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Reactivity and Enantioselectivity in the Reactions of Scalemic Stereogenic α-(*N*-Carbamoyl)alkylcuprates

R. Karl Dieter,* Gabriel Oba, Kishan R. Chandupatla, Chris M. Topping, Kai Lu, and
Rhett T. Watson

*Howard L. Hunter Laboratory, Department of Chemistry, Clemson University,
Clemson, South Carolina 29634-0973*

dieterr@clemson.edu

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Stereogenic 2-(*N*-carbamoyl)pyrrolidinylcuprates prepared from scalemic (i.e., enantioenriched) *N*-Boc-2-lithiopyrrolidine and THF soluble $CuCN\cdot 2LiCl$ react with vinyl iodides, vinyl triflates, *β*-iodo-α,*β*-enoates, propargyl mesylates, and allyl bromide to afford the substitution products with excellent enantioselectivity. Excellent enantiomeric ratios are obtained in the conjugate addition reactions with methyl vinyl ketone while low enantiomeric ratios can be achieved with acrylate esters using HMPA/TMSCl activation. Enantiomeric ratios vary with substrate substitution patterns and the observed enantioselectivities appear to be more a function of cuprate−electrophile reactivities than of the reaction type (e.g., substitution, conjugate addition). Low enantiomeric ratios are obtained with the α-(*N*-carbamoyl)benzylcuprates. The lithium−copper transmetalation and cuprate vinylation reactions proceed with retention of configuration.

Introduction

Stereogenic organometallic compounds[1] containing a C−M bond between an asymmetric carbon atom and the metal counterion display a wide range of configurational stabilities depending upon the metal ion, substrate structure, and reaction conditions. They offer a potentially powerful strategy for asymmetric synthesis despite daunting challenges for stereocontrol in the formation of the reagents and in their subsequent reactions with electrophiles. Since the early work on scalemic (i.e., enantioeriched) α-alkoxyalkyllithium reagents[2] impressive progress has been achieved with scalemic lithiated *O*-allyl and alkyl carbamates (i.e., lithiation adjacent to oxygen),[3] α-lithio *N*-alkyl carbamates (i.e., lithiation adjacent to nitrogen),[3−5] α-lithio formamidines,[6] α-lithioamides,[7] and α-lithio amines.[1,3,4,8] Enantioselective reactions have also been achieved in a variety of lithiated benzylic systems.[3,4] Configurational stability increases with the covalent character of the C−M bond (i.e., in configurational stability Zn[9,10] > Mg[11] > Li[1−7]) and significant progress has also been made with organozinc reagents,[10] although attempts to prepare stereogenic zinc reagents by direct reduction with active zinc results in racemization.[9]

Modest configurational stability of stereogenic C−Cu bonds was first demonstrated by Whitesides in norbornyl systems[12a] and later extended to small and modest sized monocyclic ring systems[12b−h] providing opportunities for diastereoselective reactions upon quenching with electrophiles. Diastereoselectivity was also observed with stereogenic cuprate reagents containing a chiral auxiliary near the reactive C−Cu bond.[12h] Early work by Fuchs[13] and Linderman[14a,b] explored the reactions of scalemic

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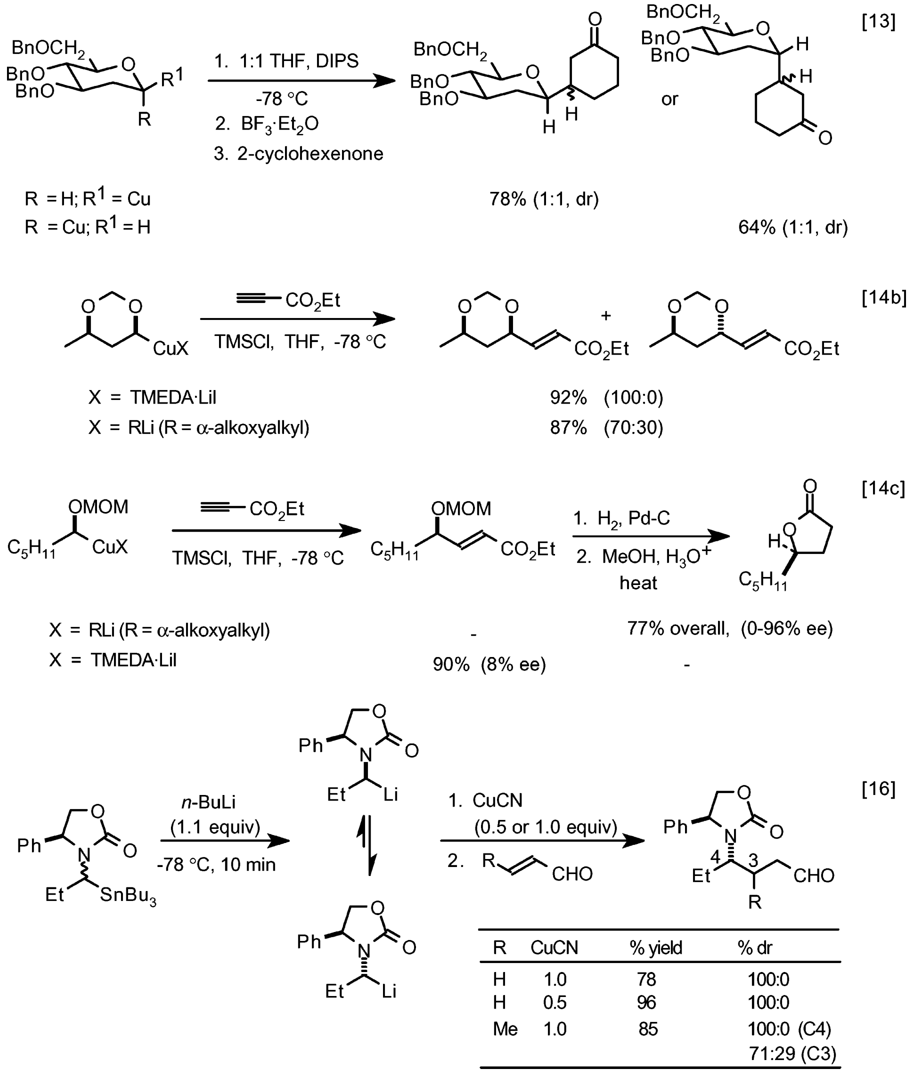
10.1021/jo035845i CCC: $27.50

SCHEME 1



R	CuCN	% yield	% dr
H	1.0	78	100:0
H	0.5	96	100:0
Me	1.0	85	100:0 (C4) 71:29 (C3)

α-alkoxyalkylcuprates prepared from configurationally stable α-alkoxyalkyllithium reagents. These reagents transferred the scalemic ligand with retention of configuration in various degrees of selectivity. Glucosyl and 4-(1,3-dioxanyl)copper reagents (i.e., RCu) gave excellent retention of configuration in conjugate addition reactions in the presence of $BF_3·Et_2O$ or TMEDA, respectively, while the dialkylcuprate derived from the 4-(1,3-dioxanylstannane) displayed poorer configurational stability (Scheme 1). Stereocontrol was capricious in acyclic cuprate reagents[14a] (Scheme 1), although a recent investigation with α-carbamoyloxy organocuprates[14c] proved more reliable. The procedure has been extended to a wider range of electrophiles with cuprates prepared from conformationally biased 4-lithio-1,3-dioxanes and good stereocontrol at the stereocenter β to the carbonyl was achieved in these systems.[14d] 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.[15] Knochel has achieved good diastereoselectivities in the reaction of zinc alkylcuprates prepared via the transmetalation sequence RBR'_2 to RZnX to RCuCNZnX[10] while scalemic alkyl Grignard reagents[11a] require the intermediacy of the zinc reagents for the preparation of stereogenic cuprate reagents with stereochemical integrity.

More recently, good diastereoselectivity has been achieved in conjugate addition reactions with stereogenic α-aminoalkylcuprates[16] under dynamic thermodynamic control (Scheme 1),[17] although poor diastereoselectivity at the β-carbon atom was obtained with acyclic α,β-enones. We have reported the first examples of high enantioselective vinylation of α-(*N*-carbamoyl)alkylcuprates via asymmetric deprotonation (reproducibly 80−87% ee, vide infra)[18a] or transmetalation[18b] and in this

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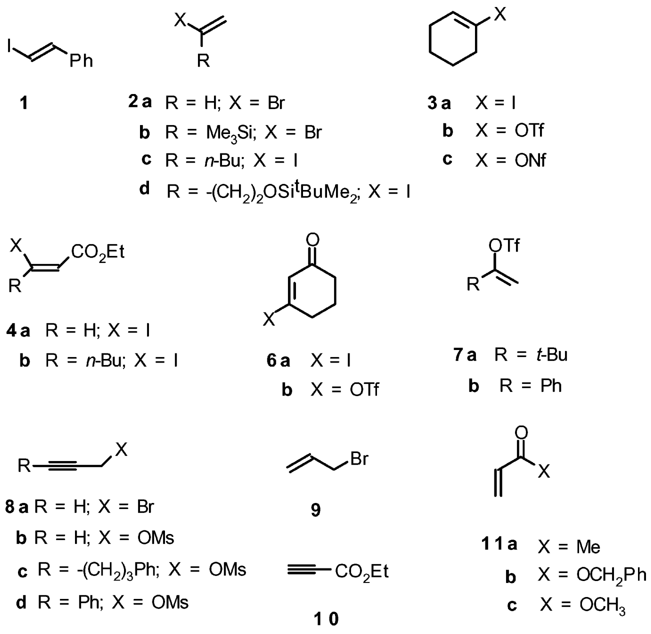
CHART 1

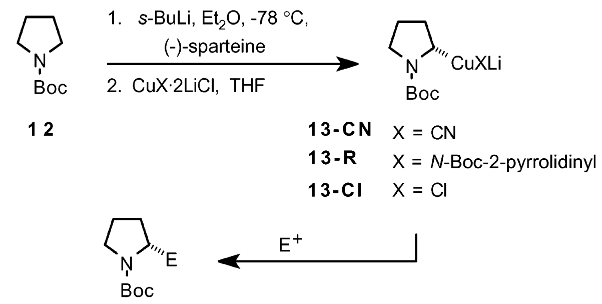


full report detail the enantioselectivities achieved with these scalemic stereogenic cuprate reagents (prepared via asymmetric deprotonation) as a function of the reaction, reagent composition, and reaction conditions. This survey reveals for the first time that enantioselectivities appear not to be an inherent function of the particular cuprate reaction (e.g., substitution vs conjugate addition) suggesting that scalemic stereogenic cuprate reagents may provide a broadly general strategy for asymmetric synthesis comparable to the emerging power of the lithium reagents in synthetic utility.

Results

N-Boc-pyrrolidinylcuprates provided an ideal system for examination, since both the asymmetric deprotonation reaction of *N*-Boc-pyrrolidine[19] and various cuprate transformations involving substitution (e.g., with vinyl triflates,[20a] vinyl iodides,[20b,c] propargyl,[21] and allylic[22] substrates) or conjugate addition[23] had been studied in detail. Anticipating reaction-dependent enantioselectivities, vinyl halides **1**, **2a**−**d**, and **3a**, β-iodo-α,β-enoates **4a**,**b**, and enone **6a**, β-trifluoromethylsulfonyloxy-α,β-enone **6b**, vinyl triflates **3b** and **7a**,**b**, nonaflate **3c**, propargyl substrates **8a**−**d**, allyl bromide **9**, and α,β-unsaturated carbonyl compounds **10** and **11a**−**c** (Chart 1) were examined.

SCHEME 2



Beak deprotonation[19] of *N*-Boc-pyrrolidine (**12**) in either THF or Et$_2$O followed by treatment with CuCN·2LiCl (Scheme 2) gave either the lithium alkylcyanocuprate **13-CN** (1.0 equiv CuCN) or the lithium dialkylcuprate **13-R** (0.5 equiv CuCN) reagent. Although *N*-Boc pyrrolidine was usually deprotonated in THF for preparation of the *N*-Boc-2-pyrrolidinyl cuprates in prior studies,[20−23] Beak had shown that this solvent was unsuitable for asymmetric deprotonation and/or carbanion configurational stability[19] and this was quickly confirmed.

Cuprate reagents **13-CN** and **13-R** prepared via deprotonation of **12** in Et$_2$O according to the Beak protocol[19] followed by addition of a THF solution of CuCN·2LiCl underwent enantioselective substitution reactions with vinyl iodides (Table 1). In all instances but one (entry 18 vs 19), **13-R** and **13-CN** gave comparable enantioselectivities (entries 1 vs 2, 4 vs 6, 9 vs 11, and 15 vs 16). Cuprate **13-CN** gave no enantioselectivity with 3-iodocyclohexenone (entry 18). Selectivity diminished as cuprate **13-R** was allowed to age at moderate (−60 to −40 °C) temperatures decreasing from a 90:10 to a 73:27 er after 2 h. Preparation of **13-R** with solid CuCN and briefly warming the solution to 25 °C to ensure complete cuprate formation resulted in little to no enantioselectivity (entry 3). Comparable enantiomeric ratios (88:15 to 88:12 vs 90:10 to 93:7) were obtained with vinyl bromide **2a** and **13-R** with significant er degradation with either a 2:1 or 4:1 THF:E$_2$O solvent mixture (entries 4 and 5). 1-Bromo-1-trimethylsilylethene required reaction at low temperatures for long times to achieve excellent ers (entry 8 vs 7) which was not required for 2-iodo-1-alkenes **2c**,**d**, 1-idodocyclohexene **3a**, or 3-iodo-α,β-enoates **4a**,**b** which gave excellent enantioselectivities upon slow uncontrolled warming of the reaction mixtures (entries 9−17). Scaling the reaction of cuprate **13-R** or **13-CN** with **4a** from 1 to 10 mmol gave very comparable ers, although there was slight variation from experiment to experiment (entries 14−16). Reaction of **13-R** with **6a** gave enantioselectivities that were sensitive to time and temperature (entries 19 and 20). The use of CuCl·2LiCl (i.e., **13-Cl)** gave very good but lower ers than **13-CN** (entries 9 and 10).

A comparison of vinyl triflates and nonaflates with the vinyl iodides was undertaken to examine the effect of leaving group upon the enantioselectivity of the reaction (Table 2). The vinyl triflates and nonaflates uniformly gave higher chemical yields with the **13-CN**/THF/TMEDA cuprate/solvent/additive system than with the

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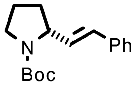
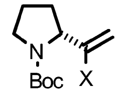
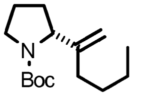
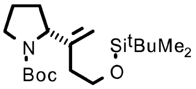
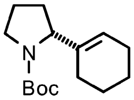
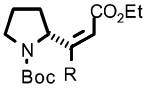
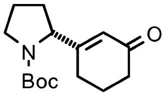
TABLE 1. Reactions of Scalemic α-(*N*-carbamoyl)alkylcuprates, Prepared from Scalemic α-Lithio *N*-Boc Pyrrolidine, with a Variety of Electrophiles

entry	E^+	Cu(I) equiv[a]	temperature Cu °C (min)[b]	solvent[c]	temperature Rxn, °C (h)[d]	Product[e]	cpd No.	% yield[f]	% er[g]
1	**1**	0.5	-78 to -60 (60)	A	-60 to 25 (12)		**14**	85-98	90:10-93:7
2	**1**	1.0	-78 to -60 (105)	A	-60 to 25 (12)		**14**	70	89:11
3	**1**	0.5[h]	-78 (45) 25 (15)	B	-60 to 25 (12)		**14**	70	51:49-55:45
4	**2a**	0.5	-78 (60)	A	-78 to 25 (12)	 **a** X = H **b** X = $SiMe_3$	**15a**	66-69	85:15-88:12
5	**2a**	0.5	-78 (60)	A 4:1[i]	-78 to 25 (12)		**15a**	59	71.5:28.5
6	**2a**	1.0	-78 (60)	A 1:1.3[i]	-78 to 25 (12)		**15a**	60	72.5:27.5
7	**2b**	0.5	-78 (60)	A	-78 to 25 (12)		**15b**	96	65.5:34.5
8	**2b**	0.5	-78 (60)	A	-60 (10)		**15b**	90	90:10
9	**2c**	1.0	-78 (60)	A 1:1.3	-78 to 25 (12		**16**	70-83	97:3-92:7
10	**2c**	1.0[j]	-78 (60)	A 1:1.3	-78 to 25 (12		**16**	63-82	86.5:13.5-82:188
11	**2c**	0.5	-78 (60)	A	-78 to 25 (12)		**16**	66	95.4:4.6
12	**2d**	0.5	-78 (60)	A	-78 to 25 (12)		**17**	79-84	94:6
13	**3a**	0.5	-78 (60)	A 1:1.3[i]	-78 to 25 (12)		**18**	58	90.7:9.3
14	**4a**	0.5	-78 (60)	A	-78 to 25 (12)	 **a** R = H **b** R = *n*-Bu	**19a**	89	95:5-96:4
15	**4a**	0.5[k]	-78 (60)	A	-78 to 25 (12)		**19a**	80	90:10
16	**4a**	1.0[k]	-78 (60)	A	-78 to 25 (12)		**19a**	88	86.5:13.5
17	**4b**	0.5	-78 (60)	A	-78 to –35 (3)		**19b**	53[l]	91:9
18	**6a**	1.0	-78 (60)	A	-78 to 25 (12)		**20**	80	50:50
19	**6a**	0.5	-78 (60)	A	-78 to 25 (12)		**20**	79	65:35
20	**6a**	0.5	-78 (60)	A	-40 (8)		**20**	79	80:20

[a] CuCN·2LiCl was employed and reactions run on a 1.0 mmol (**12**) scale unless otherwise noted. [b] Temperature and time at which cuprate formation was achieved. [c] A = THF/Et_2O solvent ratio (1:1 (v/v) unless otherwise noted) arose by deprotonation of carbamate in Et_2O followed by addition of a THF solution of CuCN·2LiCl. B = Et_2O. [d] Temperature and time at which the cuprate/electrophile reaction was allowed to proceed. [e] Transmetalation and cuprate reactions are assumed to proceed with retention of configuration[13,14,18a] from scalemic *N*-Boc-α-lithiopyrrolidine.[19] Confirmed for **14**. [f] Based on products purified and isolated by flash column 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] 2.0-mmol scale. [j] CuCl·2LiCl was employed. [k] 10-mmol scale. [l] TMSCl (5.0 equiv) was employed.

13-R/THF/Et_2O/(−)-sparteine system (entries 1 vs 2, 3 vs 6, 7 vs 8, and 9 vs 10). For Nonaflate **3c**, where a direct comparison of the two cuprates was made, the chemical yields are a function of both the solvent and the cuprate reagent since **13-R** gives higher chemical yields than **13-CN** in either solvent and both reagents give higher chemical yields in THF alone (entries 3−6). The α-substituent in the vinyl substrate has a small effect upon the chemical yields. Since an α-phenyl substitutent with a smaller *A*-value[24] than a *tert*-butyl substituent gives a lower chemical yield (entries 9 and 10 vs 7 and 8) electronic factors appear to be more important than steric factors. The vinyl iodide analogue of **7b** failed to undergo substitution reactions with pyrrolidinyl cuprates. Chemical yields for the cyclohexenyl derivatives **3a**−**c** decreased along the series Tf > I > Nf for both cuprate−solvent−additive systems [**13-CN**/THF/TMEDA: 80, not available, 53; entries 1 and 3 Table 2; **13-R**/THF/Et_2O/(−)-sparteine: 65, 58, 50 entries 2 and 6 Table 2, entry 13, Table 1]. Despite the chemical yield variation as a function of leaving group and substrate structure, vinyl iodide **3a** and triflates **3b** and **7a**,**b** gave excellent ers (i.e., 89.5:10.5 to 95.5:4.5, entry 13 Table 1, entries 2, 8, and 10 Table 2) upon reaction with **13-R** in THF/Et_2O. For **13-R** and **3a**−**c** the er was comparable along the series OTf ≈ ONf ≈ I, while **13-CN** gave a low er with **3c** (Table 2, entry 4) in contrast to vinyl iodides **1**, **2c**, and **4a** and vinyl bromide **2a**, all of which gave modest to excellent ers (Table 1, entries 2, 9, 16, and 6).

The reaction of *N*-Boc-2-pyrrolidinylcuprates with propargyl substrates generally gave modest chemical yields and variable ers (Table 3). The alkylcyanocuprate reagent **13-CN** gave significantly better chemical yields than the dialkylcuprate reagent **13-R** (entries 2 vs 3, 4 vs 5, and 6 vs 7) in the THF/Et_2O mixed solvent system and the high chemical yields were uniformly obtained with **13-CN** in THF alone (70−86%). Unfortunately, no to poor enantioselectivities were obtained with **13-CN** and **8b**,**c** (entries 2 and 4) while **13-CN** and **8d** gave modest ers comparable to **13-R** and **8d** (entries 6 and 7). Excellent ers could be achieved with **13-R** and **8c** (entry 5) while modest ers were achieved with propargyl bromide (**8a**,

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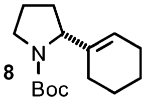
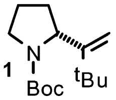
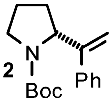
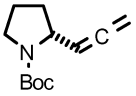
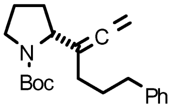
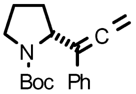
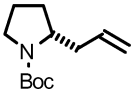
TABLE 2. Reactions of Racemic and Scalemic 2-Pyrrolidinylcuprates with Enol Triflates or Nonaflates

entry	ester	Rxn cond[a]	RCuCN·2LiCl (equiv)[b]	product	% yield[c]	% er[d]
1	**3b** Tf	A	1.0	**18** 	80	-
2	**3b** Tf	B	0.5		65	94.3:5.7
3	**3c** Nf	A	1.0		53	-
4	**3c** Nf	B	1.0		36	63.5:36.5
5	**3c** Nf	A	0.5		80	-
6	**3c** Nf	B	0.5		50	92:8
7	**7a** Tf	A	1.0	**21** 	71	-
8	**7a** Tf	B	0.5		60	89.5:10.5
9	**7b** Tf	A	1.0	**22** 	55	-
10	**7b** Tf	B	0.5		45	95.5:4.5

[a] Conditions for the deprotonation of the *N*-Boc carbamate: A = *s* −BuLi, TMEDA, THF, −78 °C, 1 h. B = *s*-BuLi, (−)-sparteine, Et_2O, −78 °C, 1 h. [b] Cuprate prepared from RLi and CuCN·2LiCl at −78 °C, 1 h. Electrophile added at −78 °C and warmed to room temperature overnight. [c] Based on products purified and isolated by chromatography. [d] Enantioselectivity (% er) was measured by chiral stationary phase HPLC on a CHIRALCEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel]. [e] Transmetalation and cuprate reactions are assumed to proceed with retention of configuration[13,14,18a] from scalemic *N*-Boc-α-lithiopyrrolidine.[19]

TABLE 3. Reactions of Scalemic α-(*N*-Carbamoyl)alkylcuprates, Prepared from Scalemic α-Lithio *N*-Boc Pyrrolidine, with Propargyl and Allylic Substrates

entry	E⁺ (LG)	Cu(I) equiv[a]	temperature Cu °C (min)[b]	temperature Rxn, °C (h)[c]	Product[d]	cpd. No.	% yield[e]	% er[f]
1	**8a** Br	0.5	-78 (60)	-78 to 25 (12)		**23**	48	75:25
2	**8b** OMs	1.0	-78 (60)	-78 to 25 (12)		**23**	76	58.4:41.6
3	**8b** OMs	0.5	-78 (60)	-78 to 25 (12)		**23**	58	74.4:25.6
4	**8c** OMs	1.0	-78 (60)	-50 (10)		**24**	79	50:50
5	**8c** OMs	0.5	-78 (60)	-78 (5)		**24**	57	90:10
6	**8d** OMs	1.0	-78 to -50 (60)	-78 (5)		**25**	40-56	68:32-77:23
7	**8d** OMs	0.5	-78 (60)	-78 to 25 (12)		**25**	33	69:31
8	**9** Br	0.5	-78 (60)	-78 to 25 (12)		**26**	100	89:11

[a] CuCN·2LiCl was employed unless otherwise noted. [b] Temperature and time at which cuprate formation was achieved. 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. [c] Temperature and time at which the cuprate/electrophile reaction was allowed to proceed. [d] Transmetalation and cuprate reactions are assumed to proceed with retention of configuration[13,14,18a] from scalemic *N*-Boc-α-lithiopyrrolidine.[19] [e] Based on products purified and isolated by flash column chromatography. [f] Enantioselectivity (% er) was measured by chiral stationary phase HPLC on a CHIRALCEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel].

entry 1) or mesylate (**8b**, entry 3) and with the phenyl-substituted propargyl mesylate **8d** (entry 7). Allyl bromide gave excellent chemical yields and enantioselectivity with **13-R** (entry 8).

Conjugate addition reactions were examined using the very reactive ethyl propiolate (**10**) and methyl vinyl ketone (**11a)** as well as the less reactive acrylate esters **11b**,**c** (Table 4). The reaction of **13-CN** with **10** gave a mixture of *E*:*Z* diastereomers each of which was obtained with the same modest er (entry 1). The very reactive **11a** gave comparable chemical yields with either **13-CN** or **13-R** and very excellent ers (entries 2−4). The use of $^{n}Bu_3P$ in place of LiCl with **13-CN** gave the same results (entries 2 and 3). Initial studes with acrylate ester **11b** gave excellent chemical yields in the presence of TMSCl and in all cases gave no enantioselectivity (entries 5 and 6). Reexamination of the reaction with methyl acrylate **11c** revealed that poor ers could be achieved with the use of the HMPA/TMSCl additive (entry 7).[25]

In an effort to explore whether reversible cuprate/enoate d−π^* complexation played any role in the diminished ers observed for the conjugate addition reactions, several control experiments were performed. Cuprate **13-R** was treated with 5,6-dihydro-2*H*-pyran-2-one and TMSCl at −78 °C for 30 min followed by addition of vinyl iodide **4a**. In two experiments, a pale yellow color appeared upon addition of the lactone to **13-R** and product **19a** obtained via coupling of **4a** with **13-R** gave good chemical yields (86−89%) and enantioselectivities (92.5:7.5% er).

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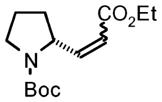
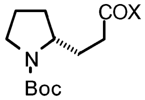
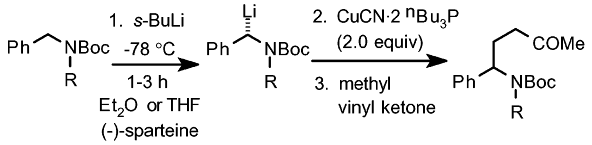
(25) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349−362.

TABLE 4. Reactions of Scalemic α-(*N*-carbamoyl)alkylcuprates, Prepared from Scalemic α-Lithio *N*-Boc Pyrrolidine with α,β-Unsaturated Carbonyl Compounds

entry	E^+	Cu(I) equiv[a]	temperature Cu °C (min)[b]	temperature Rxn, °C (h)[c]	Product[d]	cpd No.	% yield[e]	% er[f]
1	**10**	1.0	-78 (60)	-78 to 35 (3)		**27**	56[g]	72:28[g]
2	**11a**	1.0	-78 (60)	-78 (30), 25 (12)	 **a** X = Me **b** X = OCH_2Ph **c** X = OMe	**28a**	54	97.6:2.4
3	**11a**	1.0 [h]	-78 (60)	-78 (30), 25 (12)		**28a**	55	98:2
4	**11a**	0.5	-78 (60)	-78 (30), 25 (12)		**28a**	91	90:10
5	**11b**	1.0	-78 (60)	-78 to 25 (12)		**28b**	95	50:50
6	**11c**	1.0	-78 (60)	-55 to 25 (12)		**28c**	72	50:50
7	**11c**	0.5	-78 (60)	-55 to 25 (12)		**28c**	88	60:40[i]

[a] CuCN·2LiCl was employed unless otherwise noted. [b] Temperature and time at which cuprate formation was achieved. 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. [c] Temperature and time at which the cuprate/electrophile reaction was allowed to proceed. TMSCl (5.0 equiv) was employed as an additive. [d] Transmetalation and cuprate reactions are assumed to proceed with retention of configuration[13,14,18a] from scalemic *N*-Boc-α-lithiopyrrolidine.[19] [e] Based on products purified and isolated by chromatography. [f] Enantioselectivity (% er) was measured by chiral stationary phase HPLC on a CHIRALCEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel]. [g] *E*:*Z* = 59:41; 72:28 er for each diastereomer. [h] $^nBu_3P$ (2.0 equiv) was added to solubilize CuCN. [i] HMPA/TMSCl (2.0 equiv) was added along with the methyl acrylate.

Several experiments were performed with acyclic benzylic stereogenic cuprate reagents and in all cases low to modest yields and enantioselectivities were obtained. Although previous studies either did not report or noted a solvent dependence[26] on the regioselective deprotonation of *N*-Boc-*N*-methylbenzylamine **29a**, deprotonation [*s*-BuLi (1.2 equiv), THF, TMEDA, −78 °C, 2 h] followed by quenching with MeI gave alkylation at the benzylic position, the methyl position, and at both sites [50.3%, 37%, and 12.7%, respectively]. Consequently, we chose to examine the *N*-ethyl analogue **29b** to minimize this complication (eq 1). *N*-Boc-*N*-ethylbenzylamine **29b** was deprotonated in Et_2O or THF and allowed to stir at −78 °C for 2−3 h to allow the dominant α-lithiocarbamate/(−)-sparteine complex to form.[26a] CuCN solubilized with *n*-Bu_3P was employed in these experiments. No enantioselectivity was observed in Et_2O when the cuprate solution was allowed to warm to room temperature slowly. Modest selectivities (36−40% ee) were obtained when the solution was rapidly warmed to room temperature irrespective of the temperature at which the electrophile was added if the temperature was at or below −60 °C. In control experiments, deprotonation of **29b** in Et_2O with the *s*-BuLi/(−)-sparteine complex [−78 °C, 5 h] followed by quenching with MeI at −78 °C gave the alkylation product (i.e., **34**) in 68% yield and with an enantioselectivity of 83:17 (66% ee), which compares favorably with the 62% ee reported[26a] for the asymmetric deprotonation and methylation of **29a**. Utilization of this longer deprotonation time did not increase the enantioselectivity of the cuprate-mediated conjugate addition reaction (31:69 er vs 28.3:71.7 to 35.7:66.3). Both procedures gave low selectivities in THF (14−19% ee) and the same selectivity was obtained with CuCN·2LiCl. The major enantiomer was the opposite of that obtained in Et_2O consistent with the results reported for quenching the benzyllithium reagent generated from **29a**.[26a] In contrast to the *N*-methyl analogue **29a**[26a] no precipitate was observed in THF during the deprotonation of **29b** with concentrations of **29b** ranging between 1 and 0.33 M. Alkylation of **30b** with MeI in THF afforded the α-phenylethylamine in good chemical yield with low enantioselectivity (9−12% ee). Again, no precipitation was observed at −78 °C after 3 h. Generation of **30b** in toluene with *n*-BuLi/(−)-sparteine [−78 °C, 4 h] followed by cuprate formation and treatment with methyl vinyl ketone gave **31b** with a diminished selectivity (er: 63.3:36.7). (*S*)-d_1-**29a** fails to undergo metalation with *s*-BuLi/(−)-sparteine[26a] and assignments of absolute stereochemistry for **30b** are predicated on the assignments and assumptions reported for **29a**, although these appear not to have been rigorously established.[26a−c] The assignments for **31b** also require the assumption that Li to Cu transmetalation and the subsequent organocopper reaction both proceed with retention of configuration as previously observed[12a,13,14] and demonstrated for **14**,[18] **15a**, **22**, and **26** (vide infra).



(1)

29a R = Me
b R = Et

30

31

Et_2O -78 to -60 °C (0.5 h), 25 °C (12 h) 48-59% (28.3:71.7 - 32:68)
THF -78 to -60 °C (4.0 -0.5 h), 25 °C (12 h) 50-79% (53.3:46.7 - 59.5:40.5)

Asymmetric deprotonation of **29b** and reaction of the alkylcyanocuprate (i.e., RCuCNLi) derived from **30** with (*E*)-1-iodo-1-hexene (**32**) gave good chemical yields of the vinylation product **33** [i.e., (*E*)-PhCH(EtNBoc)-CH=CH^{n}Bu] but no enantioselectivity, while utilization of the dialkylcuprate (i.e., R_2CuLi) gave no vinylation product. Scalemic (*R*) α-phenylethylbenzylamine **34**

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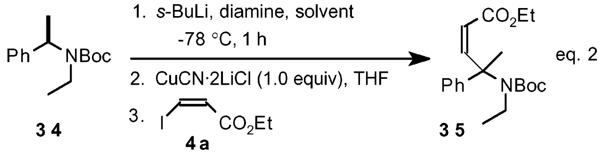
[26] (a) Schlosser, M.; Limat, D. *J. Am. Chem. Soc.* **1995**, *117*, 12342−12343. (b) Voyer, N.; Roby, J. *Tetrahedron Lett.* **1995**, *36*, 6627−6630. (c) Barberis, C.; Voyer, N.; Roby, J.; Chénard, S.; Tremblay, M.; Labrie, P. *Tetrahedron* **2001**, *57*, 2965−2972. (d) Park, Y. S.; Boys, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3757−3758. (e) Park, Y. S.; Beak, P. *Bull. Korean Chem. Soc.* **1998**, *19*, 1253−1256. (f) Dieter, R. K.; Yu, H. *Org. Lett.* **2000**, *2*, 2283−2286.

showed similar enantioselectivities in THF/TMEDA, THF/(−)-sparteine, and Et_2O/TMEDA (eq 2) but reduced selectivity in Et_2O/(−)-sparteine consistent with the solvent-dependent enantioselection reported for **30a**.[26a] Initial deprotonation of **34** must lead to the (*R*)-benzyllithium reagent and, assuming retention (relative to the stereogenic C−Li bond) of configuration during cuprate formation and subsequent reaction, assignment of the *S*-configuration to the major enantiomer of **35** can be made. Related studies on scalemic α-phenylethylamines have employed *n*-BuLi/(−)-sparteine for deprotonation.[27] Nevertheless, benzylic cuprates derived from **34** show modest enantioselectivity for the sequence of events involving deprotonation, cuprate formation, and the vinylation reaction (eq 2). Further efforts to optimize these results were not undertaken.



Diamine	solvent	% yield	er
TMEDA	THF	47	77.5:22.5
TMEDA	THF	62	75:25
TMEDA	Et_2O	55	65:35
(-)-sparteine	THF	44	69:31
(-)-sparteine	Et_2O	48	58:42

The absolute configuration of **14** was established by chemical correlation with (*S*)-proline, using an established procedure.[28a] Oxidation of **14** [$NaIO_4$, $ReCl_3{\cdot}H_2O$, CCl_4, CH_3CN, 25 °C] to *N*-(*tert*-butoxycarbonyl)proline followed by amide formation [dicyclohexylcarbodimide, 3,4-dimethylaniline, hydroxybenzotriazole] gave material with an enantiomeric purity of 89.5:10.5 as determined by chiral stationary phase HPLC on a CHIRALCEL OD column, which compares favorably with the 91.4:8.6 er determined for the starting material **14**. The major isomer eluted first at 11.50 min with the minor isomer eluting at 16.08 min while the amide prepared from commercially available (*S*) proline eluted at 15.74 min.[18a] Formation of the (*R*)-amide establishes that cuprate formation and the cuprate vinylation reaction[18a] both proceed with retention of configuration from (*S*)-*N*-Boc-2-lithiopyrrolidine.[19,28a] The (*S*)-ethyl carbamate analogue of **15a** ($[\alpha]^{24}_D$ +13.3 (*c* 1.43, THF) for er 88:12) has a reported[28a] specific rotation of $[\alpha]^{22}_D$ −23.2 (*c* 1, EtOH) for an er 83:17, resulting in assignment of the (*R*)-configuration to **15a** consistent with retention of configuration in cuprate formation and reaction with vinyl bromide. Similarly, **26** ($[\alpha]^{24}_D$ +38.0 (*c* 3.69, THF) for er 89:11) can by assigned the (*R*)-configuration by comparison with the reported[28b] specific rotation for the known (*S*)-enantiomer ($[\alpha]^{25}_D$ −32.4 (*c* 1.56, $CHCl_3$)). Ozonolyis of **22** gave the corresponding ketone in 95% yield with a specific rotation $[\alpha]^{24}_D$ +28.1 (*c* 1.35, $CHCl_3$), the opposite rotation to that reported in the literature ($[\alpha]^{23}_D$ −63.1 (*c* 1.02, $CHCl_3$))[28c] for the (*S*)-enantiomer. This is again consistent with both cuprate formation and vinylation proceeding with retention of configuration.

Discussion

Organocopper reagents are generally prepared by transmetalation reactions and the stereochemical integrity of this event, as well as that of the subsequent reaction with an electrophile, increases the difficulties of developing synthetically useful stereogenic organocuprate methodologies. Stereogenic cuprate reagents may lose stereochemical integrity during either transformation or as an epimerization process competitive with the cuprate−electrophile reaction. Previous studies offer no consistent explanation for the loss of stereochemical integrity in stereogenic organocopper reagents. The 2-endonorbornylcuprate study showed that cuprate configurational integrity decreased along the series RCu^tBuLi (99:1) > RCuMeLi (94:6) > $R_2CuMgBr$ (i.e., Grignard + 5 mol % of $ICuPBu_3$, 81:19) > $RCuPBu_3$ (47:53) [R = 2-endonorbornyl, 99:1) in the conjugate addition reactions with mesityl oxide. The greater loss of stereochemical integrity with cuprates derived from 65:35 *endo*:*exo* equilibrium mixtures of 2-norbornylmagnesium bromides suggests formation of byproducts that increase epimerization of the cuprate reagents.[12a]

Racemization in α-alkoxyalkylcuprates occurs at higher temperatures in both cyclic and acyclic systems and is reported to be highly dependent upon trace impurities [e.g., oxygen, Cu(II), or tin impurities] in the reaction mixture.[13,14a,b] Oxygen-induced dimer formation from an enantiopure α-alkoxyalkylcuprate with retention of configuration (40% yield, >90% retention) suggests that racemization does not occur during the transmetalation step. Racemization increases with increasing amounts of dimer and both events may be induced by trace amounts of oxygen.[14] Both the norbornyl and the stereogenic α-alkoxyalkylcuprate studies confirm that the conjugate addition is not proceeding by a radical pathway and racemization has been postulated to occur prior to the enone oxidative addition−reductive elimination sequence even though the fast 1,4-addition process racemizes the stereogenic ligand significantly faster than the dimerization pathway.[14a] In the cyclic systems, enantiopure α-alkoxyalkylcopper reagents prepared from $CuBr{\cdot}SMe_2$[13] or CuI·TMSI [e.g., >98% de vs 40% de with ethyl propiolate][14a] give retention of configuration to a greater extent in conjugate addition reactions than $R_2CuLi{\cdot}LiCN$ reagents (Scheme 1). More recently, it has been suggested that racemization is faster or more facile in the first transmetalation step forming RCuMgX then in the second transmetalation step forming R_2CuMgX during the preparation of magnesium cuprates from stereogenic Grignard reagents.[11a]

Although no kinetic measurements were undertaken, the present survey of enantioenriched lithium 2-pyrrolidinylcuprates suggests that relative rates between racemization and cuprate−electrophile reaction in this series may be the principal factor governing stereoselectivities and stereochemical integrity. While the ers listed in Tables 1−4 range from nonexistent to excellent, poor

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(27) Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561−11570.

(28) (a) Serino, C.; Stehle, N.; Park, Y. S.; Florio, S.; Beak, P. J. *J. Org. Chem.* **1999**, *64*, 1160−1165. (b) Park, S. O.; Kang, H. J.; Ko, S.; Park, S.; Chang, S. *Tetrahedron*: *Asymmetry* **2001**, *12*, 2621−2624. (c) Ookawa, A.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1465−1471.

ers could often be improved by optimization of reaction parameters including cuprate reagent, substrate structure, solvent, temperature, and time elements, as well as the use of additives.

This exploratory survey demonstrates that stereogenic α-(*N*-carbamoyl)alkylcuprates can be prepared efficiently from *N*-Boc-2-lithiopyrrolidine when soluble forms of Cu(I) salts are employed and that configurational integrity is maintained in the copper-mediated reactions with certain electrophiles. Use of soluble Cu(I) salts promotes rapid cuprate formation at −78 °C where racemization of the precursor organolithium reagent is slowed. When pyrrolidinylcuprates **13-CN** and **13-R** were allowed to age at −60 (105 min, 89:11 er) and −40 °C (120 min, 73:27 er), respectively, before addition of *trans-β*-iodostyrene (**1**), good enantioselectivities were still obtained. These results indicate that **13-CN** and **13-R** racemize slowly at temperatures below −40 °C. The reactions of cuprates **13-CN** and **13-R** with electrophiles to give **14**, **15a**, **22**, and **26** were shown to proceed with retention of configuration about the stereogenic carbon center consistent with previous observations.[12−14,16] When these results are taken as a whole, the principal pattern that emerges is one of relative reactivities involving both the cuprate reagents and electrophiles governing stereochemical outcome. Thus, the enantioselectivity of the reactions appears to be less a function of the reaction type (e.g., vinyl vs propargyl substitution vs conjugate addition) than of the reactivity of the electrophile and/or cuprate employed. The vinylation reactions listed in Table 1 generally proceed with comparable or higher ers when lithium dialkylcuprate **13-R** is used and either a 2:1 or 4:1 THF:Et_2O solvent mixture (achieved upon addition of CuCN·2LiCl/THF) gives significantly lower ers (entries 4 and 5). Although rate acceleration of organocuprate substitution reactions occurs in polar solvents[29] (e.g., THF), there is also an increase in the rate of racemization[1b] of the stereogenic organometallic reagents. Increasing amounts of THF may accelerate the substitution reaction while also enhancing the rate of racemization of the stereogenic cuprate reagent and/or the organolithium reagent during cuprate formation. The organolithium reagent appears to racemize more rapidly as evidenced by the lower er observed in a 2:1 or 4:1 THF:Et_2O mixture obtained during mixing of the organolithium reagent with the THF solution of CuCN·2LiCl (entry 5) and the slow racemization of the cuprate reagents (i.e., both **13-R** and **13-CN**) as the solution is allowed to stand at −60 to −40 °C for 1.75−2 h. Rapid racemization also occurs when solid CuCN is employed and the reaction mixture is warmed to 25 °C for brief periods of time (Table 1, entry 3). The slow formation of the cuprate reagent with solid CuCN again points toward rapid racemization of the organolithium reagent as solvent polarity and temperature are increased.

The importance of relative reactivity also emerges from a comparison of the Gilman reagent **13-R** (R_2CuLi) and the cyanocuprate **13-CN** (RCuCNLi) since the latter is significantly less reactive in vinylation and conjugate addition reactions.[20c] With reactive electrophiles (e.g., **1**, **2c**, **4a**) both reagents give comparable ers while with less reactive electrophiles **13-CN** gives reduced ers (vinyl bromide **2a**) while high ers are still obtained with **13-R**. This view is bolstered with the observation that **13-R** reacts with sterically hindered 1-iodovinyl silane **2b** to give modest enantioselectivity when the solution slowly warms to room temperature and excellent ers when the reaction mixture is stirred at −60 °C for 10 h. This result suggests that when the reaction of the cuprate with an electrophile is slow racemization becomes a competitive process. As noted above, it appears that both cuprate reagents begin to racemize slowly around −60 to −40 °C. Thus a more reactive **13-R** may undergo complete reaction at lower temperatures while a less reactive **13-CN** may require higher temperatures where racemization now becomes competitive.[30] It has recently been reported[11a] that greater racemization occurs in the initial transmetalation to form RCuCNMgX than in the second transformation to form R_2CuMgX for enantioenriched magnesium cuprate reagents and this does not seem to be the case with the lithium α-(*N*-carbamoyl)alkylcuprates.

The importance of relative reactivity is also seen in the combination of cuprate reagent and leaving group. For **13-R** and **3a-c** the enantioselectivity is nearly identical within experimental error along the series OTf ≈ ONf ≈ I (Tables 1 and 2) while nonaflate **3c** gives low chemical yields and low enantioselectivity with the less reactive cuprate **13-CN**. It should be noted that while triflate **7b** gave good ers the corresponding vinyl iodide failed to afford significant amounts of **22**. When a particular vinyl iodide gives low chemical yields or enantioselectivities, better results can generally be achieved by carrying the reaction out at lower temperatures for longer periods of time. This optimization protocol suggests that in difficult reactions vinyl iodide decomposition pathways are suppressed at lower temperature and similar decomposition pathways are unavailable to the vinyl triflates. The chemically unstable vinyl triflate **6b** gave racemic **20**. Electronic factors are also important in determining resultant chemical yields as the more sterically hindered **7a** (*A* value > 4.5)[24a,b] gives a higher yield of **21** than **7b** (*A* value = 2.9)[24a,c] does of **22**. Although we do not have rate data to quantify this perspective, it appears that the relative reactivities of both the cuprate and substrate play important roles in determining both chemical yields and enantioselectivities.

The relative cuprate/substrate reactivity profiles are also important in the proparyl substitution reactions (Table 3). Propargyl bromide **8a** and propargyl mesylates **8b**,**c** react with the less reactive cuprate **13-CN** to give higher chemical yields but no enantioselectivity while the more reactive cuprate **13-R** gives modest to excellent ers but low chemical yields. The chemical yield profile remains the same for propargyl mesylate **8d** but both cuprates now give comparable ers. Excellent chemical yield and enantioselectivity is observed with the very reactive allyl bromide.

Initial conjugate addition studies with acrylic esters gave no eantioselectivity, suggesting a dependence upon

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[29] House, H. O.; Wilkins, J. M. *J. Org. Chem.* **1978**, *43*, 2443−2454.

[30] A referee has pointed out that "increase selectivity [of **13-R** at lower reaction temperatures can occur] by increased kinetic differentiation between two diastereomeric reaction pathways [leading] to different enantiomers". This effect would also account for **13-R** giving higher ers than the less reactive **13-CN**. The formation of diastereomeric cuprate−substrate complexes would provide such a pathway, although their involvement in vinylation reactions is unclear.

reaction type and pathway. Control experiments involving formation of nonproductive olefin−cuprate π-complexes with nonreactive α,β-unsaturated lactones followed by addition of reactive electrophiles showed no diminution in the ers. This is consistent with stereochemical integrity during reversible olefin−cuprate complexation events. Subsequent work with methyl vinyl ketone revealed that excellent enantioselectivities could be achieved in conjugate addition reactions with **13-R** and with **13-CN**. Modest selectivities were achieved with ethyl propiolate and with methyl acrylate when the rate-accelerating additive HMPA/TMSCl was employed. These observations again suggest that ers are largely governed by relative reactivities. Reactive substrates and cuprates give excellent ers even when the more reactive cuprate gives lower chemical yields.

The benzylic substrates pose challenging problems for both the organolithium[26a−e] and organocopper[31] reagents. The configurational stability of benzylic lithium reagents is dependent upon a combination of the *N*-substitution pattern as well as solvent, additives, and temperature.[1b,3,4,26,27] In some instances, the benzylic carbanions in these systems approach planarity[26a,c] and the chirality arises via facial selectivity in the complexation of the benzylic lithium reagent with the chiral diamine (e.g., sparteine). Benzylic lithium/(−)-sparteine contact species (CS) derived from **29a** exhibit dynamic properties and opposite enantioselection was observed in hexane or Et_2O (retention) and THF (inversion).[26a] In THF, little enantioselectivity was observed until a benzyllithium/sparteine complex precipitated from solution[26a] and a 68:32 er (36% ee, conditions not specified) has been reported[26d,e] in the reaction with methyl iodide. Treatment of racemic **30a** with (−)-sparteine followed by CO_2 affords the racemic acid in Et_2O[26c] and the scalemic acid in THF (82% ee).[26a] These results (for **29a**/**30a**) have been interpreted in terms of a dynamic kinetic resolution mechanism,[26a] an enantioselective deprotonation−substitution mechanism, or a competition of the two pathways.[26c] The evidence on whole suggests an enantioselective deprotonation−substitution in Et_2O and a dynamic resolution in THF. Reactions of the organocuprates derived from **29b** with methyl vinyl ketone displayed enantioselectivities in Et_2O [28.3:71.7 to 35.7−66.3 vs (24.5:75.5 to 16.5−83.5)[26a] and (21:79)[26c] for lithium reagent **30a** with various electrophiles] and in THF [53.3:46.7 vs 68:32 for methylation of **30a**,[26d,e] and 57:43 for carboxylation of **30a**[26c]] comparable to the lithium reagent derived from **29a**. Although significantly lower ers were observed for the cuprate reagent derived from **30b** in THF than those reported by Schlosser for the lithium reagent **30a**, the lithium reagent **30b** never formed a precipitate with sparteine as did **30a**, which was required for high enantioselectivity. Similar ers were observed for the tertiary alkylcuprate derived from **34** in both THF and ether with TMEDA but low ees were obtained with Et_2O/(−)-sparteine. This is consistent with the solvent-dependent stereoselection observed for **30a** and for the cuprates derived from **30b**. The use of (*R*)-**34**/*s*-BuLi−(−)-sparteine is expected to correspond to a matched pair in the asymmetric deprotonation[26a] accounting for the similar enantioselectivities observed with TMEDA and (−)-sparteine. Significantly, the ers observed for the organocopper reactions in this study largely mirror those reported for the organolithium reactions, suggesting that preservation of stereochemical integrity during Li−Cu transmetalation and cuprate reaction is a general phenomenon and not inherently a function of the cuprate reaction.

Summary

In summary, we have shown that excellent enantioselectivities can be achieved in the substitution (e.g., vinylation, allylation, and propagylation) and conjugate addition reactions of stereogenic α-(*N*-carbamoyl)alkylcuprates. The cuprate enantioselectivities largely mirror the organolithium selectivities and deviations from the lithium reagents appear to be a function of the relative reactivity of the cuprate/electrophile pair and not of the intrinsic reaction type or mechanistic pathway. This observation holds considerable promise for future development and synthetic applications since reactivity patterns can be modulated by judicious choice of cuprate reagent, substrate structure, solvent combinations, temperature, time combinations, and additives.

Experimental Section

General Procedure. *N*-Boc pyrrolidine (0.17 g. 1.0 mmol), (−)-sparteine (0.28 g, 1.2 mmol), and diethyl ether (4.0 mL) were added to a flame-dried round-bottom flask equipped with a septum and stirring bar and placed under an argon atmosphere. The flask was cooled to −78 °C, *s*-BuLi (0.75 mL, 1.6 M, 1.2 mmol) was added dropwise under argon, and the reaction mixture was stirred at this temperature for 1 h. In a second flask under argon, a mixture of CuCN (0.045 g, 0.5 mmol) and LiCl (0.043 g, 1.0 mmol) in 3.0 mL of THF was stirred at room temperature for 10 min to afford a solution of CuCN·2LiCl. This solution was added via syringe to the α-lithio-*N*-Boc-pyrrolidine solution and the mixture was stirred for an additional hour (shorter times may be used). The electrophile was added to the reaction mixture at −78 °C and allowed to warm to room temperature overnight at an unsupervised rate. The reaction mixture was quenched with saturated aqueous NH_4Cl (4.0 mL) and diluted with diethyl ether (3.0 mL), and the aqueous phase was extracted with Et_2O (3 × 5.0 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo, and the residue was purified by column flash chromatography (silica gel, ethyl acetate/petroleum ether, 94/6 (v/v)).

1-[(1,1-Dimethylethoxy)carbonyl]-2-ethenylpyrrolidine (15a). $[\alpha]^{24}{}_{D}$ +13.3 (*c* 1.43, THF) for sample with er 88:12 by chiral HPLC; $[\alpha]^{24}{}_{D}$ +9.1 (*c* 1.43, THF) for sample with er 72.9:27.1 by chiral HPLC; IR (neat) 1698, 1651, 1365, 1253 cm^{-1}; NMR δ 1.36 (s, 9H), 1.55−2.10 (m, 4H), 3.12−3.37 (m, 2H), 4.10−4.30 (m, 1H), 4.85−5.10 (m, 2H), 5.62−5.80 (m, 1H); ^{13}C NMR δ 23.1 (br s), 28.3, 31.2 (br, s), 46.2, 58.7, 78.9, 113.7, 149.0, 154.4; mass spectrum *m*/*z* (rel intensity) EI 197 (0.5, M^+), 141 (33), 124 (12), 96 (27).

***N*-[(1,1-Dimethylethoxy)carbonyl]-2-(1-trimethylsilylethenyl)pyrrolidine (15b).** IR (neat) 3051, 2965, 2871, 1700, 1478, 1453, 1384, 1239, 1162, 1111, 1085, 931 cm^{-1}; ^1H NMR δ 0.03 (s, 9H), 1.28−1.35 (m, 9H), 1.37−1.49 (m, 1H), 1.63−1.73 (m, 2H), 1.78−1.95 (m, 1H), 3.28−3.35 (m, 2H), 4.34−4.43 (m, 1H), 5.22 (br s, 1H), 5.36 (br s, 1H); ^{13}C NMR δ −1.0, 21.7 (22.7), 28.3, 31.3 (32.0), 46.4 (46.7), 60.6 (61.2), 78.7, 121.1 (121.8), 152.4 (151.4), 154.3 (rotamer); mass spectrum, *m*/*z* (rel intensity) EI 269 (2, M^+), 213 (14), 198 (100), 114 (88), 70 (80), 57 (84).

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(31) (a) Linderman, R. J.; Godfrey, A.; Horne, K. *Tetrahedron* **1989**, *45*, 495−506. (b) Van Heerden, P. S.; Bezuidenhoudt, B. C. B.; Steenkamp, J. A.; Ferreira, D. *Tetrahedron Lett.* **1992**, *33*, 2383−2386.

***N*-[(1,1-Dimethylethoxy)carbonyl]-2-[2-(1-hexenyl)]pyrrolidine (16).** $[\alpha]^{24}_{D}$ +28.8 (*c* 3.19, THF) for sample with er 97.8:2.2 by chiral HPLC; IR 2965, 2934, 2879, 1701, 1389, 1366, 1178, 1124, 878, 770 cm^{-1}; ^{1}H NMR δ 0.91 (t, J = 7.5 Hz, 3 H), 1.17−1.64 (m, 13 H), 1.64−1.92 (m, 3 H), 1.92−2.39 (m, 3 H), 3.44 (br s, 2 H), 4.19 (4.28) (br s, 1 H), 4.71 (s, 1 H), 4.75 (s, 1H) (rotamer); ^{13}C NMR δ 13.9, 22.6, 23.0, 28.4, 30.2, 31.3, 32.7, 46.5, 61.3, 78.9, 107.2, 150.2, 154.6; mass spectrum *m/z* (rel intensity) EI 253 (0.5, M$^+$), 197 (13), 180 (13), 154 (18), 144 (100), 83 (1). Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.15; H, 10.67. Found: C, 70.87; H, 10.69.

***N*-[(1,1-Dimethylethoxy)carbonyl]-2-[1-(1-methylidine-3-*tert*-butyldimethylsilyloxy)propyl]pyrrolidine (17).** IR (neat) 3068, 2948, 2880, 1709, 1649, 1470, 1384, 1247, 1162, 1102, 837, 760; ^{1}H NMR δ 0.01 (s, 6H), 0.84 (s, 9H), 1.35 (s, 9H), 1.70−1.81 (m, 3H), 1.83−1.94 (m, 1H), 2.13−2.35 (m, 2H), 3.37−3.39 (m, 2H), 3.69−3.83 (m, 2H), 4.11−4.31 (m, 1H), 4.73 (s, 2H); ^{13}C NMR δ 1.4, 18.2, 22.4 (22.7), 25.9, 28.4, 31.3 (31.0), 36.6 (36.3), 46.5 (46.3), 61.4, 62.5, 78.9, 108.9, 140.8 (140.7), 154.5 (rotamer); mass spectrum, *m/z* (rel intensity) EI 355 (0.4, M$^+$), 282 (12), 255 (12), 242 (64), 212 (39), 198 (51), 182 (21), 122 (35), 110 (97), 75 (44), 57 (100). Anal. Calcd for $C_{19}H_{37}NO_3Si$: C, 64.22; H, 10.42. Found: C, 64.39; H, 10.50.

1-[(1,1-Dimethylethoxy)carbonyl]-2-[1-cyclohexenyl]pyrrolidine (18). IR (neat) 1695, 1629, 1454, 1395 cm^{-1}; ^{1}H NMR δ 1.21−2.00 (m, 21H), 3.21−3.50 (m, 2H), 3.84−4.24 (m, 1H), 3.32 (s, 1H); ^{13}C NMR δ 22.6, 23.1, 24.7, 28.3, 31.2, 46.6, 61.3, 62.5, 78.6, 120.0, 137.5, 155.0; mass spectrum, EI, *m/z* 251(0.5, M$^+$), 195 (44), 178 (9), 114 (100). Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.73; H, 9.95. Found: C, 71.75; H, 10.08.

***N*-[(1,1-Dimethylethoxy)carbonyl]-2-(3-oxo-1-cyclohexenyl)pyrrolidine (20).** ^{1}H NMR δ 1.27−1.34 (m, 9H), 1.64−1.78 (m, 3H), 1.85−2.30 (m, 7H), 3.31−3.43 (m, 2H), 4.15−4.28 (m, 1H), 5.76 (s, 1H); ^{13}C NMR δ 22.6 (23.2), 26.1 (26.6), 28.2, 30.4, 31.8, 37.5, 46.7, 61.8 (61.3), 79.5, 123.6 (123.1), 154.5, 166.7 (166.1), 199.3 (rotamer); mass spectrum, *m/z* (rel intensity) EI 266 (1, M$^+$ + 1), 209 (50), 192 (23), 164 (18), 137 (44), 114 (46), 70 (51), 57 (100).

1-[(1,1-Dimethylethoxy)carbonyl]-2-[1-(1,1-dimethylethyl)ethenyl]pyrrolidine (21). $[\alpha]^{24}_{D}$ +39.9 (*c* 2.68, THF) for sample with er 89.5:10.5 by HPLC; IR (neat) 1697, 1652, 1476, 1392, cm^{-1}; NMR δ 1.08 (s, 9H), 1.37 (s, 9H), 1.55−2.60 (m, 4H), 3.21−3.54 (m, 2H), 4.29−4.47 (s, 1H), 4.64−4.82 (s, 1H); ^{13}C NMR δ 21.9, 28.6, 30.4, 30.6, 33.1, 35.0, 46.9, 57.8, 78.7, 105.6, 158.7; mass spectrum, *m/z* (rel intensity) EI 253 (0.5, M$^+$), 197 (14), 114 (100). Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.14; H, 10.67. Found: C, 70.72; H, 10.88.

1-[(1,1-Dimethylethoxy)carbonyl]-2-[1-phenylethenyl]pyrrolidine (22). *N*-Boc pyrrolidine (**12**, 171 mg, 1.0 mmol) was dissolved in freshly distilled Et_2O (3.0 mL) along with (−)-sparteine (234 mg, 1.0 mmol). The reaction mixture was cooled to −78 °C under an argon atmosphere and *s*-BuLi (1.0 mL, 1.0 mmol) was added dropwise by syringe. The resultant solution was stirred at −78 °C for 1 h. Then a solution containing CuCN (90 mg, 1.0 mmol) and LiCl (90 mg, 2.0 mmol) in THF (3.0 mL) was added dropwise by syringe. The mixture was allowed to stir at −78 °C for 30 min before the addition of enol triflate **7b** (252 mg, 1.0 mmol). The reaction mixture was allowed to warm quickly to −50 °C and then slowly to room temperature overnight. The reaction mixture was diluted with Et_2O (20 mL) and quenched with HCl (5% aqueous, 15 mL). Upon separation of the layers, the organic layer was dried ($MgSO_4$) and concentrated in vacuo to give an oil that was purified by column chromatography (R_f 0.25, petroleum ether/Et_2O, 85:15, v/v) affording **22** as a clear colorless oil (56%, 91% ee): IR (neat) 1697, 1623, 1558, 1446, 1394 cm^{-1}; ^{1} H NMR δ 1.50 (1.56) (s, 9H), 1.66−2.16 (m, 4H), 3.42−3.71 (m, 2H), 4.82 (d, J = 8.0 Hz, 1H), 4.92 (d, J = 8.0 Hz, 1H), 5.05 (s, 1H), 5.27 (5.30) (s, 1H), 7.30−7.41 (m, 5H); ^{13}C NMR δ 22.2, 28.4, 31.5, 46.5, 60.6, 79.2, 110.8, 126.7, 127.4, 128.3, 140.1, 150.0, 154.4; mass spectrum, *m/z* (rel intensity) EI 273 (0.5, M$^+$), 217 (23), 114 (100). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.72; H, 8.42. Found: C, 74.71; H, 8.61.

Carbamate **22** (137 mg, 0.5 mmol) was dissolved in methylene chloride (10 mL), cooled to −78 °C, and then treated with ozone for 5 min. When a slight blue color was observed, Me_2S (122 mg, 2.0 mmol) was added and stirring continued for 30 min while warming to room temperature. Then aqueous $NaHCO_3$ (5 mL) was added and the layers were separated. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give a clear yellow oil that was purified by column chromatography (R_f 0.40, petroleum ether/EtOAc, 80:20 (v/v)) to give the known ketone (2-benzoylpyrrolidine-1-carboxylic acid, *tert*-butyl ester)[28c] as a clear colorless oil (95%): $[\alpha]^{23}_{D}$ +28.1 (*c* 1.35, $CHCl_3$); IR (neat) 2985 (m), 1703 (vs), 1411 (vs), 1170 (s), cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23 (1.43) (2 s, 9H), 1.75−2.05 (m, 3H), 2.25−2.40 (m, 1H), 3.35−3.75 (m, 2H), 5.14 (5.30) (dd, J = 3.7 Hz, J = 5.0 Hz, 1H), 7.35−7.60 (m, 3H), 7.85−8.00 (m, 2H) (rotamers); ^{13}C NMR ($CDCl_3$) δ 23.1 (24.1), 28.2 (28.4), (29.8) 30.8, 46.6, (46.8), (61.1) 61.3, (79.6) 79.7, 128.1, 128.7 133.2, 133.2, 135.3, 153.8, (198.4) 198.9 (rotamers); mass spectrum, *m/z* (rel intensity) 275 (0.5, M$^+$), 202 (10), 170 (48), 158 (12), 130 (6), 114 (91), 70 (100), 57 (82).

***N*-[(1,1-Dimethylethoxy)carbonyl]-2-[1-(1,2-propadienyl)]pyrrolidine (23).** IR (neat) 3068, 2974, 2880, 1948, 1690, 1463, 1181, 1295, 1181, 1102, 844; ^{1}H NMR δ 1.41 (s, 9H), 1.75−1.85 (m, 4H), 3.32 (br s, 2H), 4.28 (br s, 1H), 4.74−4.77 (m, 2H), 5.17 (br s, 1H); ^{13}C NMR δ 22.5 (23.6), 28.5, 32.3 (31.2), 45.8, 57.5, 77.2, 79.0, 93.0 (92.5), 154.5, 207.0 (rotamer); mass spectrum, *m/z* (rel intensity) 170 (4), 153 (40), 136 (13), 114 (70), 70 (79), 57 (100). Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.90; H, 9.10; N, 6.70. Found: C, 69.01; H, 9.15; N, 6.72.

***N*-[(1,1-Dimethylethoxy)carbonyl]-2-[1-[1-(3-phenylpropyl)-1,2-propadienyl]]pyrrolidine (24).** IR (neat) 3017, 2969, 2921, 2872, 1963, 1689, 1439, 1391, 1359, 1254, 1166, 1109, 844; ^{1}H NMR δ 1.41 (s, 9H), 1.74−1.92 (m, 8H), 2.63 (t, J = 7.4 Hz, 2H), 3.29−3.35 (m, 2H), 4.12−4.21 (m, 1H), 4.71−4.76 (m, 2H), 7.14−7.26 (m, 5H); ^{13}C NMR δ 22.6 (23.2), 28.4, 28.6 (3C), 29.2, 30.2 (31.2), 35.4, 45.9, 58.9 (58.7), 78.2, 78.7, 106.2 (105.8), 125.5, 128.1, 128.3, 142.1, 154.2, 204.4 (rotamer); mass spectrum, *m/z* (rel intensity) 271 (28), 254 (5), 167 (37), 114 (100), 91 (32), 70 (91), 57 (94), 41 (45), 29 (16).

***N*-[(1,1-Dimethylethoxy)carbonyl]-2-[1-(1-phenyl-1,2-propadienyl)]pyrrolidine (25).** IR (neat) 3051, 2972, 2884, 1944, 1689, 1442, 1386, 1243, 1171, 1115, 1075, 868, 797; ^{1}H NMR δ 1.38−1.44 (m, 9H), 1.77−2.09 (m, 4H), 3.30−3.48 (m, 2H), 4.75−4.91 (m, 1H), 5.03−5.16 (m, 2H), 7.09−7.41 (m, 5H); ^{13}C NMR 22.5 (23.5), 28.4, (30.9) 32.0, 45.9 (46.2), 57.3 (57.0), 80.1, 78.9, 109.4 (108.3), 126.8, 126.4, 128.4, 135.2 (134.7), 154.3, 207.0 (rotamer); mass spectrum, *m/z* (rel intensity) 281 (2), 229 (77), 212 (13), 184 (28), 114 (100), 89 (16), 70 (78), 57 (89).

***N*-[(1,1-Dimethylethoxy)carbonyl]-2-(2-propen-1-yl)pyrrolidine (26).** $[\alpha]^{24}_{D}$ +38.0 (*c* 3.69, THF) for sample with er 89.0:11.0 by HPLC [lit.[28b] $[\alpha]^{25}_{D}$ −32.4 (*c* 1.56, $CHCl_3$)]; IR (neat) 1696, 1645, 1365, 1252 cm^{-1}; ^{1}H NMR δ 1.41 (s, 9H), 1.54−1.84 (m, 4H), 2.00−2.20 (m, 1H), 2.32−2.54 (m, 1H), 3.14−3.40 (m, 2H), 3.61−3.80 (m, 1H), 4.91−5.12 (m, 2H), 5.58−5.72 (m, 1H); ^{13}C NMR δ 23.1, 28.5, 30.0, 28.1, 45.6, 53.7, 78.8, 116.9, 135.2, 145.0; mass spectrum, *m/z* (rel intensity) EI 170 (6.4), 114 (54), 70 (100).

5-Phenyl-5-[[(1,1-dimethylethoxy)carbonyl]ethylamino]pentan-2-one (31). ^{1}H NMR δ 0.80−0.95 (m, 3H), 1.56 (s, 9H), 2.22 (s, 3H), 2.23−2.40 (m, 2H), 2.52−2.70 (m, 2H), 2.92−3.10 (m, 2H), 5.20−5.45 (m, 1H), 7.25−7.42 (m, 5H); ^{13}C NMR δ 15.0, 24.5, 28.5, 30.1, 38.1, 40.4, 56.3, 78.9, 127.3, 127.7, 128.3, 140.5, 156.3, 208.1; mass spectrum, *m/z* (rel intensity) EI 305 (0.5, M$^+$), 249 (22), 204 (7), 178 (42); high-resolution mass spectrum *m/z* 305.1997 (M$^+$) (calcd for $C_{18}H_{27}NO_3$ 305.1991).

1-[(1,1-Dimethylethoxy)carbonyl]ethyl[(*E*)-1-phenyl-2-heptenyl]amine (33). IR (neat) 2961, 2930, 2868, 1683, 1443, 1412, 1381, 1272, 1164, 963, 877 cm^{-1}; ^{1}H NMR δ 0.97−1.13 (m, 6H), 1.34−1.66 (m, 14H), 2.17−2.24 (m, 2H), 3.09−3.30

(m, 2H), 5.68−5.85 (m, 2H), 7.27−7.50 (m, 5H); ^{13}C NMR δ 13.8, 14.8, 22.1, 28.4, 31.2, 32.0, 39.7, 61.3, 79.2, 126.8, 127.3, 128.1, 134.5, 144.2, 155.4; mass spectrum, *m/z* (rel intensity) EI 317 (0.5, M$^+$), 261 (78), 216 (16), 204 (87), 173 (42), 160 (25), 133 (42), 117 (95), 104 (29), 91 (62), 57 (100).

Ethyl (*Z*)-4-Phenyl-4-[[(1,1-dimethylethoxy)carbonyl]-ethylamino]-2-pentenoate (35). ^{1}H NMR δ 1.20−1.42 (m, 15H), 1.94 (s, 3H), 3.46−3.64 (m, 2H), 4.15 (q, *J* = 6.0 Hz, 2H), 5.79 (d, *J* = 12.0 Hz, 1H), 6.37 (d, *J* = 12.1 Hz, 1H), 7.32−7.42 (m, 5H); ^{13}C NMR δ 14.0, 15.5, 26.9, 28.1, 40.4, 60.2, 64.29, 79.62, 117.30, 125.4, 126.7, 127.9, 146.5, 150.6, 155.0, 166.8; mass spectrum, *m/z* (rel intensity) EI 291 (20), 245 (19); high-resolution mass spectrum, *m/z* 347.2095 (M$^+$) (calcd for $C_{20}H_{29}NO_4$ 347.2097).

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Supporting Information Available: Expanded Tables 1, 3, 4, and 5 (for eq 1), materials (references for the preparation of **1**, **2c**,**d**, **3a**−**c**, **4a**-**b**, **6a**,**b**, **7a**,**b**, and **8b**−**d** and for data reductions of **14**, **15a**, **19a**, **b**, **26**, **27**, **28a,** and **28c**), general experimental information, ^{13}C NMR spectra for compounds **15a**, **15b**, **16**, **17**, **18**, **19a**, **20**, **21**, **22**, **23**, **24**, **25**, **26**, **31**, **33**, and **35**, and chiral HPLC traces for **14**, **15a**,**b**, **16**, **18**, **19a**, **20**, **21**, **22**, **23**, **25**, **26**, **28a**, **31**, and **35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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