ORGANIC LETTERS

2004
Vol. 6, No. 2
253−256

Enantioselective Reactions of Scalemic Acyclic α-(Alkoxy)alkyl- and α-(*N*-carbamoyl)alkylcuprates

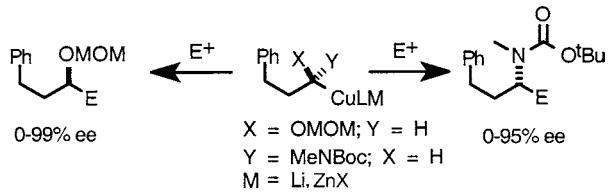
R. Karl Dieter,* Rhett T. Watson, and Rajesh Goswami

Department of Chemistry, Hunter Laboratory, Clemson University, Clemson, South Carolina 29634-0973

dieterr@clemson.edu

Received November 14, 2003

ABSTRACT



Scalemic acyclic α-(alkoxy)alkyl- and α-(*N*-carbamoyl)alkylcuprates prepared from organostannanes via organolithium reagents react with vinyl iodides, propargyl mesylates, and α,β-enones to afford coupled products with enantioselectivities ranging from 0 to 99% ee depending upon cuprate reagent, substrate structure, solvent, and temperature. In general, lithium cuprates give higher chemical yields and lower enantioselectivities, while the trends are reversed for the corresponding zinc cuprate reagents.

Stereogenic organometallic compounds[1] containing a metal atom bound to an asymmetric carbon atom offer powerful synthetic strategies and daunting challenges for stereocontrol. In recent years, intense activity has focused on stereogenic organolithium reagents.[2] Since the pioneering work of Still,[3] impressive progress has been achieved with scalemic α-lithiated *O*-allyl and alkyl carbamates (i.e., lithiation adjacent to oxygen),[4] *N*-alkyl carbamates (i.e., lithiation adjacent to nitrogen),[5] formamidines, amides, and amines.[1,2b] Stereogenic cuprate reagents, however, remain a spectacularly underdeveloped area of cuprate chemistry, with few developments having arisen since the early work of Fuchs[6] and Linderman[7] on α-(alkoxy)alkylcuprates. The glycosyl cuprates of Fuchs and Beau[8] and 1,3-dioxanyl cuprates[9] involve cycloalkylcuprate reagents where increased configurational stability arises in part due to an increased barrier to inversion at a stereogenic center within the framework of a small ring. Although stereocontrol was capricious in Linderman's early examination of acyclic α-(alkoxy)alkylcuprates,[7a] a recent example involving α-carbamoyloxy organocuprates proved to be more reliable.[10] Stereogenic α-alkoxyalkylcuprates prepared via deprotonation of *O*-alkyl carbamates appear to also afford reliable enantioselectivities, although problems of reactivity were observed with both the zinc and lithium alkylcyanocuprate reagents.[11] We have confirmed Nakai's

(1) For use of the term and a review, see: Gawley, R. E. *Curr. Org. Chem.* **1997**, *1*, 71.

(2) For reviews and monographs, see: (a) Basu, A.; Thayumanavan, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 716. (b) Clayden, J. *Organolithiums: Selectivity for Synthesis;* Pergamon: Oxford, UK, 2002; Chapter 5, pp 169−240. (c) Hodgson, D. M., Ed. Organolithiums in Enantioselective Synthesis. In *Topics in Organometallic Chemistry*; Springer-Verlag: Berlin, 2003; Vol. 5.

(3) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201−1202.

(4) For reviews see: (a) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2283−2316. (b) Hoppe, D.; Marr, F.; Bruggemann, M. *Top. Organomet. Chem.* **2003**, *5*, 61−138.

(5) For reviews, see: (a) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552−560. (b) Beak, P.; Johnson, T. A.; Kim, D. D.; Lim, S. H. *Top. Organomet. Chem.* **2003**, *5*, 139−176.

(6) Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 4930−4939.

(7) (a) Linderman, R. J.; Griedel, B. D. *J. Org. Chem.* **1990**, *55*, 5428−5430. (b) Linderman, R. J.; Griedel, B. D. *J. Org. Chem.* **1991**, *56*, 5491−5493.

(8) Prandi, J.; Audin, C.; Beau, J.-M. *Tetrahedron Lett.* **1991**, *32*, 769−772.

(9) Rychnovsky, S. D.; Buckmelter, A. J.; Dahanukar, V. H.; Skalitzky, D. J. *J. Org. Chem.* **1999**, *64*, 6849−6860.

(10) Tomooka, K.; Shimizu, H.; Nakai, T. *J. Organomet. Chem.* **2001**, *624*, 364−366.

(11) Papillon, J. P. N.; Taylor, R. J. K. *Org. Lett.* **2002**, *4*, 119−122.

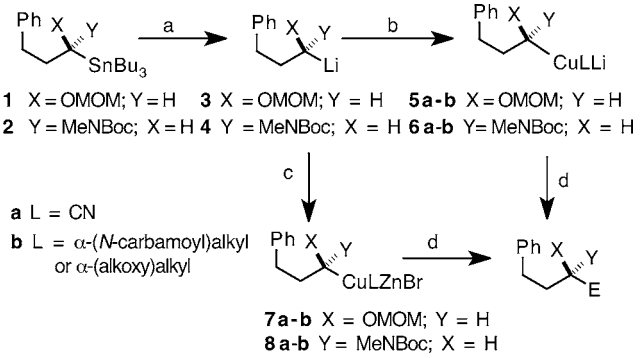
10.1021/ol036237s CCC: $27.50
Published on Web 12/23/2003

observation of significant carbene formation from these lithium α-(*O*-carbamoyl)alkylcuprates.

Previously, we reported the first examples of configurationally stable scalemic stereogenic cyclic α-(*N*-carbamoyl)-alkylcuprates affording excellent enantioselectivities, and this study,[12] along with the alkylborane-zinc−copper transmetalation methodology of Knochel,[13] represented the first major advances in scalemic stereogenic cuprate methodology since the early work of Fuchs and Linderman 16 years ago. The *N*-Boc-2-pyrrolidinylcuprate reagents gave excellent enantiomeric ratios (ers) with vinyl iodides and poor to no enantioselectivity with ethyl propiolate or methyl acrylate.[12] More recent reports from other laboratories point to the emerging development of scalemic stereogenic organocuprates, involving in some instances dynamic thermodynamic control,[14,15] and to the problems of cuprate reactivity and configurational stability that need to be addressed.[9−11,16] Intrigued by the excellent but capricious ers reported for the reaction of acyclic α-(alkoxy)alkylcuprates, a study directly comparing acyclic α-(alkoxy)alkyl- and α-(*N*-carbamoyl)-alkylcuprates was undertaken. We now report that excellent ers can be achieved with acyclic α-(heteroatom)alkylcuprates by modification of solvent, temperature, cuprate reagent, and the metal counterion of the cuprate reagent (e.g., Li or ZnX). This is the first report of configurationally stable acyclic α-(*N*-carbamoyl)alkylcuprates.

Although frequently described in the literature, the preparation of α-alkoxy-[17] and α-carbamoylstannanes[18] proved to be difficult to execute on a large scale. Modest levels of optical purity and low overall chemical yields were frequently obtained by the asymmetric reduction of acyl stannanes. Chemical resolution of the scalemic α-hydroxy stannanes via carbamates derived from norephedrine according to a recent report[19] also proved to be problematic on a large scale. Following the lead of Hoppe[20] and Nakai,[21] we effected asymmetric deprotonation of 3-phenylpropyl-*N*,*N*-diisopropyl carbamate with *s*-BuLi/(−)-sparteine followed by quenching with $^{n}Bu_3SnCl$ to afford the stannane. Carbamate cleavage[19] and reaction of the alcohol with MOMCl afforded **1**, while

Scheme 1[a]



[a] Conditions: (a) A = ^{n}BuLi, THF, −95 °C, 5 min. B = ^{s}BuLi, Et_2O, −78 °C, 120−180 min. C = PhMe/TMEDA (1.0 equiv), ^{n}BuLi, 4 h, −78 °C. (b) CuCN·2LiCl, THF, −95 or −78 °C, 0.5 h. (c) (i) $ZnBr_2$, THF; (ii) CuCN·2LiCl. (d) E^+, −95 or −78 to 25 °C, 12 h.

mesylation of the alcohol and substitution with NaN(Me)-$CO_2{}^{t}$Bu afforded stannyl carbamate **2** in an efficient procedure reported by Nakai[21] during the course of our independent efforts.

Stannanes **1** and **2** underwent transmetalation with *n*-BuLi in THF, *s*-BuLi in Et_2O, or *n*-BuLi in PhMe/TMEDA (1.0 equiv) to afford the lithium reagents **3** and **4**, which could be converted into lithium cuprate reagents **5a**,**b** and **6a**,**b**, respectively, or zinc cuprates **7a**,**b** and **8a**,**b**, respectively (Scheme 1), and reacted with electrophiles **9**−**13** (Figure 1).

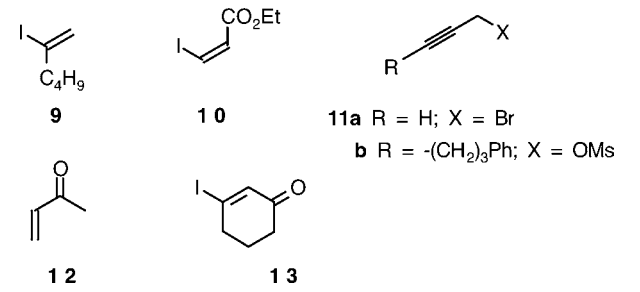


Figure 1. Electrophiles reacted with stereogenic scalemic α-(alkoxyl)alkyl- and α-(*N*-carbamoyl)alkylcuprates.

In preliminary studies, the reactivity of various cuprate reagents were examined. Reaction of α-(alkoxy)alkylcuprates [L = CN, α-(alkoxy)alkyl)] derived from the α-methoxy analogue of **1** with vinyl iodide **9** gave **14c** in 40% yield for the RCuCNLi reagent, while the dialkylcuprate reagent gave **14c** in higher yields (70%, Table 1, entry 4). The dialkylcuprate prepared from the α-methoxyalkylstannane gave significantly lower yields than those obtained with the MOM derivative **1** (entries 1 and 4). With stannanes **1** and **2** in hand, we examined the preparation and reactions of the stereogenic scalemic cuprates derived from the lithium reagents **3** and **4**.

(12) Dieter, R. K.; Topping, C. M.; Chandupatla, K. R.; Lu, K. *J. Am. Chem. Soc.* **2001**, *123*, 5132−5133.

(13) (a) Boudier, A.; Darcel, C.; Flachsmann, F.; Micouin, L.; Oestreich, M.; Knochel, P. *Chem. Eur. J.* **2000**, *6*, 2748. (b) Knochel, P.; Betzemeier, B. Transmetalation Reactions Producing Organocopper Reactions. In *Modern Organocopper Chemistry*; Krause, N., Ed.; John Wiley & Sons: New York, 2002: pp 45−78, and references therein.

(14) For a review, see: Beak, P.; Anderson, D. R.; Curtis, M. D.; Laumer, J. M.; Pippel, D. J.; Weisenburger, G. A. *Acc. Chem. Res.* **2000**, *33*, 715−727.

(15) For an example of a stereogenic α-(amido)alkylcuprate under dynamic thermodyanic control, see: Tomoyasu, T.; Tomooka, K.; Nakai, T. *Tetrahedron Lett.* **2000**, *41*, 345−349.

(16) (a) Hoffmann, R. W.; Hölzer, B. *J. Am. Chem. Soc.* **2002**, *124*, 4204−4205. (b) Hoffmann, R. W.; Nell, P. G.; Leo, R.; Harms, K. *Chem. Eur. J.* **2000**, *6*, 3559−3365.

(17) (a) Marshall, J. A.; Garofalo, A. W.; Hinkle, K. W. *Org. Synth.* **1999**, *77*, 98−106. (b) Chen, P. C.-M.; Chong, J. M. *J. Org. Chem.* **1988**, *53*, 5584−5586.

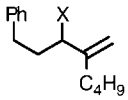
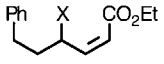
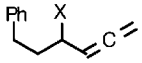
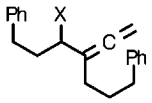
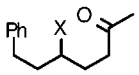
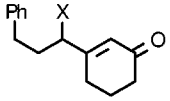
(18) Chong, J. M.; Park, S. B. *J. Org. Chem.* **1992**, *57*, 2220−2222.

(19) Kells, K. W.; Nielsen, N. H.; Armstrong-Chong, R. J.; Chong, M. J. *Tetrahedron* **2002**, *58*, 10287−10291.

(20) Christopher, G.; Hoppe, D. *Org. Lett.* **2002**, *4*, 2189−2192.

(21) (a) Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870−11871. (b) Tomoyasu, T.; Tomooka, K.; Nakai, T. *Tetrahedron Lett.* **2003**, *44*, 1239−1242.

Table 1. Reactions of Stereogenic α-Alkoxylalkyl and α-(*N*-carbamoyl)alkylcuprates with Vinyl Iodides, Propargyl Mesylates, and Methyl Vinyl Ketone (Scheme 1)

entry	Sn	E^+	solvent[a], T °C, time (min)	CuCN·2LiCl[b] equiv, RM	product	cpd no.	% yield[c]	% ee[d,e]
1	**1**	**9**	THF, -95 (5)	0.5 + RLi		**14a**	96	50
2	**1**	**9**	THF, -95 (5)	1.0 + RZnBr		**14a**	0	-
3	**1**	**9**	THF, -95 (5)	0.5 + RZnBr		**14a**	0	-
4	-	**9**	THF, -78 (5)	0.5 + RLi		**14c**	70	-
5	**2**	**9**	THF, -95 (5)	0.5 + RLi	**14a** X = OMOM	**14b**	50	0
6	**2**	**9**	THF, -95 (5)	1.0 + RZnBr	**b** X = MeNBoc	**14b**	0	-
7	**2**	**9**	THF, -95 (5)	0.5 + RZnBr	**c** X = OMe	**14b**	0	-
8	**1**	**10**	Et_2O, -78 (180)	0.5 + RLi		**15a**	43	99
9	**2**	**10**	THF, -78 (5)	1.0 + RZnBr		**15b**	58	67
10	**2**	**10**	THF, -95 (5)	1.0 + RZnBr	**15a** X = OMOM	**15b**	46	78
					b X = MeNBoc			
11	**1**	**11a**	THF, -95 (5)	0.5 + RLi		**16a**	96	60
12	**1**	**11a**	Et_2O, -78 (120)	0.5 + RLi		**16a**	98	75
13	**1**	**11a**	THF, -95 (5)	1.0 + RLi		**16a**	93	71
14	**1**	**11a**	THF, -95 (5)	1.0 + RZnBr	**16a** X = OMOM	**16a**	70	80
15	**1**	**11a**	THF, -95 (5)	1.0 + RZnBr[f]	**b** X = MeNBoc	**16a**	71	88
16	**1**	**11a**	PhMe[g], -78 (240)	1.0 + RZnBr		**16a**	74	99
17	**1**	**11a**	THF, -95 (5)	0.1 + RZnBr		**16a**	30	99
18	**1**	**11a**	THF, -95 (5)	0.5 + RZnBr		**16a**	99	77
19	**2**	**11a**	THF, -95 (5)	0.5 + RLi		**16b**	70	72
20	**2**	**11a**	Et_2O, -78 (120)	0.5 + RLi		**16b**	50	0
21	**1**	**11b**	THF, -95 (5)	0.5 + RLi		**17a**	38	17
22	**1**	**11b**	THF, -95 (5)	1.0 + RLi		**17a**	59	0
23	**1**	**11b**	THF, -95 (5)	1.0 + RZnBr		**17a**	64	59
24	**2**	**11b**	THF, -95 (5)	1.0 + RZnBr	**17a** X = OMOM	**17b**	47	95
					b X = MeNBoc			
25	**1**	**12**	THF, -78 (5)	0.5 + RLi		**18a**	88	-
26	**1**	**12**	THF, -95 (5)	0.5 + RLi		**18a**	91	70
27	**1**	**12**	Et_2O, -78 (120)	0.5 + RLi		**18a**	52	0
28	**2**	**12**	THF, -95 (5)	0.5 + RLi	**18a** X = OMOM	**18b**	79	70
29	**2**	**12**	Et_2O, -78 (120)	0.5 + RLi	**b** X = MeNBoc	**18b**	76	0
30	**1**	**13**	THF, -95 (5)	0.5 + RLi		**19a**	26	24
31	**1**	**13**	THF, -95 (5)	1.0 + RLi		**19a**	34	5
32	**1**	**13**	THF, -95 (5)	1.0 + RZnBr		**19a**	46	74
33	**2**	**13**	THF, -95 (5)	1.0 + RZnBr	**19a** X = OMOM	**19b**	42	78
34	**2**	**13**	THF, -78 (5)	1.0 + RZnBr	**b** X = MeNBoc	**19b**	48	71

[a] Stannane to RLi transmetalation was achieved with *n*-BuLi in THF or PhMe and *s*-BuLi in Et_2O. [b] CuCN·2LiCl was added as a THF solution such that solvent/THF = 1:1 for the solvent composition containing the cuprate reagent. [c] Yields based upon isolated products purified by column chromatography. [d] Enantiomeric excess (% ee) was calculated from the enantiomeric ratio (er) measured by chiral stationary phase HPLC on a CHIRALCEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel]. [e] Corrected for the enantiomeric purity of **1** (96.6% ee) or **2** (95.0% ee). [f] $ZnBr_2$/THF solution was cooled to −78 °C before addition, and CuCN·2LiCl was cooled to −95 °C before addition to the RLi solution. [g] TMEDA (1.2 equiv) was added.

Lithium di[(alkoxy)alkyl]cuprate **5b** reacted with vinyl iodide **9** to give **14a** in excellent chemical yield and modest enantiomeric excess (50% ee, Table 1, entry 1), while the zinc α-[(alkoxy)alkyl]cyanocuprate **7a** and the zinc di-[(alkoxy)alkyl]cuprate **7b** were unreactive toward **9** (Table 1, entries 2 and 3). In contrast, the lithium di-α-(*N*-carbamoyl)alkylcuprate **6b** reacted with vinyl idodide **9** to give **14b** in lower chemical yield and with no enantioselectivity (entry 5). Both α-(*N*-carbamoyl)alkyl zinc cuprates **8a** and **8b** were unreactive toward **9** (entries 6 and 7). The more reactive vinyl iodide **10** gave **15a** in excellent enantioselectivity with the lithium di[α-(alkoxy)alkyl]cuprate **5b** in Et_2O (entry 8), while the zinc carbamoyl(cyano)cuprate **8a** gave comparable yields of **15b** and good ees when the transmetalation was performed at −95 °C instead of −78 °C (entries 9 and 10).

A more systematic study was undertaken with propargyl bromide as the substrate (Table 1, entries 11−20). The enantioselectivity in the reaction of lithium α-(alkoxy)alkylcuprates **5a**,**b** with **11a** increased on going from THF to Et_2O/THF (1:1) (entries 11 and 12), and cuprates **5a**,**b** gave comparable enantioselectivity (entries 11 and 13) with slightly higher ees for **5a**. The corresponding zinc [α-(alkoxyalkyl)]cyanocuprate **7a** gave better enantioselectivity but lower chemical yields (entries 14−17). The zinc alkylcyanocuprate reagent **7a** gave very good ers (90:10 to 94:6) in THF, and higher enantioselectivity was achieved when the $ZnBr_2$ and CuCN·2LiCl were cooled to −78 and −95 °C,

respectively, before addition to the reaction medium (entries 14 and 15). Exceptional ers were obtained in PhMe (i.e., 99.5:0.5) with comparable chemical yields (entry 16). Utilization of catalytic amounts of CuCN·2LiCl also gave excellent ers but low chemical yields (entry 17), while the reagent prepared from 2 equiv of RZnBr and 1.0 equiv of CuCN·2LiCl gave excellent chemical yields but reduced ers (entry 18). Reaction of the corresponding carbamate-derived lithium dialkylcuprate **6b** gave good ers in THF (86:14) and no enantioselectivity in Et_2O (entries 19 and 20). The presumed less reactive propargyl mesylate **11b** gave reduced chemical yields with the lithium α-(alkoxy)alkylcuprates **5a**,**b** and little or no enantioselectivity, respectively (entries 21 and 22). Excellent enantioselectivity and modest chemical yields could be achieved with zinc cyanocuprate reagent **7a** (entry 23). Similarly, the carbamoyl-derived zinc alkyl(cyano)cuprate **8a** gave excellent enantioselectivity but a modest chemical yield (entry 24).

A conjugate addition reaction was examined using methyl vinyl ketone (**12**) as a substrate (Table 1, entries 25−29). Both the racemic and scalemic lithium α-di[(alkoxy)alkyl]cuprates gave comparable yields, and the scalemic reagent gave good ers in THF when the reagent was prepared at −95 °C (entries 25 and 26). A similar chemical yield and enantioselectivity was achieved in the reaction of the carbamoyl-derived lithium dialkycuprate **6b** in the conjugate addition reaction with **12** (entry 28). In these conjugate addition reactions, both the α-(alkoxy)alkyl- and α-(*N*-carbamyl)alkylcuprates gave no enantioselectivity when conducted in Et_2O alone (entries 27 and 29) where the transmetalations were achieved over a period of 2 h. *β*-Iodoenone **13** can, in principle, proceed either by a direct vinylation reaction or by a conjugate addition−elimination sequence. Reaction of **13** with the α-(alkoxy)alkylcuprates **5a**,**b** gave low chemical yields and low enantioselectivities (entries 30 and 31), while reaction of **13** with either zinc α-[(heteroatom)alkyl]cyanocuprate **7a** or **8a** gave modest chemical yields and good enantioselectivities (entries 32−34). Again, higher ees were achieved when the transmetalation and cuprate formation were performed at −95 °C instead of −78 °C.

These preliminary studies indicate that enantioselectivity is largely a function of cuprate configurational stability and cuprate−substrate reactivity. In this regard, the formation of alkylzinc reagents and transmetalation to the corresponding zinc cuprate reagents generally affords good to excellent enantioselectivity if the substrate is sufficiently reactive toward these less reactive zinc cuprate reagents. The scalemic α-(alkoxy)alkyllithium and α-(*N*-carbamoyl)alkyllithium reagents are sufficiently configurationally labile at −78 °C over 5 min, and increased enantioselectivity can be achieved by conducting the Sn−Li transmetalation and cuprate formation at −95 °C. The lithium dialkylcuprates generally give higher chemical yields and higher enantioselectivities than the corresponding lithium alkyl(cyano)cuprate reagents. The only case where they gave comparable results was with propargyl bromide. It is interesting in this regard that the zinc alkyl(cyano)cuprate reagents gave good chemical yields and enantioselectivities with vinyl iodide **10**, propargyl substrates **11a**,**b** and *β*-iodo-α,*β*-enone **13**. It is unclear whether this reflects the increased configuational stability of the zinc cuprate reagents or a better matching of cuprate and substrate reactivity profiles. In fact, the relative reactivity of the lithium and zinc alkyl(cyano)cuprate reagents is uncertain. Finally, the evidence suggests, on the basis of chemical yields and enantioselectivities, that the α-(alkoxy)alkylcuprates are more reactive and more configurationally stable than the corresponding α-(*N*-carbamoyl)alkylcuprate reagents.

In summary, excellent enantioselectivities can be achieved in the reactions of α-(alkoxy)alkylcuprates and α-(*N*-carbamoyl)alkylcuprates with vinyl iodides, propargyl mesylates, and methyl vinyl ketone. High enantioselectivities require a balance in the cuprate−substrate reactivity profile, and higher ees can be achieved in less polar solvents and with the zinc cuprate reagents if the substrate is sufficiently reactive. These results suggest that there are considerable opportunities for effecting enantioselective control by variation of the cuprate reagent, substrate structure, solvent, and temperature. Extension of these protocols to less reactive substrates is under investigation.

Acknowledgment. This work was generously supported by the National Science Foundation (CHE-0132539). Support of the NSF Chemical Instrumentation Program for purchase of a JEOL 500 MHz NMR instrument is gratefully acknowledged (CHE-9700278).

Supporting Information Available: General experimental procedures for preparation and reactions of α-(heteroatom)alkylcuprates, data reduction for compounds **14**−**19a**,**b**, ^{1}H and ^{13}C NMR spectra (**14b**, **15a**, **16b**, **17b**, **18a**,**b**, **19a**), and chiral HPLC traces (**15b**, **18a**,**b**). This material is available free of charge via the Internet at http://pubs.acs.org.

OL036237S