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Enantioselectivity in the Reactions of Chiral α-(*N*-Carbamoyl)alkylcuprates

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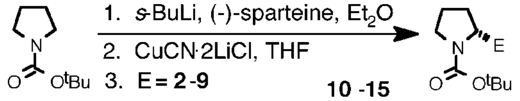
Although significant progress has been made in asymmetric organocopper reactions employing chiral anionic (e.g., RCuL*Li) or neutral nontransferable heteroatom ligands [e.g., (RCuL)Li·L*],[1] the use of chiral cuprates possessing a stereogenic center at the carbon atom bound to copper in the transferable ligand remains underdeveloped. Scalemic[2] α-alkoxyalkylcuprates display considerable varibility in enantioselectivity (0−96% ee) during 1,4-addition reactions[3] and asymmetric variations have not been examined in a wider range of copper-mediated transformations. Methylation of a chiral *N*-protected α-aminoalkylcuprate reagent (i.e., RCuCNLi) displayed no diastereoselectivity.[4] Thermodynamically controlled configurational stability has been demonstrated for α-aminoalkylcuprate reagents derived from a chiral lactam[5] and the configurational stability of zinc cuprates derived from organoboranes has been examined in substitution reactions.[6]

Pioneering work by Hoppe[7] and Beak[8] demonstrated the viability of configurationally stable scalemic alkyl- and allyllithium[9] reagents derived from carbamate derivatives. α-Lithio carbamate configurational stability is solvent, reaction temperature, and electrophile dependent.[10] Our successful development of α-(*N*-carbamoyl)alkylcuprate chemistry prompted us to explore the preparation and utilization of scalemic α-(*N*-carbamoyl)alkylcuprates.[11] Expansion of scalemic α-lithio carbamate chemistry to organocopper reagents requires carbanion configurational stability during transmetalation to the copper reagent and during the subsequent copper-mediated transformations. We report here the first examples of configurationally stable α-(*N*-carbamoyl)alkyl cuprates not under dynamic thermodynamic control.[5,12]

N-Boc pyrrolidinylcuprates provided an ideal system for examination since both the asymmetric deprotonation reaction[8,12] and various cuprate transformations[11] had been studied in detail. The known behavior of scalemic *N*-Boc 2-lithiopyrrolidine (**1**)[13] provided a reference against which the configurational stability of the reagents could be measured for the cuprate preparation and reaction sequences. Anticipating that α-(*N*-carbamoyl)alkylcuprate configurational stability might be reaction and electrophile dependent, vinylation reactions with (*E*) 1-iodo-2-phenylethene (**2**), 2-iodo-4-*tert*-butyldimethylsilyloxy-1-butene (**3**), (*Z*)-ethyl 3-iodo-2-propenoate (**4**), ethyl propiolate (**5**), (*Z*)-ethyl 3-iodo-2-heptenoate (**6**), and 3-iodo-2-cyclohexenone (**7**) were examined along with conjugate addition reactions on benzyl 2-propenoate (**8**) and propargyl substitution reactions on the mesylate (**9**) of 3-phenyl-2-propyn-1-ol (eq 1). It was readily confirmed by deuterium quenching that complete deprotonation of *N*-Boc pyrrolidine could be achieved with *sec*-BuLi/(−)-sparteine in Et_2O at −78 °C over 1 h. Although THF was the solvent of choice for the cuprate reactions, the configurational lability of **1** in THF was problematic. Generation of **1** in THF with *sec*-BuLi/(−)-sparteine followed by cuprate formation and reaction with **2** gave racemic **10** as determined by chiral HPLC analysis in good yield (Table, entry 1). Cuprate reagents prepared via asymmetric deprotonation of *N*-Boc protected pyrrolidine [*sec*-BuLi, (−)-sparteine, Et_2O, −78 °C, 1 h][13] followed by transmetalation with either solid CuCN or a THF solution of CuCN·2LiCl permitted, respectively, use of Et_2O and Et_2O/THF solvent systems. Quenching the dialkylcuprate reagent (i.e., $R_2CuLi\cdot LiCN$), prepared from CuCN·2LiCl, with **2** at −78 °C afforded the vinylation product (Table 1, entry 2) in good yield and with excellent enantioselectivity (93:7% er). Excellent reproducibility was obtained over several experiments ranging between 85 and 98% yield and 90:10 to 93:7 er. Increasing the temperature of the reaction mixture during the cuprate formation stage or aging the cuprate reagent resulted in slight deterioration of the enantioselectivity (entries 3 and 4). Utilization of solid CuCN required brief warming to 25 °C to ensure complete cuprate formation and this protocol resulted in significant loss of enantioselectivity (entry 5). Reaction of the dialkylcuprate with vinyl iodide **3** also gave excellent yields and enantioselectivity (entries 6 and 7).



(1)

Mixed results were obtained with vinyl iodides **4**, **6**, and **7** containing electron-withdrawing groups. Reaction of the dialkyl pyrrolidinylcuprate, $R_2CuLi\cdot LiCN$, with **4** or **6** gave **12a**,**b**, respectively, in good yields and excellent enantioselectivity (entries 8−9, and 11) while reaction with **7** gave excellent yields but modest enantioselectivity (entries 13 and 14). Reaction of **7** with the alkyl(cyano)cuprate, RCuCNLi, gave excellent yields but no enantioselectivity (entry 12). In contrast to the vinylation reactions, conjugate addition of either pyrrolidinylcuprate with benzyl acrylate (**8**) gave no enantioselectivity (entries 15−17), while the RCuCNLi reagent gave modest selectivity with **5** (entry 10). With the propargyl mesylate (**9**), the cyanocuprate reagent gave modest chemical yields and poor to modest enantioselectivity (entries 18 and 19) while the dialkylcuprate gave poor chemical

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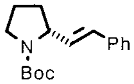
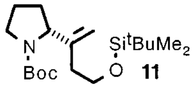
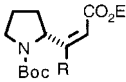
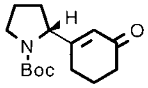
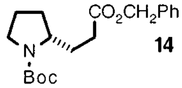
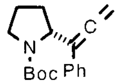
Table 1. Reactions of Scalemic α-(*N*-carbamoyl)alkylcuprates, Prepared from Scalemic α-Lithio *N*-Boc Pyrrolidine (**1**), with a Variety of Electrophiles

entry	E	Cu(I) equiv[a]	temperature Cu °C (min)[b]	solvent[c]	temperature Rxn, °C (h)[d]	Product[e]	% yield[f]	er[g]
1	**2**	0.5	-78 to -60 (60)	THF	-60 to 25 (12)	 **10**	85-90	0
2	**2**	0.5	-78 to -60 (60)	THF/Et_2O	-60 to 25 (12)		85-98	90:10-93:7
3	**2**	1.0	-78 to -60 (105)	THF/Et_2O	-60 to 25 (12)		70	89:11
4	**2**	0.5	-78 to -40 (120)	THF/Et_2O	-60 to 25 (12)		86	73:27
5	**2**	0.5[h]	-78 (45) 25 (15)	Et_2O	-60 to 25 (12)		70	51:49-55:45
6	**3**	0.5	-78 (60)	THF/Et_2O	-78 to 25 (12)	 **11**	79	94:6
7	**3**	0.5	-78 (60)	THF/Et_2O	-78 to 25 (3-4)		84[i]	94:6
8	**4**	0.5	-78 to -50 (60)	THF/Et_2O	-50 to 25 (4)	 **12a** R = H **12b** R = *n*-Bu	63	93:7
9	**4**	0.5	-78 (60)	THF/Et_2O	-78 to 12 (12)		89	95:5
10	**5**	1.0	-78 (60)	THF/Et_2O	-78 to –35 (3)		56[i,j]	72:28
11	**6**	0.5	-78 (60)	THF/Et_2O	-78 to –35 (3)		53[i]	91:9
12	**7**	1.0	-78 (60)	THF/Et_2O	-78 to 25 (12)	 **13**	80	0
13	**7**	0.5	-78 (60)	THF/Et_2O	-78 to 25 (12)		79	65:35
14	**7**	0.5	-78 (60)	THF/Et_2O	-40 (8)		79	80:20
15	**8**	1.0	-78 (60)	THF/Et_2O	-78 to 25 (12)	 **14**	95[i]	0
16	**8**	1.0	-78 (60)	THF/Et_2O	-50 (10)		39[i]	0
17	**8**	0.5	-78 (60)	THF/Et_2O	-78 to 25 (12)		60[i]	0
18	**9**	1.0	-78 to -50 (30)	THF/Et_2O	-78 to 25 (12)	 **15**	57	65:35
19	**9**	1.0	-78 to -50 (60)	THF/Et_2O	-78 (5)		40-56	68:32-77:23
20	**9**	0.5	-78 (60)	THF/Et_2O	-78 to 25 (12)		33	69:31

[a] CuCN·2LiCl was employed unless otherwise noted. [b] Temperature and time at which cuprate formation was achieved. [c] THF/Et_2O solvent ratio (1:1, v/v) arose by deprotonation of carbamate in Et_2O followed by addition of a THF solution of CuCN·2LiCl. [d] Temperature and time at which the cuprate/electrophile reaction was allowed to proceed. [e] Cuprate reactions assumed to proceed with retention of configuration[3] from scalemic **1**.[13] [f] Based on products purified and isolated by chromatography. [g] Enantioselectivity (er) was measured by chiral stationary phase HPLC on a CHIRALCEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel]. [h] Solid CuCN was used. [i] TMSCl (5 equiv) was employed. [j] *E*:*Z* = 59:41, 72:28 er for each diastereomer.

yields and a modest er (entry 20). Oxidative cleavage of **10** followed by amide formation[14] gave the *R* amide confirming retention of configuration in the cuprate formation and reaction steps.[13]

These results establish that configurational stability can be achieved in the generation and reaction of chiral α-(*N*-carbamoyl)-alkylcuprates containing a stereogenic center at the carbon bound to copper, although the enantioselectivity is a function of the particular reaction, substrate, temperature, solvent, and cuprate reagent. The high enantioselectivities observed in the vinylation reactions with **2**−**4** and **6** suggest that these reactions proceed with configurational stability in the cuprate reagent. The slight loss of er when the cuprate reagent is formed or aged at higher temperatures (e.g., −60 to −40 °C) could reflect slow racemization of either the organolithium reagent or the cuprate reagent. The presumably slow formation of the cuprate reagent in Et_2O with insoluble CuCN requires elevated temperatures for complete cuprate formation and this procedure shows almost complete loss of enantioselectivity consistent with rapid racemization of the organolithium reagent at elevated temperatures.

Reaction of RCuCNLi with **7** gave good yields of **13** but no enantioselectivity while reaction with $R_2CuLi{\cdot}LiCN$ gave a low er that could be increased by longer reaction at lower temperature. This suggests that **7**, in contrast to **4**, may react by competing reaction pathways involving conjugate addition−elimination and direct substitution with the latter pathway giving rise to the observed enantioselectivity. The absence of enantioselectivity with RCuCNLi may reflect the lower reactivity of the reagent requiring higher temperatures to effect the reaction where competing racemization becomes a problem. Alternatively, the RCuCNLi reagent may effect the transformation via the conjugate addition−elimination pathway only.

Reaction of either cuprate reagent with **8** where only the 1,4-addition pathway is available gives no enantioselectivity suggesting that configurational lability of the chiral α-(*N*-carbamoyl)-alkylcuprate occurs along the reaction coordinate leading to conjugate addition. The loss of enantioselectivity in these 1,4-addition reactions may arise from an equilibrium between a cuprate−enone d,π^* complex and starting cuprate and enone, consistent with the er increasing with increasing substrate reactivity (e.g., **5** vs **8**). The modest er values observed with the propargyl substrate clearly indicate a temperature dependence.

In summary, chiral α-(*N*-carbamoyl)alkylcuprates with a stereogenic center bound to copper can display excellent configurational stability during cuprate formation and reaction depending upon solvent, temperature, particular cuprate reaction, and cuprate reagent. Although the absence of enantioselectivity in the conjugate addition reactions with enoates appears to be intimately involved with the reaction pathway, the observed er values in the substitution reactions appear to revolve around temperature and substrate reactivity effects. Use of chiral α-(*N*-carbamoyl)-alkylcuprates is a synthetically viable strategy for direct substitution reactions with vinyl iodides.

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Supporting Information Available: Synthesis of **10** and **12a** and absolute configuration for **10** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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