Synthesis and Use of a Phosphoramidite Ligand for the Copper-Catalyzed Enantioselective Allylic Substitution. Tandem Allylic Substitution/Ring-Closing Metathesis

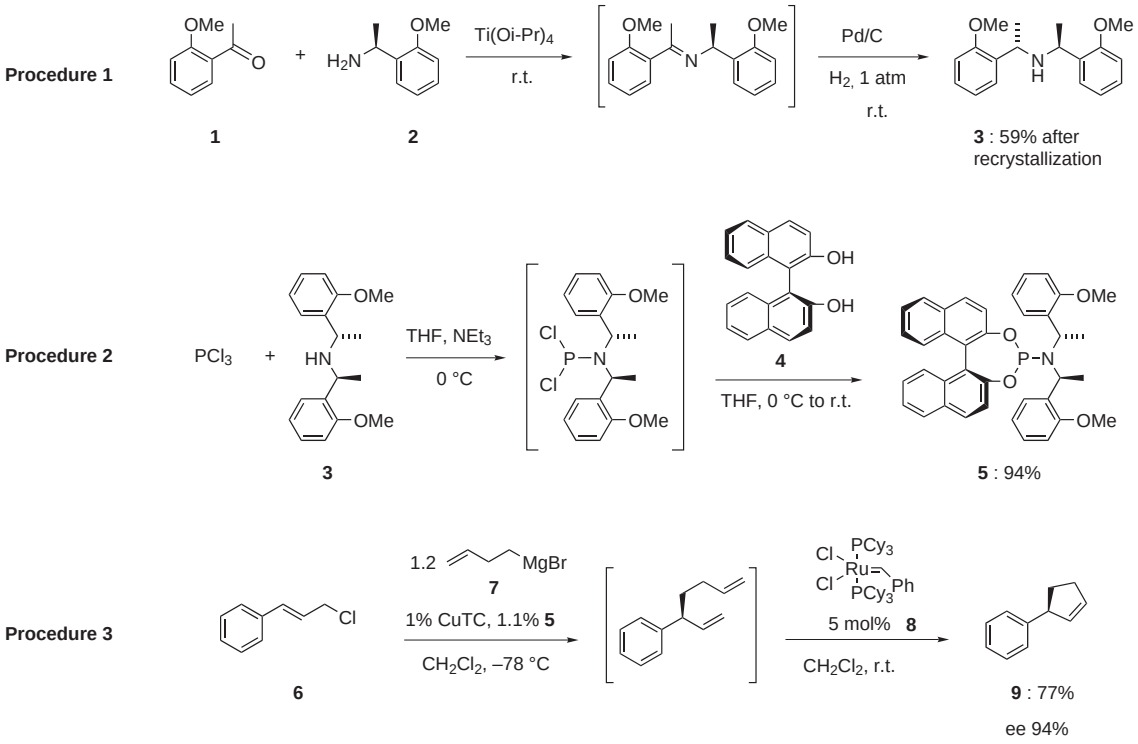
Karine Tissot-Croset, Damien Polet, Ségolène Gille, Christine Hawner, Alexandre Alexakis*

Department of Organic Chemistry, University of Geneva, 30 quai Ernest-Ansermet, 1211 Genève 4, Switzerland
Fax +41(22)3793215; E-mail: alexandre.alexakis@chiorg.unige.ch

Received 26 April 2004; revised 11 May 2004

Abstract: A new one-pot method of reductive amination is used to prepare a chiral *C2* symmetrical amine. This amine is used for the synthesis of a new chiral phosphoramidite ligand. The new ligand is, in turn, used to illustrate the enantioselective copper-catalyzed allylic substitution with Grignard reagents. When a remote double bond is located on the Grignard reagent, the newly formed alkene undergoes an in situ ruthenium-catalyzed ring-closing metathesis to afford the cyclized product in 77% yield and 94% ee.

Key words: allylic substitution, copper catalysis, ruthenium catalysis, enantioselectivity, Grignard reagents

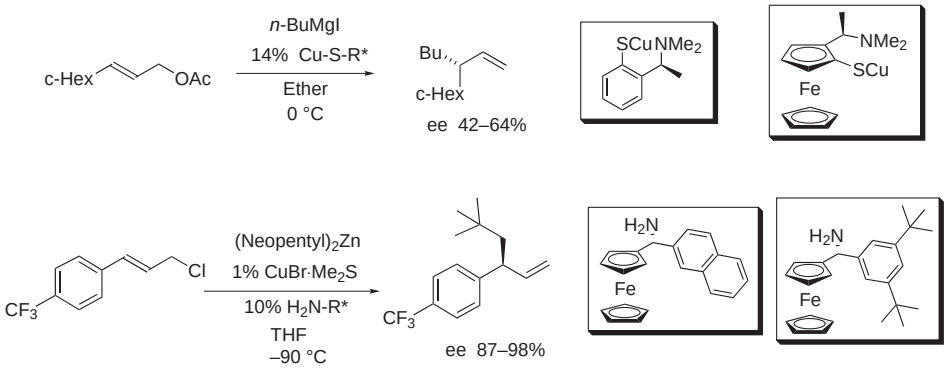


Scheme 1

Allylic substitution is a fundamental transformation in organic synthesis.[1] It is even more important in the field of asymmetric synthesis. The reaction usually involves a transition metal, in catalytic amount, and a chiral ligand, most often a phosphorus-based one.[2] Whereas most transition metals (Pd, Mo, Ir, etc.) allow the efficient introduction of soft nucleophiles such as malonates or amines, Cu allows the introduction of hard nucleophilic groups, such as alkyl groups.[3]

The copper-catalyzed allylic substitution has only recently been studied.[4] The first catalytic example reported by Bäckvall and van Koten in 1995[5a] with 42% ee was later improved to 64%.[5b] It involved an allylic substrate bearing an alkyl group and a Grignard reagent. This is a unique case where a Grignard reagent is used as primary source of organometallics. The next report, by Knochel in 1999,[6] dealt with diorganozincs as primary organometallics (Scheme 2). Following these pioneering reports, several others followed, all using diorganozincs.[7]

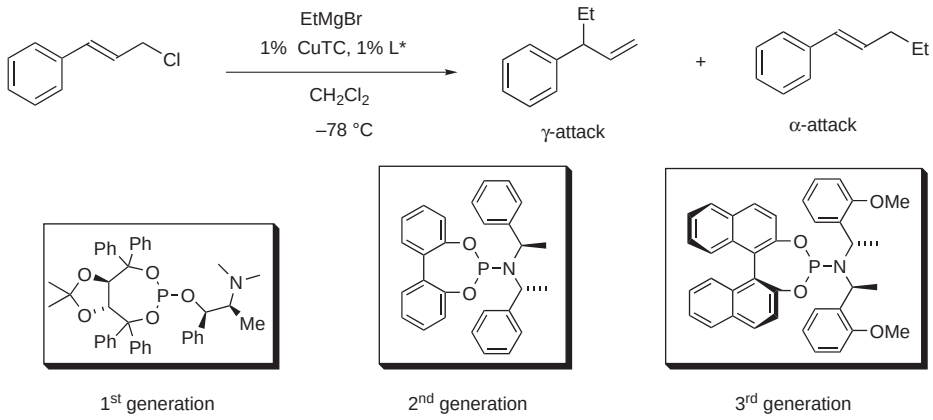
SYNTHESIS 2004, No. 15, pp 2586–2590
Advanced online publication: 30.07.2004
DOI: 10.1055/s-2004-829188; Art ID: Z08004SS



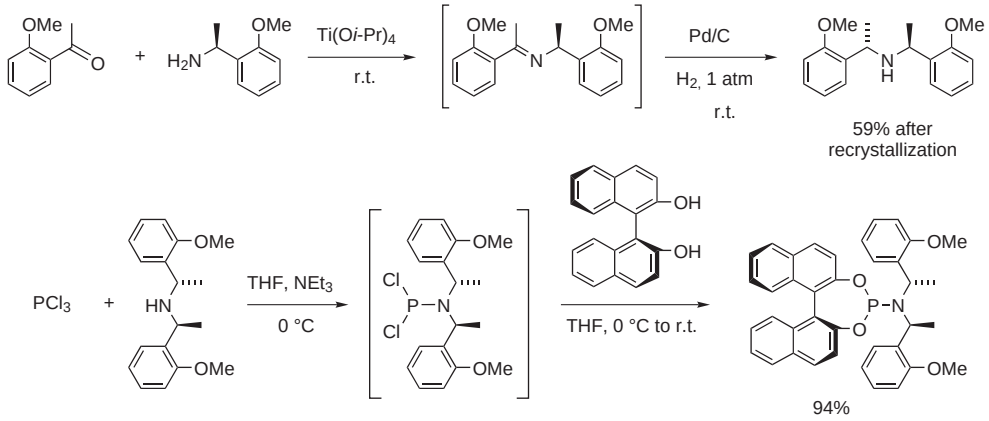
Scheme 2 Enantioselective allylic substitutions by Bäckvall and Knochel

Our work focused essentially on the use of Grignard reagents, and in 2001, we reported that EtMgBr reacts with cinnamyl chloride, in the presence of 1% CuCN and 1% of a chiral phosphite ligand, to afford the desired product with 73% ee and 94% γ-selectivity.[8a] A second generation phosphoramidite ligand allowed us, in 2002, to improve the ee to 86%.[8b] A last improvement (96% ee, 99% regioselectivity) was reached with our third generation ligand in 2004 (Scheme 3).[8c]

We report herein the detailed description of the synthesis of the 3rd generation ligand, along with one of the applications of this reaction: the tandem allylic substitution-ring closing metathesis. This ligand is composed of two parts, a chiral binaphthol of *S*-configuration, and a chiral *S,S*-amine. The chiral amine is, itself prepared by a new methodology of reductive amination, where the $Ti(O\textit{i}\text{-}Pr)_4$ promoted formation of the imine and the Pd-catalyzed reduction are run in a one-pot procedure, without any solvent (Scheme 4).[9]



Scheme 3 Enantioselective allylic substitution by Alexakis



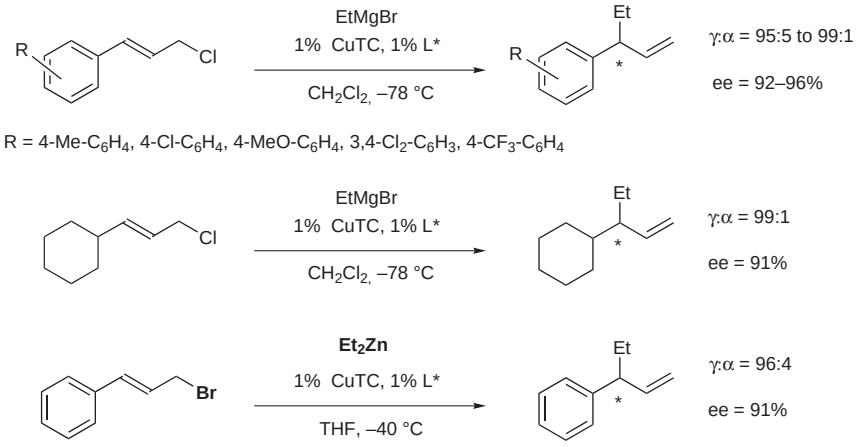
Scheme 4 Synthesis of the 3rd generation ligand

The formation of the ketimine is usually a tedious process (several days), when the dehydration is done in a Dean–Stark apparatus.[10] The alternative procedure with $TiCl_4$ and Et_3N is usually preferred because it is fast and quantitative. However, the formed $Et_3N{\cdot}HCl$ has to be removed by filtration before the reduction step.[11] In our new procedure $Ti(O\textit{i}\text{-}Pr)_4$ [or $Ti(OEt)_4$] replaces advantageously $TiCl_4$ and the homogeneous liquid mixture does not impede the further reduction step. In addition, the whole process may be run in the absence of any solvent.

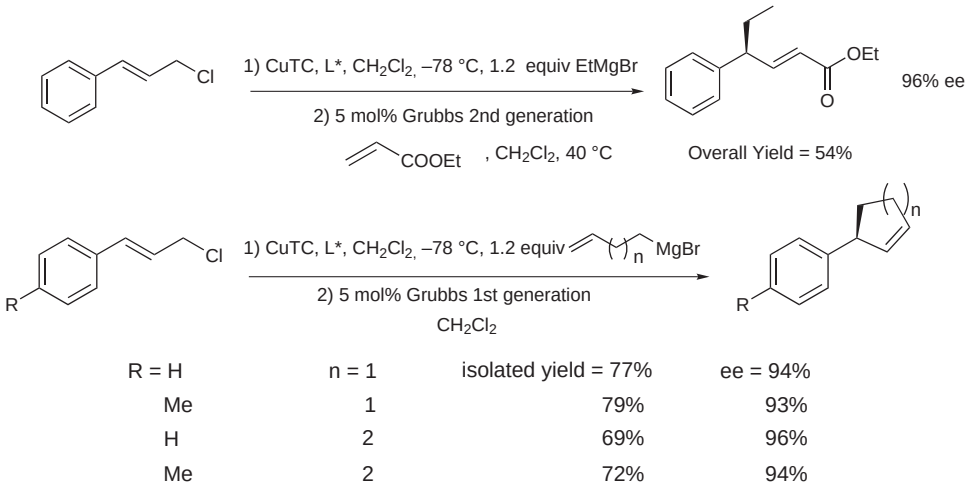
The new phosphoramidite ligand allows the introduction of Grignard reagents to a variety of cinnamyl-type allylic chlorides. The electron-withdrawing or -donating nature of the groups on the aromatic ring does not influence the enantioselectivity, which remains constantly above 92%.[8c] On the other hand, and in contrast to most other systems, this ligand is also efficient with allylic chlorides bearing an alkyl group, such as cyclohexyl.[8c] Finally, it should be noted that our third generation ligand is the only one to also allow diethyl zinc as a source of primary organometallics (Scheme 5).[8c]

Other Grignard reagents react with the same efficiency. Of particular interest are the reagents bearing a remote double bond. Indeed, the resulting olefin is amenable to further synthetic transformations, such as a metathesis reaction.[12] Both cross metathesis and ring-closing metathesis have been successfully performed without any loss of optical purity.[8b] From a practical point of view, it would be desirable to run both the allylic substitution and the metathesis in the same pot, provided the Ru catalyst is compatible with the excess of Grignard reagent and the presence of Cu salts and phosphoramidite ligand. This is indeed the case as illustrated in Scheme 6.[8c]

In conclusion, we have developed a new phosphoramidite ligand with highly improved efficiency in the copper catalyzed allylic substitution, which greatly enlarge the scope of the methodology. In addition, we coupled this reaction with the ring-closing metathesis in a one-pot practical procedure. The synthesis of the chiral ligand also exploits a new method for the reductive amination.



Scheme 5 Allylic substitutions with the 3rd generation ligand



R = H	n = 1	isolated yield = 77%	ee = 94%
Me	1	79%	93%
H	2	69%	96%
Me	2	72%	94%

Scheme 6 Tandem allylic substitution-metathesis

Procedures (Scheme 1)

^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were recorded on a Bruker AC-400 (400 MHz) spectrometer. Chemical shifts are quoted in ppm relative to tetramethylsilane (0 ppm) and referenced to the residual undeuterated solvent. Coupling constants (*J*) are given in Hertz (Hz). Optical rotations were measured at 20 °C in a 10 cm cell in the stated solvent; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} (concentration *c* given as g/100 mL). Enantiomeric excesses were determined by chiral SFC with the stated column. Retention times (R_t) are given in min. Flash chromatography were performed using silica gel 32–63 μm, 60 Å. PCl_3 was distilled under argon at ambient pressure and then degassed four times in vacuo at –78 °C to remove the residual HCl. Et_3N was freshly distilled on CaH_2. Anhyd THF and CH_2Cl_2 were distilled from sodium using benzophenone ketyl as indicator and CaH_2, respectively. Cinnamyl chloride (**6**) and 4-bromobut-1-ene were commercial products and used as received.

Bis[1-(2-methoxyphenyl)ethyl]amine (3)

A 250 mL, three-necked flask equipped with a vacuum/argon stopcock and a magnetic stirring bar was flame-dried. A static argon atmosphere was maintained in the reaction vessel. The flask was charged with (*S*)-1-(2-methoxyphenyl)ethylamine[13] (5.0 g, 33.09 mmol) and 2-methoxyacetophenone (5.0 g, 33.3 mmol). Then Ti(O*i*-Pr) (30 mL, 101.32 mmol) was added via syringe. The reaction mixture was stirred at r.t. over 20 min before adding 10% Pd/C (180 mg, 0.17 mmol). The reaction flask was purged five times with a light vacuum-argon sequence and five times with a light vacuum-hydrogen sequence. The reaction mixture was stirred under one atmosphere (balloon) of H_2 over 48 h, compensating from time to time the consumption of H_2 by refilling the balloon. The balloon of H_2 was removed, the flask was opened to air and cooled in an ice bath, 10% aq NaOH (55 mL) was added, causing the precipitation of titanium salts. This mixture was treated with EtOAc (50 mL), triturated and decanted. The organic phase was transferred into a 250 mL Erlenmeyer flask. This sequence was repeated three times. The combined organic phases were filtered on Celite. The Celite cake was rinsed with EtOAc (25 mL). The resulting clear filtrate was then dried over 60 g of anhyd Na_2SO_4, filtered, transferred to a 250 mL flask and concentrated on a rotary evaporator yielding 9.5–9.8 g of a mixture of **3** as a 82:18 mixture of (*S*,*S*)- and *meso*- isomers as a viscous colorless oil, which gradually solidified. Under an efficient hood, the solid was suspended in EtOAc (40 mL) and an aq 65% HBr (2. 5 mL) was added dropwise, causing the precipitation of a white solid, which was directly recrystallized from a mixture of 75:27 EtOAc–EtOH (102 mL) at r.t. affording the hydrobromide salt of **3** as colorless crystals; yield: 4.77–5.18 g (40–43%). Recrystallization of the residue from the filtrate from a mixture of 75:27 EtOAc–EtOH (67 mL) gave a second crop; yield: 1.89–2.32 (16–19%); total yield: 7.07–7.09 g (59%). The hydrobromide salt of **3** was neutralized with aq 10% NaOH and extracted with CH_2Cl_2. The ratio of (*S*,*S*)-/*meso*-isomers >99.5:0.5 was determined by GC/MS analysis; $[\alpha]_D^{22}$ –92 (*c* = 0.98, $CHCl_3$).

IR ($CHCl_3$): 2955, 2924, 1597, 1584, 1485, 1451, 1436, 1229, 1095, 1083, 1025 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 7.04 Hz, 2 H), 7.22 (t, *J* = 7.04 Hz, 2 H), 6.96 (t, *J* = 7.32 Hz, 2 H), 6.85 (d, *J* = 8.08 Hz, 2 H), 3.89 (q, *J* = 6.56 Hz, 2 H), 3.73 (s, 6 H), 2.12 (br, 1 H), 1.30 (d, *J* = 6.84 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.2, 133.7, 127.3, 127.1, 120.4, 110.3, 54.9, 50.1, 22.9.

***O*,*O*′-[(*S*)-1,1′-Dinaphthyl-2,2′-diyl]-*N*,*N*′-bis[(*S*,*S*)-1-(2-methoxyphenyl)ethyl]phosphoramidite (5)**

A 250 mL, two-necked flask, equipped with vacuum/argon stopcock and a magnetic stirring bar was flame-dried. A static argon atmosphere was maintained in the reaction flask. The flask was charged with anhyd THF (40 mL) and freshly distilled Et_3N (9 mL, 64.6 mmol). The reaction mixture was cooled to 0 °C and PCl_3 (0.9 mL, 10.5 mmol) was added dropwise to the solution. A flame-dried, 25 mL flask was charged with **3** (3 g, 10.5 mmol) and THF (12 mL). This solution was added dropwise to the reaction mixture kept at 0 °C, and THF (3 mL) was used to rinse the flask containing **3**. After the addition was complete, the ice bath was removed and the mixture was stirred at r.t. for 4 h. In the meantime, a flame-dried 50 mL flask was charged with (*S*)-binaphthol (**4**; 3.02 g, 10.5 mmol) and THF (25 mL). The resulting solution was added slowly over 2 min to the reaction mixture containing **3** and PCl_3 at 0 °C and THF (3 mL) was used to rinse the flask containing **4**. The mixture was stirred at r.t. overnight, filtered over Celite, the filter cake was washed with Et_2O and the organic phase was concentrated in vacuo. The product was purified by column chromatography (150 g silica gel, eluent: Et_2O; R_f 0.78). The solvent was evaporated in vacuo to afford 5.89 g of **5** as a white foam (94% yield, 95% purity according to ^{31}P NMR); $[\alpha]_D^{22}$ +144.3 (*c* = 1.1, $CHCl_3$).

IR ($CHCl_3$): 3010, 1594, 1492, 1463, 1328, 1237, 1209, 1099, 1070, 947 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04–6.52 (m, 20 H), 4.99 (dq, J_1 = 1.24 Hz, J_2 = 7.08 Hz, 2 H), 3.58 (s, 6 H), 1.55 (d, *J* = 7.08 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 149.9, 132.8, 132.5, 131.4, 130.3, 129.2, 128.3, 128.0, 127.7, 127.6, 127.4, 127.3, 125.9, 125.6, 124.7, 124.5, 124.2, 122.7, 1212.5, 119.6, 109.2, 54.6, 50.3, 50.2, 22.6, 22.5.

^{31}P NMR (162 MHz, $CDCl_3$): δ = 152.25.

Butenyl Grignard 7

To a suspension of Mg (2.52 g, 111 mmol) in anhyd Et_2O (10 mL) under N_2 at r.t. was added a single crystal of I_2. A solution of 4-bromobut-1-ene (10 g, 74 mmol) in anhyd Et_2O (5 mL) was then added dropwise. After completion of the addition, the reaction mixture was stirred at r.t. for 2 h. The concentration of the Grignard reagent was estimated to be 2.8 M by titration.[14]

(–)-(3*S*)-Phenylcyclopentene (9)[15]

A flame-dried 50 mL three-necked flask equipped with a magnetic stirring bar and a thermometer was charged with copper thiophene-2-carboxylate[16] (CuTC; 0.019 mg, 0. 1 mmol) and **5** (0.066 g, 0.11 mmol) under argon. Anhyd CH_2Cl_2 (20 mL) was added and the mixture was allowed to stir at r.t. over 20 min. To the mixture was added cinnamyl chloride (1.52 g, 10 mmol). The mixture was stirred at r.t. for 5 min, then kept in an EtOH bath thermostated at –80 °C until the internal temperature reached –75 °C. In the meantime, a flame-dried 25 mL, two-necked flask was charged with anhyd CH_2Cl_2 (5.7 mL) and the Grignard reagent prepared as above (4.3 mL, 12 mmol, 2.8 M in Et_2O) and stirred over 2 min at r.t. under argon. The Grignard solution was then added to the above mixture over exactly 4 h with a syringe pump, maintaining the needle immersed in the reaction mixture. After the completion of addition, the reaction mixture was stirred at the same temperature during one extra hour, then the thermostated bath was removed, allowing the reaction flask to warm up to r.t. Grubbs 1st generation catalyst (0.5 mmoL, 0.142 g) was added as a solid and the mixture was stirred at r.t. for 3 h. Aq 1 N HCl (20 mL) was added, the two layers were separated and the aqueous phase was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo. Kugelrohr distillation (60 ° C/1 mm Hg) afforded 1.11 g of **9** (77%) with a GC-purity of 99% and an enantiomeric excess of 94% of the *S*-enantiomer; $[\alpha]_D^{22}$ –166.9 (*c* = 1.05, $CHCl_3$) for 94% ee. Ee was measured by chiral SFC with a chiralcel OJ column (1% MeOH, flow rate 2 mL/min, 200 bar, 30 °C); R_t: 3.66 (*S*), 4.01 (*R*).

IR ($CHCl_3$): 3060, 3011, 2944, 2855, 1601, 1491, 1453, 1214, 1011, 914 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.19 (m, 5 H), 5.96 (m, 1 H), 5.80 (m, 1 H) 3.90 (m, 1 H), 2.52–2.40 (m, 3 H), 1.74 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.6, 134.3, 131.9, 128.4, 127.2, 126.0, 51.3, 33.8, 32.5.

Acknowledgment

The authors thank Stephane Rosset and Caroline Falciola for help, the BASF company for generous gift of chiral amines, Frontier Scientific Ltd for CuTC, the Swiss National Research Foundation No 20-068095.02 and COST action D24/0003/01 (OFES contract Nr. C02.0027) for financial support.

References

(1) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901.
(2) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.
(3) (a) Posner, G. H. *Org. React.* **1975**, *22*, 253. (b) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.
(4) Karlström, A. S. E.; Bäckvall, J.-E. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, **2001**, 259–288.
(5) (a) van Klaveren, M.; Persson, E. S. M.; del Villar, A.; Grove, D. M.; Bäckvall, J.-E.; van Koten, G. *Tetrahedron Lett.* **1995**, *36*, 3059. (b) Karlstrom, A. S. E.; Huerta, F. F.; Meuzelaar, G. J.; Bäckvall, J.-E. *Synlett* **2001**, 923.
(6) (a) Dubner, F.; Knochel, P. *Angew. Chem. Int. Ed.* **1999**, *38*, 379. (b) Dubner, F.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 9233.
(7) (a) Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2001**, *40*, 1456. (b) Malda, H.; van Zijl, A. W.; Arnold, L. A.; Feringa, B. L. *Org. Lett.* **2001**, *3*, 1169. (c) Ongeri, S.; Piarulli, U.; Roux, M.; Monti, C.; Gennari, C. *Helv. Chim. Acta* **2002**, *85*, 3388. (d) Piarulli, U.; Daubos, P.; Claverie, C.; Roux, M.; Gennari, C. *Angew. Chem. Int. Ed.* **2003**, *42*, 234. (e) Murphy, K. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4690. (f) Piarulli, P.; Claverie, C.; Daubos, P.; Gennari, C.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 4493. (g) Shi, W.-J.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2003**, *14*, 3867. (h) van Zijl, A. W.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Adv. Synth. Catal.* **2004**, *346*, 413.
(8) (a) Alexakis, A.; Malan, C.; Lea, L.; Benhaim, C.; Fournioux, X. *Synlett* **2001**, 927. (b) Alexakis, A.; Croset, K. *Org. Lett.* **2002**, *4*, 4147. (c) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2426.
(9) Alexakis, A.; Gille, S.; Prian, F.; Rosset, S.; Ditrich, K. *Tetrahedron Lett.* **2004**, *45*, 1449.
(10) Overberger, C. G.; Marullo, N. P.; Hiskey, R. G. *J. Am. Chem. Soc.* **1961**, *83*, 1374.
(11) Storace, L.; Anzalone, L.; Confalone, P.; Davis, W. P.; Fortynak, J. M.; Giangiordano, M.; Haley, J. J. Jr.; Kambolz, K.; Li, H.-Y.; Ma, P.; Nugent, W. A.; Parsons, R. L. Jr.; Sheeran, P. J.; Silverman, C. E.; Waltermire, R. E.; Wood, C. C. *Org. Process Res. Dev.* **2002**, *6*, 54.
(12) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.
(13) (a) Saudan, L. A.; Bernardinelli, G.; Kundig, E. P. *Synlett* **2000**, 483. (b) This compound is available from BASF AG on the following website: http://www.basf.de/en/produkte/chemikalien/interm/.
(14) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.
(15) Gilbertson, S. R.; Fu, Z. *Org. Lett.* **2001**, *3*, 161.
(16) CuTC can either be purchased from Frontier Scientific Ltd or prepared according to the literature procedure: Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.