ee, in the case of ligand **4** of 73% (Table 3).[26] It is evident that the choice of solvent, which has a significant effect on regioselectivity, is critical to enantioselectivity. The optimum enantioselectivity favors a 1:1 ratio of copper(I)-catalyst to ligand and is most efficient when just 1 mol% is employed (entry 3). The rate of addition of the Grignard reagent was also shown to be of significance, when the Grignard reagent was added over 40 min the ee was increased by 10% (entry 4).

The choice of leaving group is critical to regio- and enantioselectivity: the use of cinnamyl bromide caused a significant drop in enantioselectivity and an unfavorable product distribution (entry 5), while cinnamyl acetate fa-



Scheme 2

Table 4 CuCN-Catalyzed Substitution of Cinnamyl Chloride with various Grignard Reagents in the Presence of Ligand **4**

Entry	Grignard	%Conversion	%Yield	S_N2' :S_N2	%ee
1	EtMgBr	100	87	94 :6	**73**
2	EtMgCl	100	96	97 :3	22
3	EtMgI	100	94	99 :1	4
4	CyclopentylMgBr	100	91	95 :5	47
5	*n*-PropylMgBr	100	91	93 :7	57
6	*n*-ButylMgBr	100	93	96 :4	52
7	NeopentylMgBr	100	96	97 :3	4
8	2-MeO-PhenylMgBr	100	91	94 :6	21[a]

Reactions carried out in CH_2Cl_2 (0.4 M with respect to substrate), in the presence of 1 mol% of CuCN and 1 mol% of chiral ligand, at −78 °C. Grignard reagents were added over 40 min as a solution (typically 3M) in diethyl ether.
[a]Reaction at −72 °C

vors the S_N2 product (see Table 1, entry 11). The saturated allylic acetate **14** gave excellent regioselectivity but no asymmetric induction under these conditions (Scheme 2).

Having confirmed the optimum conditions for the reaction in question new Grignard reagents were introduced in order to test the scope of the reaction (Table 4). Ethyl magnesium bromide is clearly preferable to other Grignard salts (entries 2 and 3) giving a greatly increased enantiomeric excess. Primary and secondary aliphatic Grignard reagents react with moderate enantioselectivity under these conditions (entries 4-6), however poor enantioselectivity is observed with sterically demanding Grignards reagents such as neopentyl magnesium bromide (entry 7).

Finally the methodology was extended to aromatic Grignard reagents. Several aromatic Grignard reagents were tested but sufficient separation by chiral GC was not obtained in the majority of cases. Application of 2-methoxyphenylmagnesium bromide, which did not undergo reaction at −78 °C, yielded a favorable product distribution at −72 °C and an ee of 21%, which has not yet been optimized. Further investigations into the application of aromatic Grignard reagents are currently underway.

In conclusion, we have reported a new chiral ligand for the enantioselective copper(I)-catalyzed allylic substitution reaction, achieving the highest ee (73%) yet reported with a Grignard reagent. It is clear from our results that the enantioselectivity of the reaction, which is truly catalytic requiring only 1 mol% of both the ligand and copper(I) catalyst, is highly dependent on the reaction conditions. The mode and time of addition of the Grignard reagent is critical to the enantioselectivity, as is the temperature of reaction. Furthermore the use of different Grignard reagents revealed that there is no single set of reaction conditions applicable to all cases. Moderate ee's (47-57%) have been achieved with a range of primary and secondary aliphatic Grignard reagents and an ee of 21% has been observed for the reaction with an aromatic Grignard reagent. Highly sterically hindered Grignard reagents are not suitable substrates for the reaction resulting in poor, if any observed enantioselectivity. The reaction has been extended to other allylic chlorides and preliminary results suggest that the regio- and enantioselectivity are of a similar range (e.g. *p*-methoxycinnamyl chloride gives 54% ee, 96:4 S_N2' :S_N2). Further investigations into the scope and limitations of the reaction are currently underway.

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(26) General procedure; To a well dried (two cycles of heating under vacuum) 25 mL two-necked flask equipped with a stirrer bar and internal thermometer and purged with argon was added copper(I) cyanide (3.6 mg, 1 mol%) and the chiral ligand, PO_3(−)-TADDOL-(−)-*N*-methylephedrine (27 mg, 1 mol%). Dichloromethane (8 mL) was added and the mixture was stirred at room temperature for 20 min. Cinnamyl chloride (0.56 mL, 4.0 mmol) was introduced dropwise and the reaction mixture was stirred at room temperature for a further 5 min before being cooled to −78 °C (internal temperature) via an acetone-dry ice cold bath. Ethyl magnesium bromide (3.0 M in diethyl ether, 1.6 mL, 4.8 mmol) in dichloromethane (2 mL) was added over 40 min via a syringe pump, whilst the internal temperature was maintained at −78 °C. Once addition was complete the reaction mixture was left at −78 °C for a further hour at which point gas chromatography of an aliquot showed that all the starting material had been converted. The reaction was quenched by addition of aqueous hydrochloric acid (1 N, 10 mL). Diethyl ether (40 mL) was added and the aqueous phase was separated and extracted further with diethyl ether (3 × 10 mL). The combined organic fractions were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and reduced in vacuo. The oily residue was purified by flash column chromatography (silica gel, eluant = cyclohexane, R_f = 0.5) to yield the product (561 mg, 3.84 mmol, 96%) as a mixture of S_N2' and S_N2 regioisomers (96:4). Gas chromatography on a chiral stationary phase (Chiraldex G-TA) showed that the S_N2' product had an ee of 73%.

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