Asymmetric Catalysis

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β-Disubstituted Allylic Chlorides: Substrates for the Cu-Catalyzed Asymmetric S_N2' Reaction**

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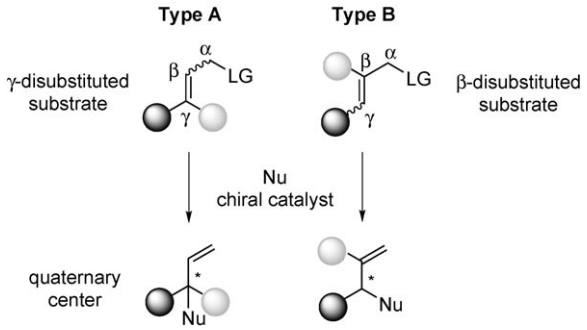
Metal-promoted asymmetric catalysis has proven to be an efficient method in carbon–carbon bond-forming reactions to obtain optically enriched compounds. Allylic substitution has attracted much attention and great effort has been put into controlling the chemo-, regio-, and enantioselective outcome of the reaction.[1] Extensive accounts report a wide variety of metals that use soft nucleophiles for the reaction (Pd, Ir, Mo, Rh, Ru).[2] In contrast, copper allows the use of hard, nonstabilized nucleophiles, such as small alkyl groups in the form of organometallic species.[3] Among the broad range of reagents available, the use of Grignard reagents in the catalyzed asymmetric allylic substitution reaction was first reported by Bäckvall et al.,[4] with chiral copper thiolates yielding moderate *ee* values. This pioneering work was soon followed by a report from Dübner and Knochel,[5] who disclosed a different system based on diorganozinc reagents. Other ligands have been introduced for the stereoselective allylic addition of organomagnesium reagents, such as chiral diaminocarbenes by Okamoto et al.,[6] and more recently ferrocenic bidentate phosphines by Feringa et al.[7]

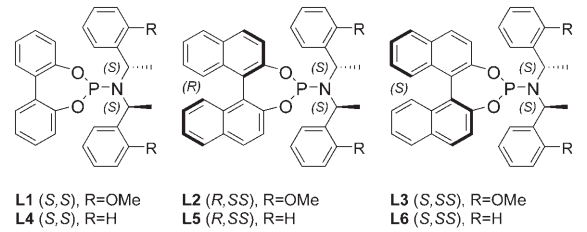
In the past few years, our group has reported highly regio- and enantioselective Cu-phosphoramidite catalytic reactions for the substitution of allylic chlorides by organomagnesium reagents.[8] This methodology was applied, in particular, to the formal synthesis of profen molecules by the highly efficient and valuable stereoselective allylic addition of MeMgBr with *ee* values up to 96%.[9] Subsequently, we focused on the application of our procedure to diverse substrates, and report herein the unprecedented Cu-catalyzed asymmetric allylic alkylation of β-disubstituted allylic halides.

The Cu-catalyzed asymmetric S_N2' reaction has mostly been limited to disubstituted olefinic systems.[10,11] Type A substrates (Scheme 1) that lead to chiral quaternary centers through catalytic allylic alkylation are scarcely documented, with the exception of reports from Hoveyda and co-workers who reached excellent enantioselectivities on γ-disubstituted allylic phosphates.[12,13] Other than the results reported by Woodward and co-workers on the stereoselective addition to Baylis–Hillman-derived allylic electrophiles,[14] copper-catalyzed asymmetric allylic alkylation on type B substrates, the β-disubstituted olefinic system, has not previously been described.

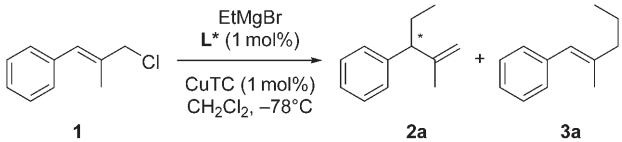


Scheme 1. Asymmetric allylic alkylation of γ- and β-disubstituted allylic substrates. LG = leaving group, Nu = nucleophile.

Preliminary experiments for this study started with a short screening of biphenol-[15] and binaphthol-based[8b,16] phosphoramidite ligands (Scheme 2) on *trans*-(3-chloro-2-methyl-prop-1-enyl)benzene (**1**), the β-methylcinnamyl chloride (Scheme 3). The results are summarized in Table 1. The allylic substitution of **1** by the slow addition of ethylmagnesium bromide, catalyzed by copper thiophene carboxylate (CuTC; 1 mol%) and different phosphoramidite ligands (1.1 mol%), gave adducts with poor-to-good γ/α ratios and provided high enantiomeric excess up to 96% *ee* with ligand **L6** (Table 1, entry 6).



Scheme 2. Chiral phosphoramidite ligands applied in the Cu-catalyzed asymmetric substitution.



Scheme 3. Asymmetric S_N2' reaction on β-methylcinnamyl chloride. L* = **L1**–**L6**.

Interestingly, the biphenol ligands **L1** and **L4** did not give product **2a** with the same absolute configuration, which is in accordance with our previous studies.[8a–c] Although we had

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Table 1: Screening of phosphoramidite ligands in the asymmetric CuTC-catalyzed allylic alkylation with EtMgBr (Scheme 3; L* = **L1**–**L6**).

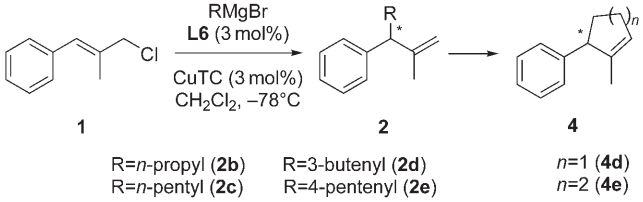
Entry[a]	Ligand	Conv. [%][b]	**2a**/**3a**[c]	*ee* [%][d]
1	**L1** (*S*,*S*)	>99	89:11	81(−)
2	**L2** (*R*,*SS*)	>99	73:27	61(−)
3	**L3** (*S*,*SS*)	>99	87:13	80(−)
4	**L4** (*S*,*S*)	>99	65:35	53(+)
5	**L5** (*R*,*SS*)	>99	30:70	27(−)
6	**L6** (*S*,*SS*)	>99	87:13	96(+)
7[e]	**L6** (*S*,*SS*)	>99 (87)	92:8	98(+)

[a] Conditions: **1** (1 mmol), CuTC (1 mol%), and L* (1.1 mol%) in CH_2Cl_2 (2 mL) at −78 °C with addition of EtMgBr in Et_2O (1.2 equiv) over 1 h. [b] Conversion determined by GC–MS (in parentheses, yield of isolated product after purification by column chromatography on silica gel). [c] Ratio determined by GC–MS and ^{1}H NMR spectroscopy. [d] Enantiomeric excess determined by chiral GC. [e] 3 mol% of CuTC and 3.3 mol% of L*.

shown that **L3** was the best ligand in different reactions with copper or iridium catalysis,[8a,b] we observed a lower enantioselective outcome of the substitution, with 80% *ee* (Table 1, entry 3). The hypothetically coordinating *ortho*-methoxy substituents seem to play a detrimental role.[17] An optimal amount (3 mol%) of CuTC/**L6** resulted in improved selectivities of 92% in favor of the γ product and 98% *ee* (Table 1, entry 7). By accelerating the reaction and thus preventing the formation of a dialkyl–cuprate complex in the reaction medium, the catalyst loading is an important parameter that favors the formation of the branched product (**2a**).[2,9,18]

To broaden the scope of the reaction, other Grignard reagents were tested and gave equally good asymmetric results (Table 2). Nonetheless, not being satisfied with the preliminary regioselectivity of **2d** and **2e** (Table 2, entries 3 and 6), we performed a slower addition of the Grignard reagents (Table 2, entries 4 and 7) and found a desirable improvement in regioselectivity (to 89 and 87% γ selectivity for **2d** and **2e**, respectively), while slightly raising the enantiomeric excess. By analogy to our previous finding, one-pot ring-closing metathesis with the Grubbs second-generation catalyst proceeded quantitatively on **2d** and **2e** without any loss of enantioselectivity in products **4d** and **4e** (with regard to open-chain intermediates; Table 2, entries 5 and 8).[19]

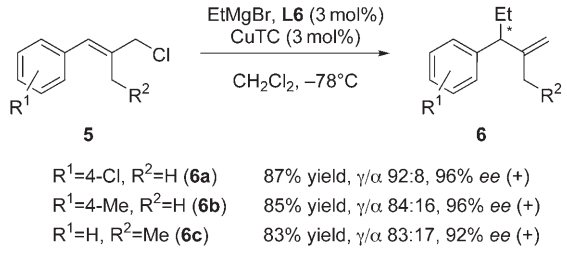
Table 2: Enantioselective Cu-catalyzed allylic alkylation on **1** with RMgX.



Entry[a]	RMgX	Yield [%][b]	Product	S_N2'/S_N2[c]	*ee* [%][d]
1	*n*-propyl-MgBr	85	**2b**	84:16	97(+)
2	*n*-pentyl-MgBr	83	**2c**	83:17	96(+)
3	3-butenyl-MgBr	84	**2d**	79:21	95(+)
4[e]	3-butenyl-MgBr	84	**2d**	89:11	97(+)
5[f]	–	69	**4d**	89:11	97(+)
6	4-pentenyl-MgBr	87	**2e**	82:18	93(+)
7[e]	4-pentenyl-MgBr	87	**2e**	87:13	96(+)
8[f]	–	68	**4e**	87:13	96(+)

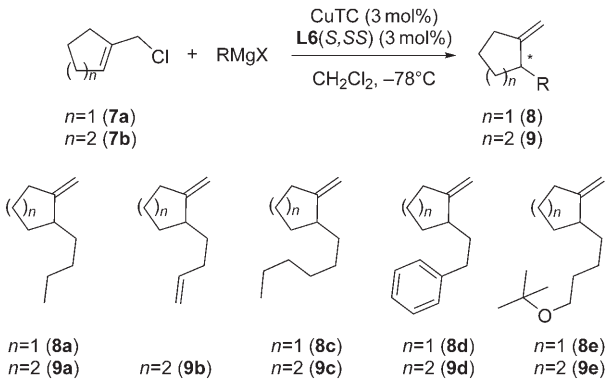
[a] Conditions: **1** (1 mmol), CuTC (3 mol%), and **L6** (3.3 mol%) in CH_2Cl_2 (2 mL) at −78 °C with addition of RMgBr in Et_2O (1.2 equiv) over 1 h. [b] Yields of isolated products of the mixture of regioisomers after purification by column chromatography on silica gel. [c] Ratio determined by GC–MS and ^{1}H NMR spectroscopy. [d] Enantiomeric excess determined by chiral GC. [e] Addition of RMgBr over 4 h. [f] After completion of the S_N2' reaction, addition of the Grubbs second-generation catalyst (6 mol%) at room temperature.

In addition, we proceeded by functionalizing the aryl moiety of the allylic substrate and varied the β substituent (Scheme 4). The enantioselectivities are within the excellent results obtained previously, between 92 and 96% *ee*. The *para*-chloro electron-withdrawing group (**5a**) does not influence the regioselective outcome of the allylic alkylation. However, the *para*-methyl substituent (**5b**) penalizes the reaction and the branched product **6b** is obtained with 84% selectivity.



Scheme 4. Enantioselective Cu-catalyzed allylic alkylation on **5a**–**c** with EtMgBr.

To confirm the efficiency of the copper-catalyzed procedure with the phosphoramidite ligand **L6**, we examined another very interesting class of β-disubstituted allylic substrates, the aliphatic endocyclic allylic chlorides **7a**,**b** (Scheme 5). Some years ago, Gais and co-workers reported the diastereoselective addition of various organocuprates and organocopper reagents to optically active endocyclic allylic sulfoximines, and they obtained S_N2' rearrangement products with low-to-high enantioselectivities (36–90% *ee*).[20] Other



Scheme 5. Formation of α-substituted chiral *exo*-methylenic cyclic compounds.

Table 3: Asymmetric CuTC-catalyzed allylic alkylation on endocyclic allylic chlorides **7a**,**b** with RMgX (Scheme 3; L* = **L2**–**L6**).

Entry	Substrate	*n*	R	L*	Conv. [%][a]	S_N2'/S_N2[b]	*ee* [%]
1	**7a**	1	**8a**	**L5**	>99	63:37	29 (*S*+)
2	**7a**	1	**8a**	**L6**	>99	96:4	98 (*S*+)
3	**7a**	1	**8c**	**L6**	>99 (44)	97:3	98 (*S*+)
4[c]	**7a**	1	**8c**	**L6**	>99 (91)	98:2	98 (*S*+)
5	**7a**	1	**8d**	**L6**	>99	97:3	98 (*R*+)
6	**7a**	1	**8e**	**L6**	96 (60)	98:2	98 (+)[d]
7	**7b**	2	**9a**	*ent*-**L2**	>99	70:30	88 (+)
8	**7b**	2	**9a**	*ent*-**L3**	75	44:56	10 (+)
9	**7b**	2	**9a**	**L6**	73	81:19	98 (+)
10	**7b**	2	**9b**	**L6**	>99 (83)	97:3	99.2 (+)
11	**7b**	2	**9c**	**L6**	>99 (67)	97:3	98 (+)
12	**7b**	2	**9d**	**L5**	>99	72:28	87 (*R*)
13	**7b**	2	**9d**	**L6**	>99 (78)	85:15	99.4 (*S*)
14	**7b**	2	**9e**	**L5**	94	73:27	74 (−)
15	**7b**	2	**9e**	**L6**	>99	91:9	98.8 (+)

[a] Conversion determined by GC–MS (in parentheses, yield of isolated products after purification by column chromatography on silica gel). [b] Ratio determined by ^{1}H NMR spectroscopy and GC–MS. [c] Reaction with 4 mmol of material; addition of RMgX over 4 h. [d] Determined by GC analysis of **8f** (R = $(CH_2)_4OCOCF_3$).

than these results, there are no accounts of copper-catalyzed asymmetric S_N2' alkylation with chiral external ligands on such allylic derivatives.

We were gratified to see that the addition of different Grignard reagents with 3 mol% of the copper catalyst proceeded highly selectively toward the γ substitution and delivered adducts **8** and **9** with excellent enantiomeric excess up to >99%. Here again, a small panel of phosphoramidite ligands were tested for their asymmetric induction of the allylic substitution, but it was clear from Table 3 that ligand **L6** (*S*,*SS*) once more was the most successful. As concerns the five-membered-ring substrate **7a**, constant *ee* values of 98% were obtained, independent of the organomagnesium reagent used (Table 3, entries 2–5). In the larger-scale synthesis of the chiral adduct **8c** (Table 3, entry 4) and allowing a slower addition time of the Grignard reagent (to prevent the reaction temperature from rising), we obtained excellent matching selectivities toward the γ product (98:2) and the enantiomeric excess (98%). The six-membered-ring allylic chloride **7b** afforded equally good *ee* values and γ selectivities according to the RMgX. The highest noteworthy enantioselectivity for such a reaction was recorded for the addition of 3-butenylmagnesium bromide on **7b** with 3 mol% CuTC/**L6** loading, to afford **9b** with 99.2% *ee* and a 97:3 branched-to-linear ratio (Table 3, entry 10). All the products obtained in this series are valuable starting materials for more elaborate chiral synthons. For example, the *n*-hexyl adduct (Table 3, entry 4) is a precursor for the formal asymmetric synthesis of lepadiformine.[21,22] Other useful transformations can be envisioned on the exocyclic double bond, such as oxidation to a ketone or selective epoxidation.

In conclusion, we have demonstrated that the asymmetric methodology developed previously by our group can be efficiently applied on more substituted allylic patterns with phosphoramidite ligand **L6** (*S*,*SS*) and a copper-catalyst loading as low as 3 mol%. Two different classes of β-disubstituted substrates, cinnamyl derivatives and aliphatic endocyclic allylic chlorides, afforded both excellent regio- and enantioselectivities. *Ee* values of up to 98 and >99%, respectively, were obtained in both applications.

Experimental Section

CuTC (3 mol%) and chiral ligand (3.3 mol%) were charged in a dried Schlenk tube under inert gas and suspended in CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 30 min, followed by addition of the allylic chloride (1 mmol) at room temperature before cooling the mixture to −78 °C in an ethanol–dry ice bath. The Grignard reagent (3 M in diethyl ether, 1.2 equiv) diluted in CH_2Cl_2 (0.6 mL) was added over 60 min with a syringe pump. Upon completion of the addition, the reaction mixture was left a further 4 h at −78 °C. The reaction was quenched by the addition of aqueous HCl (1 N, 2 mL) and then Et_2O (10 mL). The aqueous phase was separated and further extracted with Et_2O (3 × 3 mL). The combined organic fractions were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in a vacuum. The oily residue was purified by flash column chromatography. Gas chromatography on a chiral stationary phase showed the enantiomeric excess of the S_N2' product.

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[1] a) B. M. Trost, C. Lee in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), 2nd ed., Wiley, New York, **2000**, p. 593; b) A. Pfaltz, M. Lautens in *Comprehensive Asymmetric Catalysis I–III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, p. 833.

[2] For reviews of asymmetric allylic alkylation with various metals, see: a) H. Miyabe, Y. Takemoto, *Synlett* **2005**, 1641; b) B. M. Trost, *J. Org. Chem.* **2004**, *69*, 5813; c) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921; d) R. Takeuchi, *Synlett* **2002**, 1954.

[3] For recent reviews of asymmetric Cu-catalyzed allylic alkylation, see: a) A. Alexakis, C. Malan, L. Lea, K. Tissot-Croset, D. Polet, C. Falciola, *Chimia* **2006**, *60*, 124; b) H. Yorimitsu, K. Oshima, *Angew. Chem.* **2005**, *117*, 4509; *Angew. Chem. Int. Ed.* **2005**, *44*, 4435; c) A. Kar, N. P. Argade, *Synthesis* **2005**, 2995.

[4] a) M. Van Klaveren, E. S. M. Persson, A. del Villar, D. M. Grove, J. E. Bäckvall, G. van Koten, *Tetrahedron Lett.* **1995**, *36*, 3059; b) A. S. E. Karlstrom, F. F. Huerta, G. J. Meuzelaar, J. E. Bäckvall, *Synlett* **2001**, 923.

[5] a) F. Dübner, P. Knochel, *Angew. Chem.* **1999**, *111*, 391; *Angew. Chem. Int. Ed.* **1999**, *38*, 379; b) F. Dübner, P. Knochel, *Tetrahedron Lett.* **2000**, *41*, 9233.

[6] a) S. Tominaga, Y. Oi, T. Kato, D. K. An, S. Okamoto, *Tetrahedron Lett.* **2004**, *45*, 5585; b) S. Okamoto, S. Tominaga,

N. Saimo, K. Kase, K. Shomoda, *J. Organomet. Chem.* **2005**, *690*, 6001.
[7] F. Lopez, A. W. van Zijl, A. J. Minaard, B. L. Feringa, *Chem. Commun.* **2006**, 409.
[8] a) K. Tissot-Croset, D. Polet, S. Gille, C. Hawner, A. Alexakis, *Synthesis* **2004**, 2586; b) K. Tissot-Croset, D. Polet, A. Alexakis, *Angew. Chem.* **2004**, *116*, 2480; *Angew. Chem. Int. Ed.* **2004**, *43*, 2426; c) A. Alexakis, K. Croset, *Org. Lett.* **2002**, *4*, 4147; d) A. Alexakis, C. Malan, L. Lea, C. Benhaim, X. Fournioux, *Synlett* **2001**, 927.
[9] K. Tissot-Croset, A. Alexakis, *Tetrahedron Lett.* **2004**, *45*, 7375.
[10] a) H. Malda, A. W. van Zijl, L. A. Arnold, B. L. Feringa, *Org. Lett.* **2001**, *3*, 1169; b) A. W. Van Zijl, L. A. Arnold, A. J. Minnaard, B. L. Feringa, *Adv. Synth. Catal.* **2004**, *346*, 413.
[11] a) U. Piarulli, P. Daubos, C. Claverie, C. Monti, C. Gennari, *Eur. J. Org. Chem.* **2005**, 895; b) U. Piarulli, P. Daubos, C. Claverie, M. Roux, C. Gennari, *Angew. Chem.* **2003**, *115*, 244; *Angew. Chem. Int. Ed.* **2003**, *42*, 234; c) U. Piarulli, C. Claverie, P. Daubos, C. Gennari, A. J. Minnaard, B. L. Feringa, *Org. Lett.* **2003**, *5*, 4493; d) S. Ongeri, U. Piarulli, M. Roux, C. Monti, C. Gennari, *Helv. Chim. Acta* **2002**, *85*, 3388.
[12] With chiral Schiff base ligands: a) K. E. Murphy, A. H. Hoveyda, *Org. Lett.* **2005**, *7*, 1255; b) M. A. Kacprzynski, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 10676; c) C. A. Luchaco-Cullis, H. Mizutani, K. E. Murphy, A. H. Hoveyda, *Angew. Chem.* **2001**, *113*, 1504; *Angew. Chem. Int. Ed.* **2001**, *40*, 1456.
[13] With chiral NHC ligands: a) J. J. Van Veldhuizen, J. E. Campbell, R. E. Giudici, A. H. Hoveyda, *J. Am. Chem. Soc.* **2005**, *127*, 6877; b) A. O. Larsen, W. Leu, C. N. Oberhuber, J. E. Campbell, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 11130.
[14] a) C. Borner, P. J. Goldsmith, S. Woodward, J. Gimeno, S. Gladiali, D. Ramazzoti, *Chem. Commun.* **2000**, *24*, 2433; b) K. Biswas, C. Boerner, J. Gimeno, P. J. Goldsmith, D. Ramazzotti, A. L. K. So, S. Woodward, *Tetrahedron* **2005**, *61*, 1433; c) P. J. Goldsmith, S. J. Teat, S. Woodward, *Angew. Chem.* **2005**, *117*, 2275; *Angew. Chem. Int. Ed.* **2005**, *44*, 2235.
[15] A. Alexakis, S. Rosset, J. Allamand, S. March, F. Guillen, C. Benhaim, *Synlett* **2001**, 1375.
[16] B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos, A. H. M. De Vries, *Angew. Chem.* **1997**, *109*, 2733; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2620.
[17] The analogous *p*-OMe ligands were also tested and gave similar results to **L4** (52% *ee*), **L5** (26% *ee*), and **L6** (96% *ee*).
[18] J.-E. Bäckvall, M. Sellén, B. Grant, *J. Am. Chem. Soc.* **1990**, *112*, 6615.
[19] The Grubbs first-generation catalyst gave poor results.
[20] a) H.-J. Gais, H. Müller, J. Bund, M. Scommoda, J. Brandt, G. Raabe, *J. Am. Chem. Soc.* **1995**, *117*, 2453; b) J. Bund, H.-J. Gais, S. Erdelmeier, *J. Am. Chem. Soc.* **1991**, *113*, 1442.
[21] a) P. Schär, P. Renaud, *Org. Lett.* **2006**, *8*, 1569; b) E. Nyfeler, P. Renaud, *Abstracts of Papers, SCS Fall Meeting 2005*, EPFL, Lausanne, Switzerland, October 13, **2005**, ORGN-278; c) P. G. Reddy, S. Baskaran, *J. Org. Chem.* **2004**, *69*, 3093.
[22] For a short review on marine alkaloid synthesis, see: P. Schär, S. Cren, P. Renaud, *Chimia* **2006**, *60*, 131.

