Notes

Enantioselective Conjugate Addition of Grignard Reagents to Enones Catalyzed by Chiral Cuprate Complexes†

Kwang-Hyun Ahn, R. Bryan Klassen, and Stephen J. Lippard*

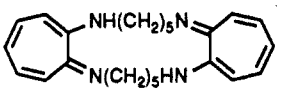
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received July 2, 1990

Summary: The enantioselective conjugate addition of Grignard reagents to enones catalyzed by copper(I) complexes with bidentate chiral auxiliary ligands, *N,N'*-dialkyl-substituted aminotropone iminates, **2** and **3**, has been studied. The enantioselectivity of the reaction was significantly increased by addition of HMPA and silyl reagents. In the reaction of *n*-BuMgCl and 2-cyclohexen-1-one, Cu(R-CHIRAMT) (0.05 mol per mol equiv of 2-cyclohexen-1-one) prepared in situ catalyzed the conjugate addition to give (*S*)-3-butylcyclohexanone with 20% enantiomeric excess (ee). In the presence of HMPA and a bulky silyl reagent, $Ph_2(t\text{-Bu})SiCl$, however, the reaction afforded (*S*)-3-butylcyclohexanone with a 74% ee. Under stoichiometric conditions, the product was obtained in 78% ee. Limitations on the scope of the enantioselectivity afforded by the Cu(R-CHIRAMT) catalyst were revealed by studies with a variety of Grignard reagent and enones. In these cases, however, the regioselectivity of the catalyst remained high. In the conjugate addition of vinylmagnesium bromide to (*S*)-4-[dimethyl(1',1'-dimethylethyl)siloxy]-2-cyclopentenone, **4**, Cu(S-CHIRAMT) catalyzed the reaction 5.6 times faster than Cu(R-CHIRAMT), indicating that these chiral catalysts might be useful for the kinetic resolution of racemic mixtures of **4**, an important precursor in prostaglandin synthesis.

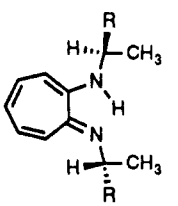
Introduction

The conjugate addition of organocuprates to α,β-unsaturated carbonyl compounds is one of the most valuable carbon–carbon bond-forming reactions.[1] Rapid progress has been made recently in this field by modifying the organocopper reagents with nontransferable ligands.[2] In some cases, the enantioselective conjugate addition of organocuprates has been achieved by addition of chiral ligands to the copper reagent.[3] Since limited structural information is available for organic cuprates,[2g,4] however, the rational synthesis of new reagents for asymmetric induction is a relatively underdeveloped area.[3b,5] Furthermore, most studies have employed stoichiometric conditions, which require large quantities of the chiral ligand. Recently, our laboratory discovered that well-characterized binuclear copper(I) complexes of the dinucleating tropocoronand macrocycle[6] (1) catalyze the conjugate addition



H_2-1

of Grignard reagents to 2-cyclohexen-1-one.[7] Interestingly, when a chiral aminotropone imine, H(R-CHIRAMT) (H-2),[7,8] was employed as the ligand, the 1,4-addition product was obtained in 14% enantiomeric excess (ee).[9]



R = phenyl (H-2; H(R-CHIRAMT))
= 1'-naphthyl (H-3; H(R-NEAT))

Because of its important catalytic nature,[10] we have extended our work to improve the enantioselectivity of the

† Dedicated to the memory of Professor John K. Stille.

(1) (a) Lipshutz, B. H., Ed. Recent Developments in Organocopper Chemistry. *Tetrahedron* **1989**, *45* (2). (b) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005. (c) Normant, J. F. *Pure Appl. Chem.* **1978**, *50*, 709. (d) Posner, G. H. *Org. React.* **1972**, *19*, 1.

(2) (a) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210. (b) Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 7788. (c) Bertz, S. H.; Dabbagh, G. *J. Chem. Soc., Chem. Commun.* **1982**, 1030. (d) Bertz, S. H.; Dabbagh, G. *J. Org. Chem.* **1984**, *49*, 1119. (e) Bertz, S. H.; Dabbagh, G.; Villacorta, G. M. *J. Am. Chem. Soc.* **1982**, *104*, 5824. (f) Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985**, *285*, 437. (g) Martin, S. F.; Fishpaugh, J. R.; Power, J. M.; Giolando, D. M.; Jones, R. A.; Nunn, C. M.; Cowley, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 7226. (h) Majid, T. N.; Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 5069.

(3) (a) Dieter, R. K.; Tokles, M. *J. Am. Chem. Soc.* **1987**, *109*, 2040. (b) Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 7114. (c) Bertz, S. H.; Dabbagh, G.; Sundararajan, G. *J. Org. Chem.* **1986**, *51*, 4953. (d) Leyendecker, F.; Laucher, D. *Tetrahedron Lett.* **1983**, *24*, 3517. (e) Imamoto, T.; Mukaiyama, T. *Chem. Lett.* **1980**, 45. (f) Tomioka, K.; Koga, K. *Asym. Synth.* **1983**, *2*, 201. (g) Yamamoto, K.; Kanoh, M.; Yamamoto, N.; Tsuji, J. *Tetrahedron Lett.* **1987**, *28*, 6347.

(4) (a) Hope, H.; Olmstead, M. M.; Power, P. P.; Sandell, J.; Xu, X. *J. Am. Chem. Soc.* **1985**, *107*, 4337. (b) van Koten, G.; Jastrzebski, J. T. B. H. *Tetrahedron* **1989**, *45*, 569 and references cited therein. (c) Dempsey, D. F.; Girolami, G. S. *Organometallics* **1988**, *7*, 1208 and references cited therein.

(5) Asymmetric induction by conjugate addition of organocuprate to enoates containing chiral auxiliary ligands has been widely studied: Oppolzer, W.; Kingma, A. J.; Poli, G. *Tetrahedron* **1989**, *45*, 479 and referenced cited therein.

(6) Villacorta, G. M.; Lippard, S. J. *Pure Appl. Chem.* **1986**, *58*, 1477.

(7) Villacorta, G. M.; Rao, C. P.; Lippard, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 3175.

(8) Brunner, H.; Knott, A.; Benn, R.; Rufinska, A. *J. Organomet. Chem.* **1985**, *295*, 211.

(9) Enantioselective conjugate addition of Grignard reagents to α,β-enones catalyzed by diamine–Zn(II) complexes has been reported with slight enantiomeric excess: Jansen, J. F. G. A.; Feringa, B. L. *J. Chem. Soc., Chem. Commun.* **1989**, 741.

(10) There are reports regarding enantioselective conjugate addition of dialkylzinc to enone catalyzed by nickel complexes: (a) Soai, K.; Hayasaka, T.; Ugajin, S. *J. Chem. Soc., Chem. Commun.* **1989**, 516. (b) Soai, K.; Yokoyama, S.; Hayasaka, T.; Ebihara, K. *J. Org. Chem.* **1988**, *53*, 4148.

0276-7333/90/2309-3178$02.50/0

reaction. In applications of organocuprates to conjugate addition, additives have become increasingly important because of their ability to improve the regio- and stereoselectivity of the reaction while still remaining compatible with the cuprate reagents.[11-14] In particular, addition of hexamethylphosphoramide (HMPA) and trimethylsilyl chloride (TMSCl) accelerate the conjugate addition of Grignard reagents catalyzed by copper salts, greatly improving both selectivity toward 1,4-addition and the yield.[14] Accordingly, we decided to employ HMPA and silyl reagents in our system. As described here, the enantioselectivity of the catalytic conjugate addition of *n*-butylmagnesium bromide to 2-cyclohexen-1-one was significantly improved. We have also extended the chemistry to a reaction employed for kinetic resolution in prostaglandin precursor syntheses and have synthesized and investigated the cuprate chemistry of a new ligand, H(R-NEAT) (3). Finally, the catalytic reactivity and enantioselectivity of our cuprates in reactions with a variety of enones and Grignard reagents have been surveyed.

Experimental Section

Reagents and Instrumentation. H(R-CHIRAMT) was prepared as described previously.[7] Tropolone was purchased from either Lancaster Synthesis or Aldrich Chemical Company. Lithium and Grignard reagents were used as received from Aldrich. 2-Cyclohexen-1-one, (*R*)- and (*S*)-α-methylbenzylamine, (*R*)-1-(1′-naphthyl)ethylamine, and CuBr·Me_2S were obtained from Aldrich. (*R,R*)-2,3-Butanediol was purchased from either Lancaster or Aldrich. ^1H and ^{13}C NMR spectra were obtained by using a Bruker 250 or Varian XL-300 instrument. High-resolution mass spectra were obtained on a Finnigan MAT System 8200, double-focusing, magnetic sector instrument. Gas chromatographic analyses were performed by using a Hewlett-Packard (HP) Model 5890 gas chromatograph, equipped with a flame ionization detector (FID) and an HP-3393A integrator. An HP-1 methylsilicone gum 0.53-mm × 10-m fused silica column was used for separations.

Synthesis of 1-[(*R*)-1′-(1″-Naphthyl)ethylamino]-7-[(*R*)-1′-(1″-naphthyl)ethylimino]-1,3,5-cycloheptatriene, H(R-NEAT) (3). H(R-NEAT) was obtained by the procedure used to prepare H(R-CHIRAMT).[7] The intermediate 2-[1′-(1″-naphthyl)ethylamino]tropone was isolated in 62% yield; mp 150–151 °C. $[\alpha]^{23}_D$ ($CHCl_3$) = −849° ($c = 11.3 \times 10^{-4}$ g/mL). ^1H NMR ($CDCl_3$, 300 MHz): δ 8.12 (ABM*X*, *J* = 7.8, 1.0, 0.9 Hz, H_{15}), 7.93 (AB*MX*, *J* = 7.8, 1.0 Hz, H_{12}), 7.78 (AB*X*, *J* = 8.6, 1.0 Hz, H_{11}), 7.59 (A*B*MX, *J* = 7.8, 6.3 Hz, H_{14}), 7.54 (ABMX, *J* = 7.8, 6.3, 0.9 Hz, H_{13}), 7.40 (A*B*X, *J* = 7.6, 1.0 Hz, H_9), 7.38 (A*B*X, *J* = 8.6, 7.6 Hz, H_{10}), 7.25–7.24 (H_2 and H_3), 6.92 (*J* = 10.8, 10.5 Hz, H_5), 6.58 (*J* = 10.8, 9.8, 3.2, 3.1 Hz, H_4), 6.20 (*J* = 10.5, 3.2 Hz, H_6), 5.44 (quintet, *J* = 6.6 Hz, H_7), 1.81 (*J* = 6.6 Hz, CH_3).

H(R-NEAT) was isolated in 24% yield; mp 85–90 °C. $[\alpha]^{23}_D$ ($CHCl_3$) = −1060° ($c = 8.3 \times 10^{-4}$ g/mL). ^1H NMR ($CDCl_3$, 300 MHz): δ 8.29 (ABM*X*, *J* = 8.6, 0.8 Hz, H_{13}), 7.90 (AB*MX*, *J* = 8.6, 1.0 Hz, H_{10}), 7.75 (AB*X*, *J* = 8.8, 0.5 Hz, H_9), 7.58 (A*B*X, *J* = 6.9, 0.5 Hz, H_7), 7.55 (A*B*MX, *J* = 8.6, 7.1, 1.0 Hz, H_{12}), 7.51 (ABMX, *J* = 8.6, 7.1, 0.8 Hz, H_{11}), 7.43 (A*B*X, *J* = 8.8, 6.9 Hz, H_8), 6.52 (*J* = 10.8, 9.5 Hz, H_3), 6.12 (*J* = 10.8 Hz, H_2), 6.01 (*J* = 9.5 Hz, H_4), 5.50 (q, *J* = 6.6 Hz, H_5), 1.81 (d, *J* = 6.6 Hz, H_6). Exact mass calcd for $C_{31}H_{28}N_2$: 428.225 25. Found: 428.225 25 ± 0.001 25.

Catalytic Conjugate Addition of Grignard Reagents to 2-Cyclohexen-1-one with Chiral Copper(I) Aminotropone Iminates. The following is a typical experimental procedure used for the catalytic reaction. It differs slightly from that reported previously[7] and leads to consistently higher yields. A THF (5-mL) suspension of CuBr·Me_2S (5.35×10^{-5} mol) was treated at −78 °C with a slight excess of Li(R-NEAT) in THF (5 mL) prepared from H(R-NEAT) (5.55×10^{-5} mol) and *n*-BuLi (1 equiv) under an argon atmosphere. The yellow slurry was stirred with gradual warming until a homogeneous burgundy solution was obtained. The solution was filtered through glass wool under argon and cooled to −78 °C. HMPA (2.76 mmol) was added to the solution, which was stirred for approximately 5 min until the HMPA dissolved. A stock solution of Grignard reagent was prepared by diluting commercially available solutions to 0.36 M. A second stock solution was prepared by dissolving 2-cyclohexen-1-one (1.45 mmol) and Ph_2(*t*-Bu)SiCl (2.77 mmol) in 5 mL of THF. Two 5-mL syringes were filled, one with Grignard reagent and the other with the enone/silyl chloride solution. The reagents were then added dropwise at equal rates for 30 min. The resulting reaction mixture was stirred for an additional 5 min at −78 °C and then quenched with a saturated NH_4Cl solution (10 mL). The mixture was diluted with ether (30 mL) and transferred to a 250-mL separatory funnel. The organic layer was washed with water four times (20-mL each), dried (K_2CO_3), and concentrated in vacuo. The residue was chromatographed on alumina (activity III). Elution with *n*-hexane/ethyl ether (10:1) gave the yellow ligand. Elution with *n*-hexane/ethyl ether (5:1) afforded (*S*)-3-butylcyclohexanone (118 mg, 53%). The optical purity (ee) of the product, determined by ^{13}C NMR measurements of the ketal derivative[15] prepared from (*R*)-(−)-2,3-butanediol, was 74%.

Conjugation Addition Reaction under Stoichiometric Conditions. A solution of Li(R-CHIRAMT) in 5 mL of THF, prepared from H(R-CHIRAMT) (331.7 mg, 1.01 mmol) and $LiN(SiMe_3)_2$ (1 mmol) in a 25-mL round-bottomed flask, was added dropwise to a mixture of CuBr·Me_2S (200.2 mg, 0.97 mmol) in 5 mL of THF at −78 °C under argon. Another 5 mL of THF, used to wash the flask, was added to the CuBr·Me_2S solution, which was then warmed slowly to room temperature, during which time the color changed from yellow to dark red. The solution was filtered through glass wool and cooled again to −78 °C. After addition of HMPA (0.35 mL, 2.01 mmol) and Ph_2(*t*-Bu)SiCl (0.522 mL, 2.01 mmol), the solution was stirred for 5 min. Then neat 2-cyclohexen-1-one (0.097 mL, 1 mmol) and *n*-BuMgCl (1.5 mL, 3 mmol) were added dropwise and simultaneously. After 30 min at −78 °C, water (10 mL) was added to quench the reaction. The mixture was warmed to room temperature, and hexane (20 mL) was added to extract the product. The organic layer was separated and washed twice with water to remove HMPA and then with 0.5 N HCl (10 mL). The color of the acid layer was yellow, indicating extraction of the ligand. The acid layer was neutralized with 10% K_2CO_3 solution, and the ligand, H(R-CHIRAMT), was extracted with methylene chloride (292.0 mg, 88%). The organic layer was separated, washed twice with water and dried with K_2CO_3. After the solvent was evaporated, the residue was chromatographed on alumina (activity III) using a mixture of hexane and ethyl ether (5:1) as eluant. The amount of the product recovered was 148.9 mg (98%). The enantiomeric excess, determined by the ^{13}C NMR spectrum of the ketal derivative prepared from (*R*)-(−)-2,3-butanediol, was 78% [*S* configuration at C(3)].

Conjugate Addition of Vinylmagnesium Bromide to (*R*)-4-(*tert*-Butyldimethylsiloxy)-2-cyclopentenone (4) Catalyzed by Cu(R-CHIRAMT) and Cu(S-CHIRAMT). To a solution of Cu(R-CHIRAMT) in THF, prepared according to the general procedure from CuBr·Me_2S (8.0 mg, 3.89×10^{-5} mol), H(R-CHIRAMT) (13.3 mg, 4.05×10^{-5} mol), and $LiN(SiMe_3)_2$ (4.2×10^{-5} mol), was added HMPA (0.1 mL, 5.75×10^{-4} mol) at −78 °C. The solution was stirred for 5 min. Solutions of vinyl magnesium bromide (3×10^{-4} mol) in THF and (*R*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-cyclopentenone[16] (1.96×10^{-4} mol) and

(11) (a) Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 947. (b) Lipshutz, B. H.; Ellsworth, E. L.; Siahaan, T. *J. Am. Chem. Soc.* **1988**, *110*, 4834.

(12) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019. (b) Johnson, C. R.; Marren, T. J. *Tetrahedron Lett.* **1987**, *28*, 27. (c) Bergdahl, M.; Lindstedt, E.-L.; Nilsson, M.; Olsson, T. *Tetrahedron* **1988**, *44*, 2055.

(13) Suzuki, M.; Suzuki, T.; Kawagishi, T.; Morita, Y.; Noyori, R. *Isr. J. Chem.* **1984**, *24*, 118.

(14) (a) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025. (b) Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029. (c) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349. (d) Horiguchi, Y.; Komatsu, M.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 7087 and references cited therein.

(15) (a) Hiemstra, H.; Wynberg, T. *Tetrahedron Lett.* **1977**, *25*, 2183. (b) Posner, G. H.; Frye, L. L. *Isr. J. Chem.* **1984**, *24*, 88.

(t-Bu)$_2$MeSiOTf (0.15 mL) in THF (5 mL) were added dropwise over 25 min. After the mixture was stirred for 30 min at −78 °C, water (10 mL) was added to quench the reaction. The solution was warmed to room temperature. Hexane (20 mL) was added to extract the organic compounds. The organic layer was washed twice with water and dried (K_2CO_3). GC analysis of the product indicated that (*R*)-4-[(*tert*-butyldimethylsilyl)oxy]-(*S*)-3-vinylcyclopentanone (**5**) was produced in 9% yield. When H(S-CHIRAMT) was substituted for H(R-CHIRAMT) in the reaction, the product was obtained in 50% yield, based on GC analysis. The product was separated with silica gel using a mixture of hexane and ethyl ether (5:1). When the reaction was allowed to proceed under identical conditions to higher levels of conversion, isolated yields of 62% and 93%, respectively, were obtained. IR (neat): 1743 cm^{-1} ($\nu_{C=O}$). ^{1}H NMR ($CDCl_3$): δ 5.87–5.73 (1 H, m), 5.12 (1 H, s), 5.08–5.05 (1 H, m), 4.12 (1 H, quintet, J = 6.17 Hz), 2.79 (1 H, quintet, J = 6.91 Hz), 2.61–2.46 (2 H, m), 2.13 (2 H, double triplet, J = 6.64, 18.8 Hz), 0.86 (9 H, s), 0.05 (3 H, s), 0.03 (3 H, s). GC–MS: m/e 225 ($M^+ - CH_3$), 183 ($M^+ - t$-Bu, 100%).

Reaction of *n*-BuMgCl with 2-Cyclohexen-1-one in the Presence of HMPA and TMSCl without Copper. A solution of 2-cyclohexen-1-one (0.1 mmol), HMPA (0.2 mmol), and TMSCl (0.2 mmol) in 10 mL of THF was stirred for 10 min at −78 °C under an argon atmosphere. Then *n*-BuMgCl (0.1 mmol) was added dropwise. The final solution was stirred for 1 h at −78 °C, and a saturated NH_4Cl solution was added to quench the reaction. The mixture was warmed to room temperature, and the organic layer was washed three times with water and dried with K_2CO_3. Only unreacted 2-cyclohexen-1-one was observed in the GC trace of the organic layer. When LiCl (4.2×10^{-5} mol) was present in the initial reaction mixture before the addition of the Grignard reagent under the identical conditions, except that only 2 mL of THF was used, 8% of the 1,2-addition product was obtained as well as 92% of unreacted 2-cyclohexen-1-one.

Reaction of *n*-BuMgCl with 2-Cyclohexen-1-one without Copper or Additives. To a solution of 2-cyclohexen-1-one (0.1 mmol) in 2 mL of THF was added *n*-BuMgCl (0.2 mmoL) dropwise at −78 °C under argon. The solution was stirred for 1 h, and water was added to stop the reaction. Analysis of the organic layer by using GC indicated the presence of 2-cyclohexen-1-one (30%), the 1,4-addition product (23%), and the 1,2-addition product (47%).

Results and Discussion

Catalytic Reaction with H(R-CHIRAMT) (2) or H(R-NEAT) (3) as Chiral Ligand. Table I summarizes the results of the enantioselective conjugate addition of Grignard reagents to 2-cyclohexen-1-one catalyzed by copper(I) aminotropone iminate complexes. The reaction showed very good selectivity for 1,4-addition even in the absence of additives, comparable to stoichiometric reactions with various organocopper reagents.[1] Thus, a major disadvantage, lack of selectivity, of conventional catalytic conjugate addition of Grignard reagents with copper(I) salts can be overcome by using the soluble aminotropone iminate copper(I) catalyst. Modest enantioselectivity (15–20% ee) was observed in the reaction without any additives (entries 1 and 2), as reported previously.[7] The new chiral ligand, H(R-NEAT), was almost as good as H(R-CHIRAMT).

A significant increase in enantioselectivity occurred when silyl reagents and HMPA were added to the reaction mixture. In the presence of 2 equiv of TMSCl and HMPA, the reaction with 4.6 mol % Cu(R-NEAT) gave a 95% yield of (*S*)-3-butylcyclohexanone having 51% ee (entry 3). When the amount of Cu(R-NEAT) was raised to 8.9 mol %, the optical purity of the reaction product was further increased (60% ee, entry 4). The effect of the silyl reagent in the catalytic reaction was quite surprising.

Table I. Catalytic Conjugate Addition Reactions of RMgX to 2-Cyclohexen-1-one

entry	catalyst[a]	R[b]	silyl reagent	yield, %	% ee[c]
1	2	*n*-Bu		96	20
2	3	*n*-Bu		89	15
3	3	*n*-Bu	Me_3SiCl	95	51
4[d]	3	*n*-Bu	Me_3SiCl	(>98)[h]	60
5[e]	3	*n*-Bu	Me_3SiCl	63	0
6	3	*n*-Bu	Ph_2(*t*-Bu)SiCl	26	70
7	3	*n*-Bu	Ph_2(*t*-Bu)SiCl	53	74
8	2	*n*-Bu	Ph_2(*t*-Bu)SiCl	57	74
9[f]	2	*n*-Bu	Ph_2(*t*-Bu)SiCl	97	78
10[g]	2	*n*-Bu	Ph_2(*t*-Bu)SiCl	51	27
11	3	*n*-Bu	(i-Pr)$_3$SiOTf	(>98)[h]	44
12	2	*n*-Bu	(t-Bu)$_2$Si(OTf)$_2$	67	40
13	2	Me	Me_3SiCl	54	−30[i]
14	2	Et	Me_3SiCl	87	14
15	2	vinyl	Me_3SiCl	92	9
16	2	phenyl	Me_3SiCl	96	0
17	2	Me	(t-Bu)$_2$MeSiOTf	(>95)[h]	−10[i]
18	2	Et	(t-Bu)$_2$MeSiOTf	54	35
19	2	phenyl	(t-Bu)$_2$MeSiOTf	57	0
20	2′	*n*-Bu	Ph_2(*t*-Bu)SiCl	53	−63[j] (−72)[k]

[a] The catalyst, typically 3–5 mol % unless stated otherwise, was **2**, Cu(R-CHIRAMT), **3**, Cu(R-NEAT); or **2′**, Cu(S-CHIRAMT). [b] RMgX. [c] Determined by ^{13}C NMR measurements of the ketal derivatives prepared from (*R*)-(−)-2,3-butanediol. [d] The mole fraction of catalyst was 8.9%. [e] The reaction was run in toluene without HMPA. [f] Stoichiometric reaction. [g] The amount of HMPA was 1.6 equiv of 2-cyclohexenone. [h] GC yield. [i] The major product was (*R*)-3-methylcyclohexanone. [j] The major product was (*R*)-3-*n*-butylcyclohexanone. [k] Determined by GC–MS of the ketal derivatives using a HP-FFAP 50-m capillary column.

Addition of a bulky silyl reagent, Ph_2(*t*-Bu)SiCl, to the reaction mixture gave (*S*)-3-butylcyclohexanone in 74% ee (entries 7 and 8). The reaction under stoichiometric conditions with Ph_2(*t*-Bu)SiCl gave a product of 78% ee (entry 9), indicating that deactivation of the chiral cuprate under catalytic conditions is insignificant. The ability of silyl reagents to influence the enantioselectivity is an important clue for understanding the mechanism of the reaction. A silylated species is therefore most likely involved in the rate-determining step. The yield of the conjugate addition reaction, determined by GC analysis of the final reaction mixture, was very high except for the reaction with Ph_2(*t*-Bu)SiCl. Most of the reactant was converted to the 1,4-addition product. In the case of reactions carried out in the presence of sterically hindered silyl reagents, the best separation of the product from the silyl additive was achieved by column chromatography with alumina. The product isolated from the reaction was always 3-butylcyclohexanone, indicating that the anticipated silyl enol ether was rapidly hydrolyzed in the workup because of the catalytic activity of HMPA.[17] The reaction was not sensitive to the purity of CuBr·Me_2S. The same results were obtained in reactions run with or without purification of CuBr·Me_2S.[18]

Parallel experiments carried out with 2-cyclohexen-1-one and other Grignard reagents such as methyl-, ethyl-, phenyl-, or vinylmagnesium halide gave poor enantioselectivities. The bulky silyl reagent, (t-Bu)$_2$MeSiOTf, however, still afforded better enantioselectivities than TMSCl. Interestingly, the reaction with MeMgCl gave excess (*R*)-3-methylcyclohexanone instead of the *S* configuration at C(3) observed in the reaction with *n*-BuMgCl. The reversal of the configuration at C(3) indicates that the

(16) Kindly provided by J. R. Behling, G. D. Searle & Co.

(17) (a) Corriu, R. J. P.; Guerin, C.; Henner, B. J. L.; Man, W. *Organometallics* **1988**, *7*, 237. (b) Corriu, R. J. P. *Pure Appl. Chem.* **1988**, *60*, 99.

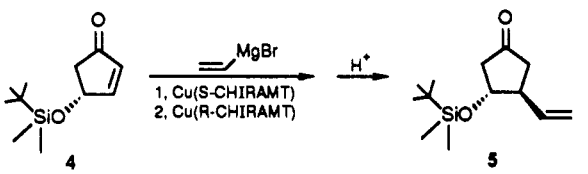
(18) Wuts, P. G. M. *Synth. Commun.* **1981**, *11*, 139.

Grignard reagent as well as the silyl reagent is involved in the rate-determining step of the reaction. Steric interactions within the alkyl–copper–enone complex may explain the effect of the Grignard reagent on the enantioselectivity.

The reaction with $Ph_2(t\text{-Bu})SiCl$ was relatively slow. When PhMgCl and $Ph_2(t\text{-Bu})SiCl$ were used in the reaction, ca. 50% 2-cyclohexen-1-one was converted to product after 1 h at −50 °C, whereas the same reaction with TMSCl or $(t\text{-Bu})_2MeSiOTf$ was complete after 1 h at −78 °C. A similar result was observed with MeMgCl. The HMPA was also found to be important in the reaction. Low enantioselectivity was obtained when the amount of HMPA was reduced (entry 10). A reaction carried out using toluene as solvent without HMPA (entry 5) did not show any enantioselectivity. Unfortunately, reactions with other enones such as 2-cyclopentenone, 4,4-dimethyl-2-cyclohexen-1-one, and 3-methyl-2-cyclohexen-1-one did not show any enantioselectivity, indicating that the reaction is very sensitive to the substituents on the enones. These catalytic reactions, however, still gave excellent regioselectivity for the 1,4-addition products, even though no enantioselectivity was observed.

We studied the reaction of *n*-BuMgCl with 2-cyclohexen-1-one in the absence of copper complex, a possible side reaction in our catalytic system. Addition of *n*-BuMgCl to 2-cyclohexen-1-one gave a 2:1 mixture of 1,2- and 1,4-addition products in 70% yield. Surprisingly, however, in the presence of HMPA and TMSCl without the copper complex, the reaction did not afford any addition products. Addition of LiCl to the reaction mixture produced only a small amount of the 1,2-addition product.

Studies with Optically Active Enones. We also investigated the conjugate addition of two optically active enones using Cu(R-CHIRAMT) and Cu(S-CHIRAMT) to examine the rate difference between these two catalysts. The conjugate addition of vinylmagnesium bromide to (*S*)-4-[dimethyl(1′1′-dimethylethyl)siloxy]-2-cyclopentenone (4) catalyzed by Cu(R-CHIRAMT) or Cu(S-CHIRAMT) in the presence of $(t\text{-Bu})_2MeSiOTf$ and HMPA gave product 5. The ratio of products obtained



in the Cu(S-CHIRAMT)- and Cu(R-CHIRAMT)-catalyzed reactions within 30 min was 5.6, indicating that Cu(S-CHIRAMT) catalyzes the reaction 5.6 times faster than Cu(R-CHIRAMT). Thus, these chiral cuprate catalysts could be used in the kinetic resolution[19] of a racemic mixture of 4, an important precursor in prostaglandin syntheses.[20] When longer reaction times were permitted, the yields of product were 62% and 93% for R-CHIRAMT and S-CHIRAMT, respectively. Although these values might not seem promising at first inspection, they mean that the ratios of product to starting material in these reactions are 1.6/1 and 12.7/1, respectively. These results reflect a lower limit for the selectivity of the catalyst. Hence, in a true competition experiment using a racemic mixture of enone and only half the amount of Grignard required for complete reaction, we might expect the relative rate of reaction to be even higher than 12.7/1.6 (7.6).

In the conjugate addition of *n*-BuMgCl to either (*R*)-carvone or (*S*)-carvone, (*R*)-carvone was found to react 1.5 times faster than (*S*)-carvone in the presence of Cu(R-CHIRAMT), HMPA, and TMSCl.

Summary

In the present investigation, we have achieved the catalytic enantioselective conjugate addition of Grignard reagents to enones by using chiral copper complexes of *N,N′*-substituted aminotropone iminate ligands. The yields ranged from moderate to very good, the regioselectivity was excellent, but the stereochemistry was found to be a delicate balance of steric factors. Appreciable enantioselectivity was obtained in some cases in the presence of HMPA and, especially, bulky silyl reagent additives. Although the reagent does not afford high ee values for a broad range of Grignard reagents and substrates, the results obtained for conjugate addition of *n*-butyl magnesium bromide to 2-cyclohexen-1-one suggest that further ligand modification might be possible to extend the generality of the system. The catalytic chemistry reported here has also been found to be of potential value in the kinetic resolution of prostaglandin precursors.

Acknowledgment. This work was supported by a grant from the National Science Foundation. We thank G. D. Searle & Co. for chiral enones and the National Science Foundation for a predoctoral fellowship to R.B.K.

(19) The kinetic resolution of 4-hydroxy-2-cyclopentenone was attempted with a chiral rhodium complex. The reaction showed k_{fast}/k_{slow} = 5:1 enantiomeric discrimination: Kitamura, M.; Manabe, K.; Noyori, R.; Takaya, H. *Tetrahedron Lett.* **1978**, *28*, 4719.

(20) (a) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847. (b) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 4718.