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Conjugate Addition Reactions of α-Aminoalkylcuprates with α,β-Enones and Enals

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Abstract—Deprotonation of Boc-protected amines with *sec*-BuLi or transmetallation of α-aminostannanes with *n*-BuLi affords α-aminoalkyllithium reagents which can be converted into α-aminoalkylcuprate reagents with CuCN or THF soluble CuCN·2LiCl. These reagents undergo conjugate addition reactions with α,β-enones and enals. Reagents prepared from 2 equiv. of the α-aminoalkyllithium reagent give higher yields of conjugate adducts than those prepared from RCuCNLi, particularly when insoluble CuCN is employed. When CuCN·2LiCl is used, the two cuprate reagents give comparable yields of 1,4-adducts and the RCuCNLi reagent, economical in α-aminoalkyl ligand, is preferred. The Boc protecting group can be removed with PhOH/TMSCl and the amino ketone isolated as the hydrochloride salt.

Introduction

For many years, organocopper chemistry[1] has been limited to a narrow range of alkyl ligands compatible with the organometallic precursors used to generate the copper reagents. Recently, the development of highly functionalized organocopper reagents has been an important focus in organocopper chemistry. Copper reagents derived from α-heteroatom stabilized carbanions have been an active area of investigation centered on oxygen,[2,3] sulfur,[4] and phosphorous[5] stabilized anions with much of the work focusing on the α-alkoxyalkylcuprates. Although sometimes limited in reactivity, the development of organozinc based copper reagents has enormously extended the range of functionalized ligands amenable to organocopper chemistry.[6] Recent advances in the use of Rieke copper provides additional opportunities to prepare functionalized organocopper reagents.[7]

Pioneering work by Meyers[8] on formamidines and Beak[9] on carbamates has provided readily accessible routes to α-aminoalkyl carbanions.[10] The general approach involves dipole stabilized anions bearing electron withdrawing groups on nitrogen which facilitate deprotonation adjacent to the nitrogen atom. Activating groups such as oxazolines,[11] dithiocarbamate thiolates,[12] phosphoramides,[13] and pivalamides[14] have been used in addition to the formamidines and *tert*-butylcarbamates. More recently, α-aminoalkyl carbanions have been generated from unactivated systems by reductive metallation of *N*,*S*-acetals[15] or transmetallations of α-aminoalkylstannanes,[16a–d] α-halomethylimides,[6c] and α-stannylimines.[16e] Although several reports have described the reaction of cuprates derived from α-nitrogen substituted carbanions with alkyl halides,[8a–c,11a] our preliminary reports[17] described the first utilization of α-aminoalkylcuprates in conjugate addition reactions. Recently, non-racemic α-aminoalkyllithium reagents derived from anilino benzylic or allylic amines have been shown to participate in asymmetric conjugate addition reactions with α,β-enones.[9e] We have extended the range of α-aminoalkylmetal chemistry by development of α-aminoalkylcopper reagents capable of participating in conjugate addition reactions,[17] and substitution reactions with acyl chlorides,[18a] vinyl triflates,[18b] vinyl iodides,[18c] epoxides, allylic,[18d] and propargylic substrates.[18e] In this full report, we detail the development of α-aminoalkylcuprates derived from *tert*-butoxycarbonyl (Boc) carbamates and their utility in conjugate addition reactions to a variety of α,β-enone, and enal acceptors.

Results

Meyers' formamidines were initially examined in an effort to effect conjugate addition of α-aminoalkyl ligands to α,β-enones.[17a] *N*,*N*-Dimethyl-*tert*-butylformamidine[8b] (**1**) was deprotonated and treated with a variety of Cu(I) salts in an effort to prepare efficacious cuprate reagents (Eq. (1), Table 1). In preliminary screening, the homocuprate

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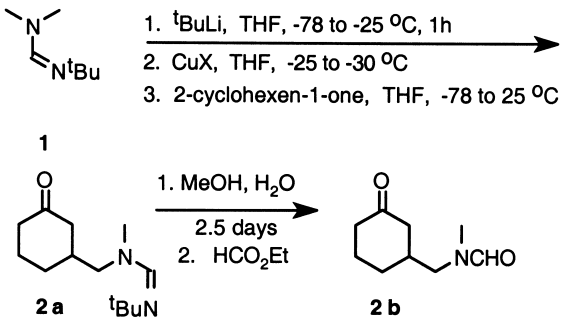
Table 1. Reaction of organocopper reagents generated from **1** with cyclohexenone (Eq. (1)) (reaction conditions as depicted in Eq. (1))

CuX or CuLXLi	*n* RLi	Solvent/additive (equiv.)	% Yield (**2a**)[a]
CuSPh	1.0	THF	86
CuSPh	1.0	THF/Et_2O[b]	66
CuSPh	1.0	THF/TMSCl (2)	49
CuI	1.0	THF/TMEDA/TMSCl (2.5)	89
$C_4H_9C{\equiv}CcuCNLi$	1.0	THF/TMSCl (5)	50
2-thienylCuCNLi	1.0	THF/TMSCl (5)	44
CuCN	2.0	THF/TMSCl (5)	85

[a] Conversion of enone (%) to **2a** as determined by ^1H NMR.
[b] Et_2O/THF (4:1).

reagent, R_2CuLi (R=α-aminoalkyl ligand), prepared from CuI failed to give conjugate addition while the mixed cuprate reagent, RCuSPhLi,[19] effected conjugate addition to cyclohexenone but failed with other enones. Interestingly, the phenylthio mixed cuprate reagent did not require the addition of TMSCl. The alkylcopper reagent, RCu/TMEDA,[20] and Lipshutz's reagent[21] (2RLi+CuCN) proved effective in the presence of trimethylsilylchloride (TMSCl), and the latter reagent was adopted for further studies examining the effect of substrate structure. The RCu reagent required the addition of TMEDA which proved difficult to remove from the basic formamidines which underwent varying degrees of decomposition upon silica gel chromatography. The reagent, (2RLi+CuCN), in the presence of TMSCl transferred the aminomethyl ligand derived from **1** to 2-cyclopentenone (83%), methyl vinyl ketone (98%), and mesityl oxide (61%) while the 2-pyrrolidinyl ligand was transferred to 2-cyclopentenone (83%), and methyl vinyl ketone (71%). Cuprates prepared by addition of RLi to $R_{nt}CuCNLi$ (R_{nt}=1-hexynyl, 2-thienyl) gave only modest yields of conjugate adducts and required the use of TMSCl. These yields were estimated from NMR molar ratios since purification resulted in significant loss of product. The reagents failed to added to 3-methyl-2-cyclopentenone. Cleavage of the formamidine protecting group to afford amino ketones proved insurmountable using either oxidation, reduction, or hydrolytic methods, although **2a** could be deprotected with MeOH/H_2O in capricious yields and then formylated to give a sample of **2b** for analysis. Given these purification and deprotection difficulties, attention turned to the utilization of Beak's carbamates[9] for the preparation of α-aminoalkylcuprates.

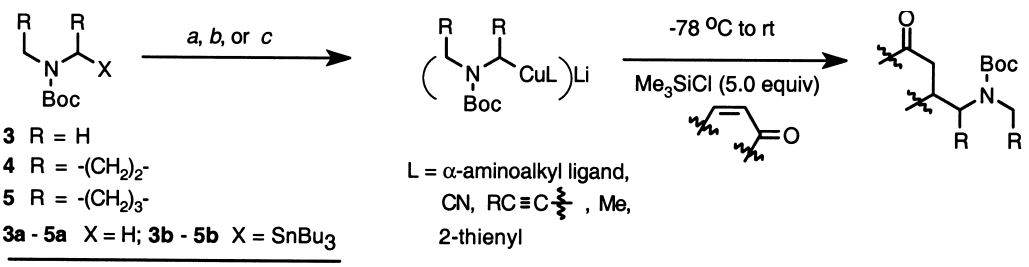


(1)

The *N-tert*-butoxycarbonyl (Boc) protected amines **3a**–**5a** were prepared in high yields from *N*,*N*-dimethylamine, pyrrolidine, and piperidine [di-*tert*-butyldicarbonate, triethylamine (TEA), CH_2Cl_2, 0°C to room temperature] and were purified by vacuum distillation.[22] α-Stannyl carbamates **3b**–**5b** were prepared by deprotonation of the carbamates with *sec*-BuLi [TMEDA, Et_2O, −78°C, 1 h] followed by quenching with tri-*n*-butyltin chloride.[9a,c–e] The organostannanes were purified by column chromatography (silica gel) followed by Kugelrohr distillation to give colorless oils which were stored in refrigeration.

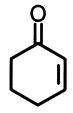
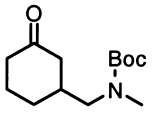
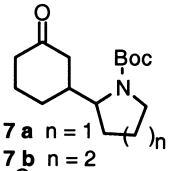
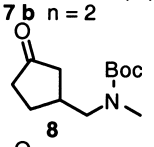
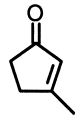
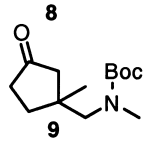
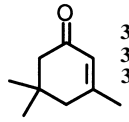
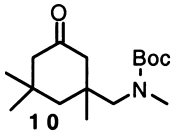
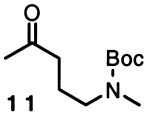
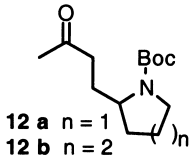
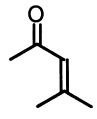
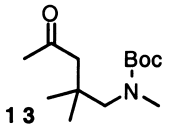
The development and subsequent optimization of the reaction resulted in several different procedures for the preparation of the α-aminoalkylcuprate reagents. The requisite α-lithio carbamates were prepared either from the α-stannyl carbamates via transmetallation or directly from the carbamates via deprotonation in either diethyl ether or THF. The cuprates were prepared from various copper(I) species, but were generally prepared from either CuCN or the THF soluble CuCN·2LiCl[6] (Scheme 1).

Initial studies involved deprotonation of **4a** [*sec*-BuLi, TMEDA, Et_2O, −78°C][9a,c–e] and cuprate formation [CuCN (0.5 equiv.), THF, −78 to −55°C] followed by addition of cyclohexenone and 5.0 equiv. of TMSCl. Upon addition of CuCN, the reaction mixtures were generally warmed to −55°C to insure cuprate formation. An early experiment afforded the conjugate adduct in 41% yield, but repeated efforts to reproduce the result were unsuccessful. Boc protected 2-lithiopyrrolidine, obtained from stannane **4b** via transmetallation, gave a cuprate reagent (2RLi+CuCN) that transferred one α-aminoalkyl ligand to 2-cyclohexenone in nearly quantitative yield in the presence of 2–5 equiv. of TMSCl (Table 2, entry 15).



Scheme 1. (a) **3a**–**5a**: i. *sec*-BuLi, Et_2O, −78°C, 2.5 h, TMEDA or (−)-sparteine. ii. CuCN, −78 to −50°C, 30 min. (b) **3b**–**5b**: i. *n*-BuLi, THF, −78°C, 15–20 min. ii. CuCN, −78 to −50°C, 20–30 min. (c) **3a**–**5a**: i. *sec*-BuLi, Et_2O, −78°C, 1–2 h, TMEDA or (−)-sparteine. ii. CuCN·2LiCl, −78 then −50°C, 45 min.

Table 2. Conjugate addition of α-aminoalkylcuprates prepared from carbamates with α,β-enones

Entry	Enone	No.[a]	Additive	Cu salt	equiv.[b]	Solvent	TMSCl equiv.	Product	% Yield[c]
1		**3b**	–	CuCN	(0.5)	THF	5	 **6**	98[d]
2		**3b**	–	CuCN	(0.5)	THF	5		56[e]
3		**3b**	–	CuCN	(0.5)	THF	2		91
4		**3b**	–	CuCN	(1.0)	THF	2		23–36
5		**3a**	TMEDA	CuCN	(0.5)	Et_2O/THF	5		63
6		**3a**	TMEDA	CuCN	(0.5)	Et_2O	5		43
7		**3a**	Sparteine	CuCN	(0.5)	Et_2O/THF	5		73
8		**3b**	–	CuCN	(1.0)		1		13
9		**3b**	–		(1.0)		2		37
10		**3b**	–		(1.0)		5		23
11		**3b**	–		(1.0)		(2)[f]		18
12		**3b**	–	CuI	(0.5)		(2)[g]		71
13		**3a**	Sparteine	CuCN·2LiCl	(0.5)	THF	5		90
14		**3a**	Sparteine	CuCN·2LiCl	(1.0)	THF	5		83
15		**4b**	–	CuCN	(0.5)	THF	5	 **7a** n = 1 **7b** n = 2	99
16		**4a**	Sparteine	CuCN	(0.5)	Et_2O/THF	5		71–99
17		**4a**	Sparteine	CuCN·2LiCl	(0.5)	THF	5		82
18		**4a**	Sparteine	CuCN·2LiCl	(1.0)	THF	5		90
19		**5a**	Sparteine	CuCN·2LiCl	(0.5)	Et_2O/THF	5		86
20		**3b**	–	CuCN	(1.0)	THF	5		50[d]
21		**3a**	Sparteine	CuCN·2LiCl	(1.0)	THF	5		64
22		**3a**	Sparteine	CuCN·2LiCl	(0.5)	THF	5	 **8**	86
23		**3b**	–	CuCN	(0.5)	THF	5	 **9**	49[d]
24		**3a**	Sparteine	CuCN·2LiCl	(0.5)	THF	5		74
25		**3a**	Sparteine	CuCN·2LiCl	(1.0)	THF	5		47
26		**3b**	–	CuCN	(0.5)	THF	5	 **10**	64[d]
27		**3b**	–	CuCN	(1.0)	THF	2		25
28		**3a**	Sparteine	CuCN·2LiCl	(0.5)	Et_2O/THF	5		83
29		**3b**	–	CuCN	(1.0)	THF	5	 **11**	62[d]
30		**3a**	Sparteine	CuCN·2LiCl	(1.0)	THF	5		62
31		**3a**	Sparteine	CuCN·2LiCl	(0.5)	THF	5		61
32		**4b**	–	CuCN	(0.5)	THF	5	 **12a** n = 1 **12b** n = 2	86[d]
33		**5b**	–	CuCN	(0.5)	THF	5		100[d]
34		**4a**	Sparteine	CuCN·2LiCl	(1.0)	THF	5		59 (85)
35		**3b**	–	CuCN	(1.0)	THF	5	 **13**	35[d]
36		**3a**	Sparteine	CuCN·2LiCl	(1.0)	THF			26

[a] The α-lithiocarbamates were prepared from the organostannanes via transmetallation [*n*-BuLi, THF, −78°C] or directly from the carbamate via deprotonation [*sec*-BuLi, diamine, THF or Et_2O, −78°C].

[b] Stoichiometry of 0.5 CuX corresponds to [2RLi+CuX] and 1.0 to [RLi+CuX]. RLi was added to the Cu(I) salt at −78°C and warmed to −55°C, followed by cooling to −78°C before addition of the enone.

[c] Isolated yields based upon the enone as limiting reagent. Purification was achieved by preparative TLC or column chromatography unless otherwise noted.

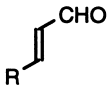
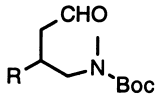
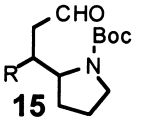
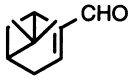
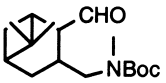
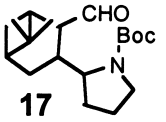
[d] Yield reflects double purification by chromatography (silica gel) followed by Kugelrohr distillation.

[e] This one experiment utilized unpurified stannane which appeared spectroscopically clean by ^1H NMR analysis and homogenous by analytical TLC.

[f] 2.0 equiv. of $BF_3{\cdot}Et_2O$ employed.

[g] 1.0 equiv. of TMSCN and 1.0 equiv. of TMSCl were used with CuI.

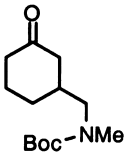
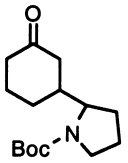
Table 3. Reaction of α-aminoalkylcuprates with α,β-enals

Entry	RCHO	R	Boc[a]	Cuprate[b]	Product	%[c] Yield
1		Me	**3a**	A		47
2		Me	**3a**	B[d,e]		95
3		Me	**3a**	C[d,e]		47
4		Me	**3b**	A[e]		50
5		Ph	**3a**	A		13[f]
6		Ph	**3a**	B[d,e]	**14a** R = Me, **b** R = Ph	75
7		Me	**4**	B[d,e]	 **15**	81
8			**3b**	A		62
9			**3a**	B[d,e]	**16**	51
10			**4**	B[d,e]	 **17**	37

[a] Carbamates **3a** and **4a** were deprotonated with *sec*-BuLi (Et_2O, TMEDA, −78°C, 1.25 h). Carbamate **3b** underwent transmetallation with *n*-BuLi (THF, −78°C, 0.25 h).
[b] A=2RLi+CuCN. B=RLi+CuCN·2LiCl. C=2RLi+CuCN·2LiCl. The α-lithiocarbamates were added to CuCN or CuCN·2LiCl at −78°C, warmed to −55 to −50°C, and then cooled to −78°C (enal added at −50°C for entries 2, 3, 6, 7, and 9). Reactions were run in an Et_2O:THF (1:1) solvent mixture unless otherwise noted and enal/5.0 equiv. TMSCl were added to the cuprate solution at −78°C.
[c] Based upon products purified and isolated by chromatography and with the aldehyde as limiting reagent.
[d] Deprotonation was achieved with *sec*-BuLi and sparteine (THF, −78°C, 1 h).
[e] The reaction was run in THF.
[f] The 1,2-addition product was isolated in 44% yield.

Similarly, a dialkylcuprate prepared from stannane **3b** reacted with 2-cyclohexenone to afford good to excellent yields of the conjugate adduct (Table 2, entries 1–3) and the yields appeared to be sensitive to impurities in the organostannane. Utilization of unpurified stannane that appeared homogeneous by TLC and spectroscopically clean gave lower yields (Table 2, entry 2). Cuprates prepared from 2 equiv. of the α-lithiocarbamate obtained from **3b** and CuCN gave modest yields of the conjugate adduct with α,β-enones such as 3-methylcyclopentenone (Table 2, entry 23) and isophorone (Table 2, entry 26). The corresponding α-aminoalkyl(cyano)cuprates generally gave significantly lower yields (Table 2, entries 4 vs. 1–3, and 27 vs. 26). The cyanocuprate reagent prepared from **3b** gave a good yield with methyl vinyl ketone (Table 2, entry 29) but a low yield with the more sterically hindered mesityl oxide (Table 2, entry 35). The cuprate prepared from **4b** or **5b** (2RLi+CuCN) gave excellent yields of conjugate adducts upon reaction with methyl vinyl ketone (Table 2, entries 32, 33) and cyclohexenone (from **4b**: Table 2, entry 15). These reaction conditions worked well for cuprates prepared from carbamates **3b**–**5b** with simple α,β-enones. Yields of conjugate adducts decreased as the alkyl substitution pattern increased on the enone system (Table 2, entries 23, 26 and 35). The reaction failed in the absence of TMSCl and low yields were obtained when $BF_3{\cdot}Et_2O$ was substituted for TMSCl (entries 10,11).

Table 4. Effects of the diamine additive on the conjugate addition reaction of α-aminoalkylcuprates with 2-cyclohexenone

Entry	SM[a]	Diamine	Cu salt[b]	equiv.	Product	%[c] Yield
1	**3a**	TMEDA	CuCN	(0.5)	 **6**	63
2	**3a**	TMEDA[d]	CuCN	(0.5)		43
3	**3a**	Sparteine	CuCN	(0.5)		73
4	**3a**	Sparteine	CuCN·2LiCl	(1.0)		83
5	**3a**	TMEDA	CuCN·2LiCl	(1.0)		74–85
6	**3a**	–	CuCN·2LiCl	(1.0)		65–69
7	**3b**	–	CuCN	(0.5)		98
8	**3b**	TMEDA[e]	CuCN	(0.5)		86
9	**3b**	TMEDA[f]	CuCN	(0.5)		74
10	**4a**	TMEDA	CuCN	(0.5)	 **7a**	0–41
11	**4a**	TMEDA	CuCN·2LiCl	(1.0)		69–72
12	**4a**	Sparteine	CuCN	(0.5)		71–73
13	**4a**	Sparteine	CuCN·2LiCl	(1.0)		90
14	**4b**	–	CuCN	(0.5)		99

[a] The carbamate starting material (SM) was deprotonated with *sec*-BuLi in Et_2O (−78°C for CuCN) or THF (−78°C for CuCN·2LiCl) unless otherwise noted.
[b] Reactions were run in Et_2O·THF (1.1) for cuprates prepared from CuCN and in THF for Cuprates prepared from CuCN·2LiCl unless otherwise noted. Cyclohexenone/TMSCl (5.0 equiv.) were added to the cuprate solutions at −78°C.
[c] Based upon isolated yields of products purified by TLC or column chromatography.
[d] Reaction run in Et_2O.
[e] Diamine added after transmetallation.
[f] Diamine added after cuprate formation.

Efforts to extend the reactions of α-aminoalkylcuprates eventually resulted in the use of THF soluble CuCN·2LiCl for preparation of the cuprate reagents from the α-lithio carbamates. Under these reaction conditions, the yields of conjugate adducts utilizing the deprotonation protocol were often comparable (Table 2, entries 13 vs. 1 and 3, 17 vs. 15) to the transmetallation procedure and in some instances superior (Table 2, entries 24 vs. 23, 28 vs. 26) for cuprates prepared from 2RLi+CuCN·2LiCl. Cyanocuprates prepared from RLi+CuCN·2LiCl via the deprotonation procedure generally gave significantly higher yields than the cuprates prepared from CuCN via the transmetallation protocol (Table 2, entries 14 vs. 4 and 8, 21 vs. 20), although comparable yields were sometimes obtained (Table 2, entries 30 vs. 29, 36 vs. 35). Simple enones gave yields only slightly lower with RCuCNLi prepared from CuCN·2LiCl via the deprotonation protocol than those obtained by using 2 equiv. of α-lithio carbamates (via transmetallation) and CuCN (Table 2, entries 14 vs 1 and 3, 18 vs. 15, 34 vs. 32). Yields obtained with the former reagents were, however, significantly lower than the 2RLi+CuCN·2LiCl reagents when 3-alkyl substituted substrates were employed (Table 2, entry 25 vs. 24). Cuprates prepared from **4a** failed to undergo reaction with sterically hindered enones such as isophorone and 3-methylcyclopentenone and gave trace amounts of adducts with sterically hindered acyclic enones such as mesityl oxide.

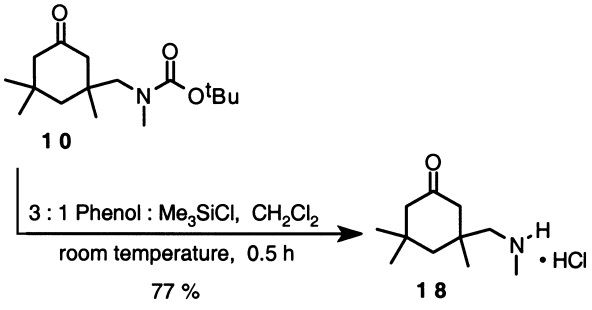
α-Aminoalkylcuprates prepared from CuCN reacted with α,β-enals, although the regiochemistry of the addition

proved highly sensitive to substrate structure. Reaction of the cuprates (2RLi+CuCN) prepared from **3a** or **3b** with crotonaldehyde gave the conjugate adducts in 47 and 50% yield (Table 3, entries 1, 4), respectively, showing no difference between the deprotonation and transmetallation protocols. However, the cuprate prepared from **3a** reacted with cinnamaldehyde to afford the conjugate adduct in 13% yield and the 1,2-addition product in 44% yield (Table 3, entry 5). Preparation of the cyanocuprates, RCuCNLi, from **3a** or **4a** and CuCN·2LiCl resulted in excellent to good yields of conjugate adducts while the reagent prepared from addition of 2RLi gave modest yields (Table 3, entries 2, 6, 7 vs. 3). The yields reflected characteristic substrate reactivity and steric hindrance factors illustrated in the reactions with myrtenal (Table 3, entries 8–10).

Initial efforts to effect conjugate addition with cuprates prepared from **4a**, via deprotonation, and CuCN were frequently unsuccessful and the focus changed to the use of organostannane **4b** for generation of the requisite α-lithio carbamate. During the course of these studies, it was observed that cuprates prepared via deprotonation of **3a** underwent conjugate addition with cyclohexenone, although the yields were sensitive to solvent (Table 4, entries 1,2). Serendipitously, it was discovered that replacement of TMEDA, used to facilitate deprotonation of **3a**, with (−)-sparteine resulted in a 10% increase in yield (Table 4, entries 1 vs. 3). Deprotonation of **4a** with *sec*-BuLi in the presence of (−)-sparteine followed by cuprate formation with CuCN afforded conjugate addition of the pyrrolidinyl ligand in 71–73% yields (Table 4, entry 12). Although these results suggested a significant effect of diamine upon the efficiency of the conjugate addition reaction with 2-pyrrolidinylcuprates, similar yields were eventually obtained in the presence of TMEDA which was distilled immediately prior to utilization. Addition of TMEDA prior to and subsequent to cuprate formation via stannane **3b** resulted in a diminution in yields (Table 4, entries 7 vs. 8, 9). The chemical yields were significantly less sensitive to the diamine employed when the cuprate reagent was prepared from THF soluble CuCN·2LiCl (Table 4, entries 4 vs. 3, 11 vs. 10, and 13 vs. 12), although these results involve a comparison between RLi+CuCN·2LiCl and 2RLi+CuCN. Variability in the yields obtained with CuCN·2LiCl appeared to correlate with a difficulty in insuring the dryness of the LiCl and latter experiments involved flame drying the reaction flask and the addition of LiCl prior to the addition of CuCN and THF.

Cuprate reagents generated from α-aminostannanes gave poor to modest yields with the RCuCNLi reagent (Table 2). Efforts to minimize the inefficient utilization of only one of the α-aminoalkyl ligands (i.e., in 2RLi+CuCN) focused on standard non-transferable ligands such as cyanide, 2-thienyl, phenylthiomethyl, and substituted alkynyl groups. The mixed cuprate 2-thienyl(R)CuLi failed to efficiently transfer the α-aminoalkyl ligand when generated via the deprotonation protocol (17%) or when $BF_3{\cdot}Et_2O$ (2.0 equiv., 14%) was used instead of TMSCl. A modest yield was obtained when this mixed cuprate was prepared from the stannane **3b** and reacted with cyclohexenone in the presence of TMSCl (48%). A mixed cuprate prepared from MeLi and the α-lithio carbamate obtained from **3b** transferred both the α-aminoalkyl and methyl ligands in 51 and 41% yields, respectively. Mixed cuprates prepared from 1-hexyne or 3-methyl-3-methoxy-1-butyne gave capricious results (0–65%), although in single experiments the desired conjugate adduct could be obtained in yields of 65 and 50% respectively. Significant yields of the conjugate adducts were only obtained when excess MeLi or *n*-BuLi were used to deprotonate the alkyne or added after the fact. The mixed alkynyl cuprate prepared from *p*-methoxyphenylacetylene and stannane **3b** transferred the α-aminoalkyl ligand in 52% yield. These yields were generally lower than those obtained from RCuCNLi prepared from CuCN. Subsequent discovery of the generally superior ability of the RLi+CuCN·2LiCl protocol provided a satisfactory solution to the problem of efficient ligand utilization (Table 2), although the use of CuCN·2LiCl did not make significant improvements in the use of other non-transferable ligands [e.g., 32% for $(Me(Boc)NCH_2CuN^iPr_2)Li$].

The Boc-protecting group can be removed with PhOH/TMSCl to afford the amino ketones as the hydrochloride salts (Eq. (2)) or as the free amine. The free amines are unstable and must be used immediately or frozen in benzene for storage.



(2)

Discussion

The development of α-aminoalkylcuprate chemistry has emerged from extensive experimentation and empirical observations. Although reliable protocols have been developed, the underlying basis for the sensitivity of these reagents to various reaction conditions is not well understood. General trends and patterns have emerged from this work, although substantial variation from experiment to experiment precludes a detailed analysis. The principal development has been the enhanced reliability, reproducibility, and chemical yields obtained with cuprates generated from CuCN·2LiCl permitting the use of reagents RCuCNLi efficient in transferable ligand.

The initial work with insoluble CuCN gave very low yields of 1,4-adducts with pyrrolidinyl cuprates generated in the presence of TMEDA, although modest yields could be achieved with the aminomethylcuprate derived from **3a**. Cuprates generated from **3a**–**4a** gave higher and more reproducible yields when (−)-sparteine was employed, although similar yields could be obtained when the TMEDA was distilled immediately before use. These results suggest that impurities present in TMEDA have a deleterious effect upon cuprate formation, stability, or reactivity.

In addition, the high yields of 1,4-adducts obtained in the absence of diamines (cuprates prepared via transmetallation of aminostannanes) and the diminished yields obtained when diamines were added at various stages in the reaction, suggests that chelation effects (e.g., lithium ions or copper species and diamines) may play a significant role. This is consistent with the improvement in yields achieved with CuCN·2LiCl where additional lithium ions have been added to the solution. Although the effectiveness of TMEDA–Li^+ coordination in THF has been called into question,[23] it is clear from synthetic,[24] mechanistic,[25] and structural studies[26] that Li^+ ions play crucial roles in cuprate structure and in conjugate addition chemistry and enone–Li^+ complexes have been observed[27] spectroscopically. In solid state structures Li^+ ions appear to be the 'glue' holding the cluster together, and in solution Li^+ ion coordination to the carbonyl oxygen at some point along the reaction coordinate appears crucial for successful conjugate addition[25] as evidenced by solvent effects[24b,28] upon reaction rates. In this regard, it is interesting that α-aminoalkylcuprates generated from formamidines appear to be more reactive than those prepared from carbamates. This is reflected in the ability to achieve conjugate addition in higher yields with mixed cuprates containing non-transferable ligands generated from the formamidines than in those generated from the carbamates. This observation is consistent with the view that THF is a more effective ligand for Li^+ than TMEDA (i.e., oxygen vs. nitrogen), but contrasts with the observed rate enhancements for cuprates with heteroatoms in the ligand[29] permitting internal complexation. The relative steric dimensions of these formamidine and carbamate ligands arising from internal complexation could also be expected to play a role.

The presence of additional lithium ions in solution may account for the differing reactivity of RCuCNLi prepared from CuCN and CuCN·2LiCl. The latter reagent permits generation of the cuprate reagents at −78°C which could have a significant and variable effect upon chemical yields since the α-lithio carbamates display a greater thermal instability than the cuprate reagents.[22] The use of CuCN·2LiCl also provides additional lithium ions for complexation to the carbonyl oxygen, and provides soluble chloride ions that could, in principle, facilitate the reductive elimination process that forms the β–C–C bond. In allylic substitutions, product yields have been correlated with CuX (yields: X=Cl>Br>I) and attributed to more electronegative ligands accelerating the rate of reductive elimination.[30] The conjugate addition reactions, however, require the presence of TMSCl suggesting that alone, chloride ions like HMPA[25c] may stabilize the copper intermediate[25d] undergoing rate-limiting reductive elimination[25e] thereby diminishing reactivity. The use of CuCN·2LiCl may also affect the aggregation state of the cuprate reagent, the extent of equilibrium between monomeric and dimeric cuprate species, or the composition of the cuprate reagent. Cryoscopic measurements in THF solution indicate that lower order cuprates prepared from CuCN can exist as either monomers or dimers while the 2RLi+CuCN reagent was measured as a monomer.[31] In this regard, it is significant that crystalline cuprate species were obtained upon mixing RLi or 2RLi+CuCN in the presence of a triamine.[26d] The resulting RCuCNLi crystal consisted of a dimer with a four member ring involving lithium coordination with the nitrile nitrogen atoms while the 2RLi+CuCN reagent gave a monomeric R_2Cu anion and a triamine complexed LiCNLi cation. Although this solid state structure need not reflect the solution phase species, it provides a picture consistent with the empirical results and parallels our reaction conditions which contained diamines in the deprotonation protocols. Computational studies suggest that dimeric cuprate and Me_2CuLi·Li clusters allow the cooperative interaction of two lithium and one copper atom with the substrate during the course of conjugate addition reactions.[32]

From a synthetic perspective, the CuCN·2LiCl protocol is the procedure of choice since higher yields, cleaner reactions, and efficient use of the aminoalkyl ligand in RCuCNLi reagents are achieved. Although the yields are slightly lower than those achieved with (2RLi+CuCN) obtained via the aminostannane protocol, the need to prepare and purify the aminostannane renders the CuCN·2LiCl direct deprotonation protocol more efficient. Whether these yields can be increased by use of TMSCl and $Sc(OTf)_3$ or other Lewis acids[33] remains to be determined. Although the Boc protecting group can be removed by use of PhOH/TMSCl in the presence of the ketone, synthetic application of this methodology must accommodate the general instability of the free amino ketones.

Summary

In summary, we have developed procedures for the preparation of α-aminoalkylcuprates from Boc-protected amines or from α-aminostannanes that efficiently transfer the α-aminoalkyl ligands to α,β-enones and enals in a 1,4-fashion. The direct deprotonation of Boc-protected amines is efficient and reliable when the cuprate reagents are generated from CuCN·2LiCl. This protocol allows the utilization of RCuCNLi reagents efficient in α-aminoalkyl ligand.

Experimental

NMR spectra were recorded at 300 MHz (^{1}H) and 75 MHz (13c). Solvents and additives were distilled from sodium benzophenone ketyl [tetrahydrofuran (THF), diethyl ether (Et_2O)], CaH_2 [CH_2Cl_2, *N,N,N′N′*-tetramethylethylenediamine (TMEDA), chlorotrimethylsilane (TMSCl)], and 4 Å molecular sieves (TMSCl), or purified by simple distillation (BF_3·Et_2O). CuCN was used without purification, but dried when necessary (≈0.005 mmHg, 90–100°C with stirring) CuI was purified[34a] and stored in the dark. CuBr·SMe_2 was prepared according to Wuts[34b] and CuSPh was purchased from Aldrich or prepared[34c] by the method of Adams. Alkyllithium reagents were obtained from Aldrich or FMC and titrated regularly by the method of Shapiro and co-workers using 1,3-diphenylacetone *p*-tosylhydrazone.[35] Glassware used in the cuprate experiments was cleaned in a potassium hydroxide–isopropyl alcohol bath, rinsed with water, 48% aq. HBr, and then with copious amounts of water. Oven-dried glassware was flame-dried and cooled

under a dry N_2 atmosphere. Cuprate reactions were conducted under a positive, dry nitrogen–argon atmosphere in round bottomed flasks fitted with new, clean rubber septa secured with Parafilm. Flask to flask transfer of air and moisture sensitive intermediates was completed using double-tipped needles (cannula) under a positive argon pressure maintained by double layered balloons filled with argon.

***N′*-(1,1-Dimethylethyl)-*N*-methyl-[*N*-(3-oxocyclohexyl)-methyl]methanimidamide (2a).** (RCuSPhLi[19] in THF): To formamidine **1** (0.1978 g, 1.5 mmol) in THF (2 mL) at −78°C was added *tert*-BuLi (0.94 mL, 1 mmol) and the resulting solution was stirred at −30°C for 75 min (faint yellow solution), then it was transferred by cannula to CuSPh suspended in THF (3 mL) at −30/−35°C (plus a 1 mL THF rinse of the formamidine pot) and the mixture was stirred for 41 min resulting in a brown–yellow solution. The reaction mixture was cooled to −78°C and 2-cyclohexen-1-one (0.09 mL, 0.95 mmol) was added dropwise by syringe. The mixture was allowed to stir for 1 h (−78°C), warmed to rt over 10 h, quenched by the addition of H_2O, and vacuum filtered through Celite with an Et_2O rinse. The filtered solution was washed with brine and back extracted with CH_2Cl_2. The combined organic phases were dried over a mixture of anhydrous Na_2SO_4 and $MgSO_4$. Evaporation of the solvent afforded crude **2a** (0.2275 g) in 86% yield as estimated by NMR analysis: IR 2966 (s), 1714 (s), 1644 (s), 1356 (m), 1264 (w) 1222 (m) 1110 (w), 1082 (m); ^{1}H NMR δ 1.14 (s, 9H), 1.57–1.74 (m, 1H), 1.84–1.87 (m, 1H), 1.96–2.15 (m, 3H), 2.21–2.24 (m, 3H), 2.81 (s, 3H), 3.10 (m, 2H), 7.30 (s, 1H); ^{13}C NMR δ 24.98, 28.60, 31.24 (3 C), 34.66, 37.99, 41.37, 45.54, 52.81, 56.14, 150.63, 210.85; mass spectrum (GC–MS) *m/z* (intensity) EI 224 (M^+), 209 (M^+–CH_3), 129 (M^+–CH=N^{t}Bu).

[*N*-Methyl-*N*-[(3-oxocyclohexylmethyl]-*N*-formyl]amine (2b). Crude formamidine **2a** (0.2945 g) was dissolved in a 1:1 mixture of MeOH–H_2O (6 mL) and stirred at rt for 2.5 days. The reaction mixture was extracted 4 times with CH_2Cl_2 and the combined extracts were dried over anhydrous K_2CO_3. Evaporation of the solvent in vacuo gave crude amino ketone (0.281 g) as a mixture of products. To this crude residue in THF (1 mL) was added ethyl formate (0.12 mL, 1.48 mmol) and the mixture was stirred at rt overnight. The solvent and excess ethyl formate were removed in vacuo. Careful fractionation by Kugelrohr distillation (40–65°C, 0.75 mmHg) afforded **2b** (0.1115 g) and the pot residue was subjected to a second Kugelrohr distillation (90–115°C, 0.005 mmHg) to give analytically pure **2b** as a colorless oil (0.0966 g, 46%): IR 2938 (s), 2868 (m), 1714 (s), 1672 (s), 1447 (m), 1498 (m), 1257 (w), 1229 (m), 1103 (w), 1068 (m), 955 (w), 871 (w); ^{1}H NMR δ 1.25–1.50 (br m, 1H), 1.56–1.75 (br m, 1H), 1.87 (m, 1H), 1.96–2.18 (br m, 3H), 2.18–2.49 (br m, 4H), 2.86 and 2.96 (s, 3H, rotamer), 3.10–3.40 (br m, 2H), 8.02 and 8.08 (s, 1H, rotamer); ^{13}C NMR δ 24.53, 24.75 (rotamer), 28.33, 28.66 (rotamer), 30.02, 35.01 (rotamer), 36.54, 36.80 (rotamer), 41.09, 44.93, 45.32 (rotamer), 49.19, 54.73 (rotamer), 162.53, 162.79 (rotamer), 209.47, 210.20 (rotamer); mass spectrum m/z (intensity) EI 170 (2.7, M+1), 169 (1.5, M^+), 97 (27.3, $CH_2(CH_3)NCHO$), 72 (91.7, cyclohexane$^+$); CI 170 (100, M+1). Anal. Calcd for $C_9H_{15}NO_2$: C, 63.93; H, 8.87. Found C, 64.08; H, 8.95.

General procedure A: conjugate addition reactions employing lithio-*N*-Boc carbamates generated from α-aminostannanes and CuCN (2RLi+CuCN)

To the α-aminostannane (1.0 mmol) in THF (2 mL) cooled to −78°C, was added *n*-BuLi (0.45 mL, 1.0 mmol) and the resulting mixture was stirred for 15 min (colorless solution). To CuCN (0.0457 g, 0.5 mmol) suspended in THF (2 mL) cooled to −78°C was added the carbanion solution by cannular transfer, plus a 1 mL THF rinse of the carbamate pot. The mixture was allowed to warm slowly to −55°C over 32 min and then cooled back to −78°C (homogenous solution). To this solution was added a cold (−78°C) solution of 2-cyclohexenone (0.04 mL, 0.41 mmol) and TMSCl (0.32 mL, 2.5 mmol) in THF (2 mL) by cannular transfer. The reaction mixture was stirred at −78°C for 40 min and monitored by analytical TLC until the reaction appeared to be complete. The reaction was quenched with H_2O, stirred at room temperature briefly, diluted with Et_2O, and vacuum filtered through Celite. The organic phase was separated, the aqueous phase extracted with Et_2O (10 mL×4) and the combined organic phases were washed with saturated NH_4Cl (aq., 1×), 5% $NaHCO_3$ (aq.), brine and dried over a mixture of anhydrous Na_2SO_4 and K_2CO_3. Evaporation of the solvent in vacuo afforded the crude 1,4-adduct.

General procedure B: conjugate addition reactions employing α-lithio-*N*-Boc carbamates generated from α-aminostannanes and CuCN (RLi+CuCN)

To α-aminostannane (0.5 mmol) in THF (1 mL) cooled to −78°C was added *n*-BuLi (0.5 mmol) and the resulting mixture stirred (≈20 min). To CuCN (0.5 mmol) suspended in THF (2 mL) cooled to −25/−30°C was added the carbanion solution by cannular transfer, plus a 1 mL THF rinse of the carbamate pot. The mixture was allowed to stir for 20–25 min and then cooled to −78°C whereupon a cold (−78°C) solution of α,β-enone (0.4–0.437 mmol) and TMSCl (1.0–2.5 mmol) in THF (2 mL) was added by cannular transfer. The mixture was stirred at −78°C for 15–25 min, allowed to warm to room temperature over 3.5–6 h, quenched with saturated NH_4Cl (aqueous) and work-up as described for procedure A.

General procedure C: conjugate addition reactions employing CuCN and α-lithio-*N*-Boc carbamates (2RLi+CuCN) generated by deprotonation

sec-BuLi (0.91 mL, 1.0 mmol) was added by syringe to (−)-sparteine (0.23 mL, 1.0 mmol) in Et_2O (1 mL) at −78°C and the resulting mixture was stirred for 15 min. The carbamate (1.0 mmol) in Et_2O (1 mL) at −78°C was added to the (−)-sparteine mixture and this solution plus a 0.5 mL Et_2O rinse of the pot was stirred for 2 h. [Alternatively, TMEDA (0.15 mL, 1.0 mmol) was added to the carbamate (1.0 mmol) in Et_2O (2 mL) and this solution was cooled to −78°C whereupon *sec*-BuLi (0.91 mL, 1.0 mmol) was added by syringe and the resulting mixture was stirred for approximately 1 h (colorless to faintly cloudy solution).] To CuCN (0.5 mmol) suspended in THF (2 mL) and cooled to −78°C was added the lithiocarbamate solution by cannular transfer, plus a 1 mL THF

rinse of the carbamate pot. The mixture was allowed to warm slowly to −56° C over 23 min and then cooled to −78°C (a white suspension resulted when TMEDA was employed and with the lithiated pyrrolidine sparteine combination). To this solution was added a cold (−78°C) solution of 2-cyclohexen-1-one (0.04 mL, 0.41 mmol) and TMSCl (0.32 mL, 2.5 mmol) in THF (2 mL) by cannular transfer. The reaction mixture was stirred at −78°C for 20–30 min (monitored by TLC). The reaction was quenched with H_2O or saturated NH_4Cl and worked up as described for procedure A. Evaporation of the solvent in vacuo afforded the crude product as the trimethylsilyl enol ether adduct by analytical TLC, and/or ^1H and ^{13}C NMR analysis. To the crude residue in THF (3 mL) at room temperature was added *tetra*-butyl ammonium fluoride (TBAF) (1.23 mL of 1 M solution in THF, 1.23 mmol) and the resulting mixture was stirred for 35 min. Evaporation of the solvent in vacuo and purification by silica gel preparative TLC [20% EtOAc–80% petroleum ether (v/v)] afforded pure conjugate addition product.

General procedure D: conjugate addition employing CuCN·2LiCl and α-lithio-*N*-Boc carbamates (2RLi+CuCN and RLi+CuCN) generated by deprotonation

To *tert*-butyl carbamate (2.0 mmol) in THF (4 mL) cooled to −78°C was added (−)-sparteine (0.46 mL, 2.0 mmol). *sec*-BuLi (2.0 mmol) was added by syringe and allowed to stir for 1 h. A light green solution of THF soluble CuCN·2 LiCl complex, prepared by dissolving CuCN (0.0895 g, 1 mmol) and LiCl (0.0840 g, 2 mmol, flamed dried under vacuum prior to use and purged with argon) in THF (2 mL) at room temperature, was added via syringe to the 2-lithio-*N*-Boc carbamate (clear to pale yellow) at −50°C. The mixture was allowed to stir at −50°C for 45 min to generate the cuprate as a clear to light yellow homogeneous solution. Next a solution of enone (1 mmol) dissolved in TMSCl (0.63 mL, 5 mmol) was added and the reaction stirred at −50°C for 30 min and then was allowed to stir at room temperature for 1.5 h. The reaction was quenched with saturated NH_4Cl (aq.), worked-up as described for procedure A and dried over $MgSO_4$. Concentration in vacuo afforded the crude 1,4-adducts. Purification by column chromatography [5% EtOAc–95% petroleum ether (v/v)] gave pure 1,4-adducts.

1,1-Dimethylethyl *N*-methyl-*N*-[(3-oxocyclohexyl)methyl] carbamate (6). General procedure A was employed. Purification by preparative TLC [silica gel, 20% EtOAc–80% petroleum ether, v/v] gave **6** (0.127 g) which was further purified by Kugelrohr distillation to afford analytically pure **6** as a colorless oil (0.0971 g, 98% yield): IR 2973 (s), 2931 (s), 1714 (s, shoulder), 1699 (s, shoulder), 1680 (shoulder), 1394 (s), 1365 (s), 1220 (s), 1160 (s), 878 (m), 773 (m); ^1H NMR δ 1.45 (s, 9H), 1.56–1.75 (m, 2H), 1.81–1.93 (m, 1H), 2.00–2.18 (m, 3H), 2.21–2.43 (m, 3H), 2.83–2.85 (m, 3H), 3.09–3.28 (m, 2H); ^{13}C NMR δ 25.07, 28.37 (3 C), 28,91, 34.97, 37.92 (38.30, rotamer), 41.36, 45.61, 53.74 (54.28, rotamer), 79.46, 155.67 (155.98, rotamer), 210.73 (211.13, rotamer). Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.75; H, 9.53. Found: C, 64.81; H, 9.65.

1,1-Dimethylethyl 2-(3-oxocyclohexyl)-1-pyrrolidinecarboxylate (7a). General procedure A was empoyed using α-aminostannane **4b** (0.4578 g, 1.0 mmol), *n*-BuLi (0.43 mL, 0.95 mmol), CuCN (0.0454 g, 0.5 mmol), 2-cyclohexenone (0.04 mL, 0.41 mmol), and TMSCl (0.32 mL. 2.5 mmol). Purification using preparative TLC [silica gel, 50% Et_2O–50% hexane, v/v] gave **7a** (0.1095 g, 100%) which was doubly purified by Kugelrohr distillation (74–112°C, 0.005 mmHg) to give analytically pure **7a** as a colorless oil (0.1084 g, 99% yield): IR 2973 (m), 1713 (shoulder), 1693 (s), 1391 (s), 1167 (m), 1106 (m), 861 (w), 772 (w); ^1H NMR δ 1.44 (br s, 11 H, 1.45 rotamer), 1.60–1.69 (m, 1H), 1.78 (br m, 5H), 2.10 (br m, 2H), 2.17–2.40 (m, 3H), 3.23 (m, 1H), 3.34–3.61 (m, 1H), 3.67–3.89 (m, 1H); ^{13}C NMR δ (rotameric and diastereomeric mixture) 22.45, 23.19, 23.77, 26.24, 26.60, 27.42, 28.22, 32.48, 41.09, 41.64, 78.91, 79.11, 81.31, 154.51, 154.75, 154.84, 155,08, 210.94, 211.28. Anal. Calcd for $C_{15}H_{25}N_2O_3$: C, 67.44; H, 9.35. Found C, 67.51; H, 9.48.

1,1-Dimethylethyl 2-(3-oxocyclohexyl)-1-piperidinecarboxylate (7b). General procedure D was employed using *N-tert*-butyoxycarbonyl piperidine **5a** (0.185 g, 1.0 mmol in ether), TMEDA (0.15 mL, 1.0 mmol), *sec*-BuLi (1.0 mmol), CuCN·2LiCl dissolved in THF, and cyclohexenone (0.096 g, 1.0 mmol) dissolved in TMSCl (0.63 mL, 5.0 mmol). Purification by flash column chromatography [silica gel, 5% EtOAc–95% petroleum ether, v/v] gave pure **7b** as an oil (0.2419 g, 86% yield); ^1H NMR δ 1.11–2.44 (m, 16H), 1.40 (s, 9H)(1.37 rotamer and/or diastereomer), 2.45–2.75 (m, 1H), 3.83 (v br s, 1H); ^{13}C NMR δ 18.9(19.1), 25.0, 25.3, 27.5(26.0), 28.4(*t*-Bu), 29.0, 37.0, 39.9(several peaks), 41.2, 45.5(44.3), 54.8(several peaks), 79.3, 155.0, 211.1 (rotamer and/or diastereomers).

1,1-Dimethylethyl [*N*-methyl-*N*-[3-oxocyclopentyl)methyl] carbamate (8): General procedure A was employed using α-aminostannane **3b** (0.2169 g, 0.5 mmol), *n*-BuLi (0.21 mL, 0.5 mmol), CuCN (0.0453 g, 0.5 mmol), 2-cyclopenten-1-one (0.34 mL, 0.41 mmol), and TMSCl (0.32 mL, 2.5 mmol). Purified by preparative TLC [silica gel, 20% EtOAc–80% petroleum ether, v/v] gave **8** (0.0556 g, 59%). Kugelrohr distillation (69°C, 0.005 mmHg) gave analytically pure **8** as a colorless oil (0.0469 g, 50% yield): IR 2973 (m), 1743 (s), 1693 (s), 1482 (m), 1398 (s), 1363 (m), 1250 (m), 1166 (s), 878 (w), 772 (w); ^1H NMR δ 1.45 (s, 9H), 1.61–1.68 (m, 1H), 1.89–1.98 (m, 1H), 2.04–2.26 (m, 2H), 2.30–2.38 (m, 2H), 2.45–2.60 (m, 1H), 2.89 (s, 3H), 3.28 (br d, J=5.98 Hz, 2H); ^{13}C NMR δ 26.78, 28.36, 34.57 (34.98, rotamer), 35.93, 37.71, 42.84, 52.69, 79.86, 155.64 (155.90, rotamer), 218.39. Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.45; H, 9.24. Found: C, 63.16; H, 9.14.

1,1-Dimethylethyl *N*-methyl-*N*-[(1-methyl-3-oxocyclopentyl)methyl] carbamate (9). General procedure A was employed using α-aminostannane **3b** (0.4322 g, 1.0 mmol), *n*-BuLi (0.42 mL, 1.0 mmol), CuCN (0.0461 g, 0.5 mmol), 3-methyl-2-cyclopenten-1-one (0.04 mL, 0.41 mmol), and TMSCl (0.32 mL, 2.5 mmol). Purification using gravity column chromatography [silica gel, 19% EtOAc–81% petroleum ether afforded **9** (0.050 g, 50%). Kugelrohr distillation (93–98°C, 0.005 mmHg) gave analytically pure **9** as a

colorless oil (0.0486 g, 49% yield): IR 2973 (m), 1743 (s), 1693 (s), 1454 (m) 1391 (m), 1363 (m), 1166 (s), 878 (w), 772 (w); ^{1}H NMR δ 1.09 (s, 3H), 1.46 (s, 9H), 1.66–1.77 (m, 1H), 1.86–2.04 (m, 2H), 2.20–2.34 (m, 3H), 2.92–2.94 (m, 3H), 3.18–3.37 (m, 2H); ^{13}C NMR δ 24.18 (24.33, rotamer), 28.24, 33.29, 36.38, 37.54, 42.13, 50.39, 57.98, 79.41 (79.96, rotamer), 156.06, 218.44. Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.75; H, 9.53. Found: C, 64.79; H, 9.64.

1,1-Dimethylethyl *N*-methyl-*N*-[(1,3,3-trimethyl-5-oxocyclohexyl)methyl] carbamate (10). General procedure A was employed using α-aminostannane **3b** (0.4380 g, 1.0 mmol), *n*-BuLi (0.41 mL, 1.0 mmol), CuCN (0.0449, 0.5 mmol), isophorone (0.06 mL, 0.4 mmol), and TMSCl (0.32 mL, 2.5 mmol). Purification using preparative TLC [silica gel, 20% EtOAc–80% petroleum ether] afforded **10** (0.079 g, 69% yield). Kugelrohr distillation (106°C, 0.005 mmHg) gave analytically pure **10** as a colorless oil (0.0733 g, 64%): IR 2959 (m), 1714 (shoulder), 1699 (s), 1391 (m), 1363 (m), 1222 (w), 1166 (m), 878 (w), 772 (w); ^{1}H NMR δ 1.03 (s, 3H), 1.04 (s, 3H), 1.08 (s, 3H), 1.46 (s, 9H), 1.64–1.77 (m, 1H), 2.00–2.43 (m, 4H), 2.85–2.96 (m, 3H), 3.06–3.17 (m, 2H); ^{13}C NMR δ 25.04, 28.27, 29.09, 34.06, 35.72, 38.37, 41.95, 47.91, 50.57, 53.77, 61.53 (61.93, rotamer), 79.41 (79.91, rotamer), 156.31 (156.72, rotamer), 211.62 (211.88, rotamer). Anal. Calcd for $C_{16}H_{29}NO_3$: C, 67.86; H, 10.24. Found: C, 67.58; H, 10.17.

1,1-Dimethylethyl *N*-Methyl-*N*-(4-oxopentyl) carbamate (11). General procedure A was employed using α-aminostannane **3b** (0.2182 g, 0.5 mmol), *n*-BuLi (0.23 mL, 0.5 mmol), CuCN (0.0438 g, 0.5 mmol), methyl vinyl ketone (0.034 mL, 0.408 mmol), and TMSCl (0.32 mL, 2.5 mmol). The crude material was purified by preparative TLC [silica gel, 20% EtOAc–petroleum ether, v/v] affording **11** (0.0707 g). Kugelrohr distillation (73–80°C, 0.005 mmHg) gave analytically pure **11** as a colorless oil (0.0545 g, 62% yield): IR 2973 (m), 2931 (m), 1715 (shoulder), 1693 (s), 1395 (m), 1367 (m), 1168 (s), 1140 (m), 880 (w), 774 (w); ^{1}H NMR δ 1.45 (s, 9H), 1.78 (quintet J=7.2 Hz, 2H), 2.15 (s, 3H), 2.43 (t, J=7.2 Hz, 2H), 2.82 (s, 3H), 3.21 (t, J=6.9 Hz, 3H); ^{13}C NMR δ 21.63, 28.39, 29.93, 33.95, 40.34, 47.59 (47.86, rotamer), 79.29, 155.83, 208.06 (208.21, rotamer). Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.42; H, 9.76. Found: C, 61.41; H, 9.82.

1,1-Dimethylethyl 2-(3-oxobutyl)-1-pyrrolidinecarboxylate (12a). General procedure A was employed using α-aminostannane **4b** (0.4612 g, 1.0 mmol), *n*-BuLi (0.41 mL, 1.0 mmol), CuCN (0.0442 g, 0.5 mmol), methyl vinyl ketone (0.033 mL, 0.408 mmol), and TMSCl (0.32 mL, 2.5 mmol). The crude material was purified by gravity column chromatography [silica gel, 20% EtOAc–80% petroleum ether] to give pure **12a** (0.0843 g, 86%). Kugelrohr distillation (85–95°C, 0.005 mmHg) afforded pure **12a** as a colorless oil (0.0849 g, 86% yield): IR 2974 (m), 1714 (shoulder), 1693 (s), 1395 (s), 1366 (m), 1152 (w), 1172 (m), 1103 (m), 771 (w); ^{1}H NMR δ 1.46 (s, 9H), 1.56–1.70 (m, 2H), 1.75 –2.00 (m, 4H), 2.15 (s, 3H), 2.45 (br, 2H), 3.21–3.58 (m, 2H), 3.81 (br s, 1H); ^{13}C NMR δ 22.84 (23.50, rotamer), 28.35 (3 C), 28.49, 29.66, 30.16 (30.59, rotamer), 40.47, 46.19, 56.35, 78.81, 154.67, 208.01 (208.41, rotamer). Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.75; H, 9.53. Found C, 64.76; H, 9.65.

1,1-Dimethylethyl 2-(3-oxobutyl)-1-piperidinecarboxylate 12b. General procedure A was employed using α-aminostannane **5b** (0.4957 g, 1.0 mmol), *n*-BuLi (0.41 mL, 1.0 mmol), CuCN (0.0450 g, 0.5 mmol), methyl vinyl ketone (0.04 mL, 0.48 mmol), and TMSCl (0.32 mL, 2.5 mmol). Purification by preparative TLC [silica gel, 30% EtOAc–70% petroleum ether] gave **12b** (0.1299 g). Kugelrohr distillation (90°C, 0.005 mmHg) afforded pure **12b** as a colorless oil (0.1278 g, 100% yield): IR 2983 (s), 2860 (m), 1717 (m), 1685 (s), 1418 (s), 1364 (s), 1264 (s), 1160 (s), 925 (w), 867 (m), 812 (w), 768 (m); ^{1}H NMR δ 1.23–1.68 (m, 17H), 1.95–2.09 (m, 1 H), 2.13 (m, 2H), 2.72 (br t, J=13 Hz, 1H), 3.95 (br d, J=10 Hz, 1H), 4.21 (br t, J=4.5 Hz, 1H); ^{13}C NMR δ 18.96, 23.50, 25.50, 28.39 (3 C), 28.91, 29.96, 38.66, 40.21, 49.71, 79.15, 155.06, 208.24. Anal. Calcd for $C_{14}H_{25}NO_3$: C, 67.36; H, 10.19. Found C, 66.86; H, 10.31.

1,1-Dimethylethyl *N*-methyl-*N*-(2,2-dimethyl-4-oxopentyl) carbamate (13). General procedure B was employed using α-aminostannane **3b** (0.2169 g, 0.5 mmol), *n*-BuLi (0.21 mL, 0.5 mmol), CuCN (0.0466 g, 0.5 mmol), mesityl oxide (0.05 mL, 0.437 mmol), and TMSCl (0.32 mL, 2.5 mmol). Purification by preparative TLC [silica gel, 10% EtOAc–90% petroleum ether, v/v] afforded pure **13** (0.043 g, 40%). Kugelrohr distillation (89°C, 0.005 mmHg) gave analytically pure **13** as colorless oil (0.0374 g, 35% yield): IR 2973 (m), 1714 (shoulder), 1693 (s), 1391 (m), 1363 (m), 1166 (m), 878 (w), 772 (w); ^{1}H NMR δ 1.02 (s, 6H), 1.45 (s, 9H), 2.12 (s, 3H), 2.38 (s, 2H), 2.90 (s, 3H), 3.19 (s, 2H); ^{13}C NMR δ 25.82 (2 C), 28.35 (3 C), 32.21, 36.45, 37.92, 52.12 (53.37, rotamer), 59.08, 79.15 (79.96, rotamer), 156.61, 208.14. Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.21; H,10.28. Found: C, 64.03; H, 10.32.

Non-transferable ligand studies: mixed cuprates (RLi+R_{nt}Li+CuCN+TMSCl)

Several mixed cuprates containing 2-thienyl, methyl, *p*-methoxyphenylethynyl, and 1-hexynyl as potential non-transferable ligands were examined. A general procedure for these experiments is summarized: To α-aminostannane **3a** (0.2166 g, 0.5 mmol) in THF (1.0 mL) cooled to −78°C was added *n*-BuLi (0.22 mL, 0.5 mmol) and the resulting mixture was stirred for 27 min. To R_{nt}Cu(CN)Li [For R_{nt}=2-thienyl, the reagent 2-thienylCuCNLi was purchased from Aldrich. For R_{nt}=Me or 1-hexynyl: prepared from CuCN (0.0457 g, 0.5 mmol in THF (2 mL) at −78°C by addition of MeLi (0.53 mL, 0.5 mmol) or 1-lithio-1-hexyne (1-hexyne (0.057 mL, 0.5 mmol) and then stirring at 0°C for 2–15 min for MeCuCNLi)] cooled to −78°C was added the carbanion solution by cannular transfer plus a 0.5 mL THF rinse and then stirred at 0°C for 1 min. The homogenous light yellow [RLi+(2-thienylCuCNLi), RLi+MeCuCNLi, and RLi+(*p*-Methoxyphenylacetylenyl)CuCNLi] or amber [RLi+1-hexynylCuCNLi] colored solution was cooled to −78°C and to this was added a cold (−78°C) solution of 2-cyclohexenone (0.02 mL, 0.206 mmol) and TMSCl (0.32 mL, 0.5 mmol) in THF (2 mL) by cannular transfer

and allowed to stir for 36 min (monitored by TLC). The reaction was quenched with H_2O and was stirred at rt briefly. The mixture was further diluted with Et_2O and vacuum filtered through Celite. The organic phase was separated and the aqueous phase was extracted 3 times with Et_2O. The combined organic phases were washed 1 time with saturated NH_4Cl (aq), 5% $NaHCO_3$ (aq), brine and dried over anhydrous K_2CO_3. Evaporation of the solvent in vacuo afforded the crude product **6**. Purification by silica gel column chromatography (gravity) eluting with 50% Et_2O–50% petroleum ether (v/v) mixture afforded pure **6** [RLi+2-thienylCuCNLi (48%); RLi+MeCuCNLi (0.051 g 51%)+3-methylcyclohexanone isolated as mixture with carbamate **3a** (0.0269 g, 38% yield as estimated by ^1H NMR analysis of this isolated mixture); RLi+1-hexynyl-CuCNLi (0.065 g, 65%)+3-butyl-2-cyclohexan-1-one (0.0228 g, 34% as determined by NMR analysis on an isolated mixture containing carbamate **3a**); RLi+*p*-methoxyphenylacetylenylCuCNLi (0.052 g, 52% yield)].

1,1-Dimethylethyl *N*-methyl-*N*-[(2-methyl-3-formyl)propyl] carbamate (14a). General procedure C was employed using carbamate **3a** (0.1453 g, 1.0 mmol in Et_2O), TMEDA (0.15 mL, 1.0 mmol), *sec*-BuLi (0.90 mL, 1.0 mmol), CuCN (0.0458 g, 0.5 mmol in THF), crotonaldehyde (0.034 mL, 0.41 mmol), and TMSCl (0.32 mL, 2.5 mmol). Purification by preparative TLC [silica gel, 20% EtOAc–80% petroleum ether, v/v] afforded **14a** (0.0486 g, 48% yield); Kugelrohr distillation (73–81°C, 0.005 mm Hg) gave pure **14a** (0.395 g, 47% yield) as an oil: IR 2973 (s), 2931 (s), 1728 (shoulder), 1699 (s), 1482 (m), 1457 (m), 1396 (s), 1367 (m), 1253 (m), 1171 (s), 1068 (w), 880 (m), 847 (m), 774 (w); ^1H NMR δ 0.95 (d, J=6.6 Hz, 3H), 1.45 (s, 11H), 2.23–2.53 (m, 2H), 2.84 (br m, 3H), 2.97–3.21 (br m, 2H), 9.75 (s, 1H); ^{13}C NMR δ 17.70, 27.34, 28.34 (3C), 33.79, 48.38, 54.18 (54.27 rotamer), 79.50, 155.94 201.64 (201.91, rotamer).

1,1-Dimethylethyl *N*-methyl-*N*-[(2-phenyl-3-formyl)propyl] carbamate (14b) and *trans*-1,1-dimethylethyl *N*-methyl-*N*-[(2-hydroxy-phenyl)-3-butenyl] carbamate. General procedure C was employed using carbamate **3a** (0.1472 g, 1.0 mmol in Et_2O), TMEDA (0.15 mL, 1.0 mmol), *sec*-BuLi (0.91 mL, 1.0 mmol), CuCN (0.0487 g, 0.5 mmol in THF), cinnamaldehyde (0.05 mL, 0.396 mmol), and TMSCl (0.32 mL, 2.5 mmol). Purification by preparative TLC [silica gel, 20% EtOAc–80% petroleum ether, v/v] afforded **14b** as an oil (0.0143 g, ≈13% yield) and 1,2-adduct as an oil (0.0461 g, 44% yield). 1,4-Adduct **14b**: IR 2980 (s), 2931 (s), 1693 (s), 1482 (s), 1398 (s), 1363 (m), 1236 (m), 1159 (s), 920 (m), 878 (m), 765 (m), 730 (m), 702 (m); ^1H NMR δ 1.40-1.45 (m, 9H), 2.69–2.79 (m, 3H), 2.88 (br s, 2H), 3.12–3.72 (m, 3H), 7.18–7.33 (m, 5H), 9.68 (s, 1H); ^{13}C NMR δ 28.26 (rotamer 28.36, 3 C), 34.47 (rotamers 34.78, 35.00), 38.55 (rotamer 38.78), 46.86 (rotamer 47.10), 54.38 (rotamer 54.83), 79.55, 127.04, 127.63 (2 C), 128.68 (2 C), 141.08 (rotamer 141.27), 155.38 (rotamer, 155.93), 200.63 (rotamer 210.10). 1,2-adduct: IR 3416 (br, m), 2973 (m), 2931 (m), 1693 (s), 1672 (s), 1398 (m), 1229 (m), 1152 (s), 969 (m), 878 (m), 751 (m), 695 (m); ^1H NMR δ 1.45 (s, 10H), 2.94 (s, 3H), 3.39 (br s, 2H), 4.52 (br s, 1H), 6.18 (dd, J=9.9 Hz, J=6 Hz, 1H), 6.68 (d, J=18.6 Hz, 1H), 7.23–7.39 (m, 5H); ^{13}C NMR δ 28.28 (3 C), 36.43 (35.77, rotamer), 55.31, 72.02, 80.12, 126.38 (2 C), 127.54, 128.44 (2 C), 129.67, 130.77, 136.61, 157.61. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.33; H, 8.29. Found: C, 69.36; H, 8.33.

1,1-Dimethylethyl 2-(1-methyl-2-formyl)ethyl]-1-pyrrolidinecarboxylate (15). General procedure D was employed using *N*-Boc pyrrolidine (**4a**) (0.188 g, 1.10 mmol in THF), (−)-sparteine (0.23 mL, 1.10 mmol), *sec*-BuLi (0.90 mL, 1.10 mmol), a mixture of CuCN (0.0979 g, 1.10 mmol) and LiCl (0.0924 g, 2.2 mmol), crotonaldehyde (0.070 g, 1.0 mmol) and TMSCl (0.63 mL, 5.0 mmol). Purification by flash chromatography [silica gel, 5% EtOAc–95% petroleum ether, v/v] gave **15** as an oil (0.195 g, 81% yield): ^1H NMR δ 0.95 (d, J=7.0 Hz, 3H) [0.92 (d, J=6.8 Hz, 3H), diastereomer, 57:43], 1.26 (s, 9H), 1.57–2.00 (m, 4H), 2.05–2.70 (m, 3H), 2.90–3.29 (m, 1H), 3.30–4.00 (m, 2H), 9.73 (s, 1H) (9.59 diastereomer+rotamer); ^{13}C NMR δ 16.0 (15.4), 24.0 (22.6), 27.2 (26.0), 28.4, 31.0 (32.0), 46.8 (46.0), 48.1 (47.3), 61.1 (60.7), 79.3 (79.2), 155.1, 202.7 [203.4, diastereomer (56:44)+rotamers].

1,1-Dimethylethyl *N*-methyl-*N*-[(bicyclo[3.1.1](4,4-dimethyl-6-formyl)heptyl)methyl] carbamate (16). To α-aminostannane **3b** (0.4327 g, 1.0 mmol) in THF (2 mL) cooled to −78°C was added *n*-BuLi (0.41 mL, 1.0 mmol) and the resulting mixture was stirred for 17 min. To CuCN (0.0455 g, 0.5 mmol) suspended in THF (2 mL) cooled to −78°C was added the carbanion solution by cannular transfer, plus a 0.5 mL THF rinse of the carbamate pot. The mixture was allowed to warm slowly to −53°C over 25 min and then cooled back to −78°C. To this solution was added a cold (−78°C) solution of (1*R*)-(−)-myrtenal (0.06 mL, 0.4 mmol) and TMSCl (0.32 mL, 2.5 mmol) in THF (2 mL) by cannular transfer. The reaction mixture was stirred at −78°C for 57 min and then allowed to warm to 0°C over 2.25 h. The reaction was quenched with saturated NH_4Cl (aq.) and was stirred at rt briefly. The mixture was further diluted with Et_2O and filtered by vacuum through Celite. The organic phase was separated and the aqueous phase was extracted 3 times with Et_2O. The combined organic phases were washed 1 time with saturated NH_4Cl (aq.), brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent in vacuo afforded the crude material (0.548 g). Purification by MPLC [silica gel, 15% Et_2O–85% petroleum ether, v/v] gave **16**; Kugelrohr distillation (103°C, 0.005 mmHg) afforded analytically pure **16** as a white solid (0.074 g, 62% yield): mp=75–76°C; IR (solution cell, $CDCl_3$) 2980 (m), 2931 (m), 1721 (s) 1679 (s), 1475 (w), 1454 (w), 1398 (m), 1370 (m), 1125 (s); ^1H NMR δ 0.67 (s, 3H), 1.17 (br s, 4H), 1.39 (br s, 12H), 1.94 (br s, 1H), 2.04 (m, 1H), 2.34–2.61 (m, 3H), 2.79 (s, 3H), 2.84–3.50 (m, 1H), 9.01 (s, 1H); ^{13}C NMR δ 22.59, 24.65, 26.57, 28.38 (3 C), 29.77, 30.36, 30.69, 34.05, 38.72, 40.98, 42.16, 57.10, 57.88, 79.35, 155.85, 156.03, 156.03, 156.40, 156.59, 203.94, 204.42. Anal. Calcd for $C_{17}H_{29}NO_3$: C, 69.17; H, 9.82. Found: C, 69.06; H, 9.97.

1,1-Dimethylethyl 2-[bicyclo[3.1.1](4,4-dimethyl-6-formyl)-heptyl]-1-pyrrolidinecarboxylate (17). General Procedure D was employed using *N*-Boc pyrrolidine (**2a**) (0.180 g, 1.05 mmol in THF), (−)-sparteine (0.23 mL, 1.05 mmol), *sec*-BuLi (0.90 mL, 1.05 mmol), a mixture of CuCN

(0.0939 g, 1.05 mmol) and LiCl (0.0882 g, 2.1 mmol) dissolved in THF (2.1 mL), and (1*R*)-(−)-mytrenal (0.150 g, 1.0 mmol) dissolved in TMSCl (0.63 mL, 5.0 mmol) in the indicated quantities. Purification by flash chromatography [5% EtOAc–95% petroleum ether, v/v] gave the 1,4-adduct as an oil (0.0867 g, 37% yield) existing as a complex mixture of diastereomers.

[*N*-Methyl-*N*-(1-methyl-3,3-dimethyl-5-oxocyclohexyl)-methyl]amine-hydrochloride (18).[36] A solution of 1 M TMSCl in CH_2Cl_2 (0.83 mL, 3.32 mmol) and 4 M phenol in CH_2Cl_2 (2.5 mL, 10 mmol) was stirred under a nitrogen atmoshphere at rt for 18 min. This solution was added by syringe to 1,4-adduct **10** (0.0634 g, 0.224 mmol) in CH_2Cl_2 (1 mL) at rt and stirred for 0.5 h. The solvent was evaporated in vacuo and then the residue was dissolved in anhydrous Et_2O. The solution was supercooled in liquid nitrogen and allowed to slowly warm to rt. A precipitate was isolated by vacuum filtration to give the γ-aminoketone hydrochloride salt **18** (0.0382 g, 77% yield) which was >95% pure by ^{1}H NMR analysis: mp 218.9–220°C (decomposed); IR (solution cell, $CHCl_3$) 2966 (s), 2727 (br), 1714 (s), 1595 (w), 1461 (m), 1285 (m), 1233 (m); ^{1}H NMR (D_2O) δ 0.80 (s, 3H), 0.85 (s, 3H), 0.92 (s, 3H), 1.51 (app. q, J=8.7 Hz, 2H), 1.99 (app. d, J=13.5 Hz, 2H), 2.23 (app. t, J=14.4 Hz, 2H), 2.50 (s, 3H), 2.77 (app. q, J=7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 26.33, 29.85, 32.48, 35.02, 35.92, 38.69, 46.63, 49.88, 53.74, 61.54, 209.43.

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