Conjugate Addition Reactions of α-Aminoalkylcuprates with α,*β*-Alkenyl-, α,*β*-Alkynyl-, α,*β*−*β*,*γ*-Allenyl-, and α,*β*−*γ*,*δ*-Dienyl Carboxylic Acid Derivatives, Nitriles, and Sulfoxides

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α-Aminoalkylcuprates prepared from α-lithio carbamates and CuCN·2LiCl participate in 1,4-addition reactions with α,*β*-unsaturated esters, thiol esters, imides, and nitriles in poor to excellent yields depending upon the electron-withdrawing substituent and the substitution pattern of the unsaturated substrate. These reagents also undergo conjugate addition reactions with α,*β*-alkynyl esters, sulfoxides, and nitriles and with α,*β*−*β*,*γ*-unsaturated allenyl esters. Excellent stereocontrol is achieved in the conjugate additions of α-aminoalkylcuprates to the allenyl esters, while poor stereoselectivity results in the conjugate additions to the alkynyl derivatives. Deprotection and cyclization of the alkynyl adducts affords pyrrolin-2-ones, while similar treatment of the allenyl adducts affords 4-alkylidine- pyrrolidin-2-ones and pyrrolizidinones.

Introduction

Organocopper[1] and palladium reagents represent the two most widely used transition organometallic reagents in organic synthesis. Although organocopper reagents effect a wide range of transformations often complementary to organolithium and Grignard reagents, their preparation from the latter species limits the compatible functional groups that can be present in the organic ligand. The copper-mediated reactions of organozinc reagents have enormously extended the range of functionalized organocopper reagents, but reactivity problems have plagued the application of this chemistry to α-aminoalkylcuprates.[2] Successful development of dipole stabilized α-lithio amine chemistry[3] encouraged the exploration of α-aminoalkylcuprate reagents. The first reported examples of α-aminoalkylcuprate conjugate addition reactions[4] were limited to α,*β*-enones and enals and early efforts to effect conjugate addition to α,*β*-enoates were unsuccessful consistent with cuprate-enoate reactivity profiles.[5] Although numerous homo and mixed organocuprates readily transfer alkyl ligands to the *β*-carbon atom of α,*β*-enones, the conjugate addition reaction is often sluggish with the less reactive enoate substrates. Cuprates prepared from CuCN (2RLi + CuCN),[6] cuprous thiophenoxides,[7] and copper(I) trimethylsilylacetylide[8] have provided partial solutions to this problem. The reactivity of the latter reagent was enhanced by solvent composition (4:1 ether/THF) and by the addition of chlorotrimethylsilane.[8] Gilman reagents also effect high yield conjugate addition reactions with mono *β*-alkyl-substituted enoates, enamides, and enecarbamates in ether in the presence of TMSCl.[9] Alkyl copper compounds also participate with enoates in conjugate addition reactions in synthetically useful yields in the presence of additives such as BF_3·Et_2O[10] and chloro- or iodotrimethylsilane.[11] These tactics proved ineffective for α-aminoalkylcuprates and their conjugate addition to α,*β*-enoates was eventually achieved by use of the THF soluble complex CuCN·2LiCl and TMSCl.[5] In this full report we describe the reactions of α-aminoalkylcuprates with α,*β*-alkenyl-, α,*β*-alkynyl- carboxylic acid derivatives[5] and nitriles and with α,*β*−*γ*,*δ*-dienoates (Scheme. 1). α-Aminoalkylcuprates also participated effectively in conjugate addition reactions with an α,*β*-alkynyl sulfoxide and with α,*β*-allenyl esters (Scheme 1).

Results

Initial efforts to effect reaction of α-aminoalkylcuprates with methyl or ethyl acrylate employing procedures that

(1) For a review on organocopper chemistry see: (a) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. (b) Lipshutz, B. H. In *Organometallics in Synthesis: A Manual*; Schlosser, M., Ed.; John Wiley & Sons: England, 1994; Chapter 4, p 283. (c) *Organocopper Reagents: A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994.

(2) For the use of CuCN·2LiCl catalyzed reactions of alkylzinc halides see: (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (b) Strekowski, L.; Gulevich, Y.; Van Aken, K.; Wilson, D. W.; Fox, K. R. *Tetrahedron Lett.* **1995**, *36*, 225. (c) Knochel, P.; Chou, T.-S.; Jubert, C.; Rajagopal, D. *J. Org. Chem.* **1993**, *58*, 588.

(3) For reviews see: (a) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275. (b) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471. (c) Meyers, A. I. *Aldrichimica Acta* **1985**, *18*, 59. (d) Gawley, R. E.; Rein, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1990; Vol. 1, Chapter 2.1 and Vol. 3, Chapter 1.2. (e) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.

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(7) Behforousz, M.; Curran, T. T.; Bolan, J. *Tetrahedron Lett.* **1986**, *27*, 3107.

(8) Sakata, H.; Kuwajima, I. *Tetranhedron Lett.* **1987**, *28*, 5719.

(9) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047.

(10) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119.

(11) (a) Bergdahl, M.; Lindstedt, E.-L.; Nilsson, M. *Tetrahedron* **1988**, *44*, 2055. (b) Bergdahl, M.; Eriksson, M.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1993**, *58*, 7238. (c) Bergdahl, M.; Iliefski, T.; Nilsson, M.; Olsson, T. *Tetrahedron Lett.* **1995**, *36*, 3227. (d) Eriksson, M.; Hjelmencrantz, A.; Nilsson, M.; Olsson, T. *Tetrahedron* **1995**, *51*, 12631. (e) Eriksson, M.; Nilsson, M.; Olsson, T. *Synlett* **1994**, 271. (f) Bergdahl M.; Eriksson, M.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1993**, *58*, 7238.

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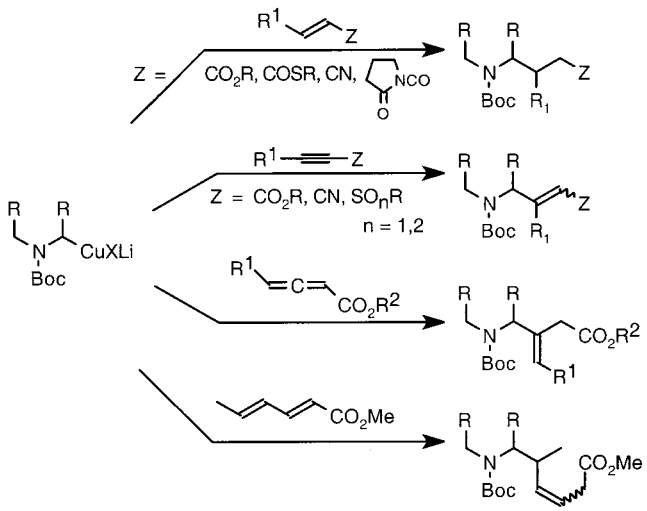
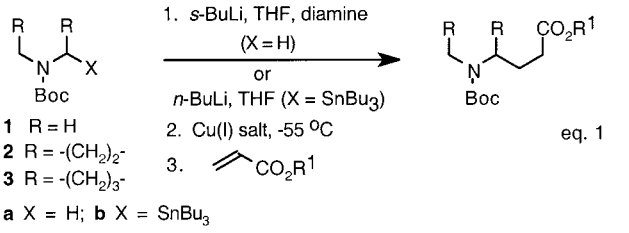
Scheme 1



were successful with α,β-enones either failed or gave low yields of conjugate adducts. Dialkylcuprates prepared via organostannanes failed completely, while the Johnson alkyl copper[12] reagent gave low to modest yields depending upon solvent (eq 1). Subsequent experimentation



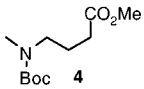
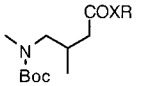
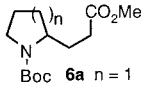
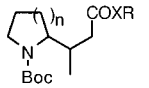
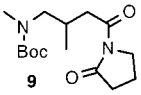
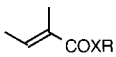
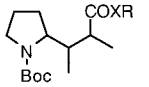
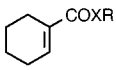
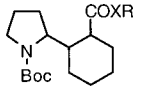
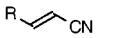
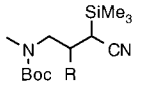
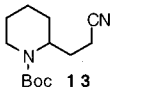
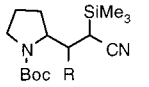
eq. 1

carbamate	diamine	Cu(I) salt	equiv	R	solvent	% yield
1a	TMEDA	CuI	1.0	H	Et_2O	9
1a	TMEDA	CuI	1.0	H	CH_2Cl_2	28
1b	-	CuI	0.5	H	THF	0
2a	sparteine	CuCN·2LiCl	0.5	H	THF	95

revealed that preparation of the cuprate reagent from **1a**, **2a**, or **3a** via Beak's deprotonation protocol[13] and LiCl-solubilized CuCN [i. *s*-BuLi, (−)-sparteine, THF, −78 °C, 1 h; ii. CuCN·2LiCl, THF, −78 to −55 °C, 45 min] generated efficacious reagents that underwent conjugate addition to methyl acrylate [THF, TMSCl, −55 °C, 0.5 h to room temperature (1.5 h)] in the presence of TMSCl in high yields (eq 1 and Table 1, entries 1, 7, and 8). Utilization of ethyl crotonate resulted in significantly reduced yields of conjugate adducts accompanied by recovered carbamates (entries 2 and 9−11). Deprotonation of **2a**, aided by either TMEDA or (−)-sparteine, gave cuprates that reacted with ethyl crotonate, giving similar yields for additives [i.e., TMEDA or (−)-sparteine, 52% vs 56−77% yields, respectively][4a] and CuCN·2LiX combinations [CuCN·2LiI (53%), CuCN·2LiCl (58%), CuCN·4LiCl (56−77%)].[4c] Cuprates prepared from **1a** failed to react with ethyl tiglate or with methyl cyclohexene-1-carboxylate, while cuprates prepared from **2a** gave low yields with the former (entry 19) and no conjugate adduct with the latter (entry 21). The lower order cuprate,

(12) Johnson, C. R.; Marren, T. J. *Tetrahedron Lett.* **1987**, *28*, 27.
(13) (a) Beak, P.; Lee, W. K. *Tetrahedron Lett.* **1989**, *30*, 1197. (b) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109.

Table 1. Conjugate Addition of α-Aminoalkylcuprates with α,β-Alkenyl Nitriles and Carboxylic Acid Derivatives

entry	amine[a]	substrate	copper reagent[b]	product[c]	% yield[d]
1	**1a**		A	 **4**	83
2	**1a**	X = O; R = Et	A		39[e]
3	**1a**	X = S; R = *n*-Bu	A	**5a** RX = EtO	78
4	**1a**		B	**b** RX, = *n*-BuS	72
5	**1a**	X = S; R = *t*-Bu	A	**c** RX, = *t*-BuS	62
6	**1a**		B		53-57
7	**2a**		A		94
8	**3a**		A	**6a** n = 1 **b** n = 2	60-70
9	**2a**	 X = O; R = Et	A		56-77
10	**2a**		B		32
11	**3a**			n = 1 **7a** RX = EtO	45
12	**2a**	X = S; R = *n*-Bu	A	**b** RX = *n*-BuS	94
13	**2a**		B	**c** RX = *t*-BuS	83
14	**2a**	X = S; R = *t*-Bu	A	**d** RX = 	100
15	**2a**		B	n = 2	88
16	**2a**		C	**8** RX = EtO	53
17	**2a**	X = N; R =-CO(CH2)3-	A		91
18	**1a**		A	 **9**	46
19	**2a**	 X = O; R = Et	A	 **10a** RX = EtO	30[e]
20	**2a**	X = S; R = *t*-Bu	A	**b** RX = *t*-BuS	37[e]
21	**2a**	 X = O; R = Et	A	 **11a** RX = EtO	0
22	**2a**	X = S; R = *n*-Bu	A	**b** RX = *n*-BuS	20[e]
23	**1a**	 R = H	A[f]	 **12a** R = H	100
24	**1a**	R = Me	B	**b** R = Me	38
25	**3a**	R = H	B	 **13**	54[g]
26	**2a**	R = H	A[f]		78
27	**2a**	R = H	B		60
28	**2a**	R = Me	A[f]		trace
29	**2a**	R = Me	B	**14a** R = H **b** R = Me	22

[a] The carbamate was deprotonated [*s*-BuLi, (−)-sparteine or TMEDA (1.0 equiv), −78 °C, 1 h] and added to the Cu(I) salt for cuprate formation. [b] A = 2RLi + CuCN·2LiCl. B = RLi + CuCN·2LiCl. C = RLi + CuCl·2LiCl. [c] Reaction of the organocopper reagent with the unsaturated substrate and TMSCl (5.0 equiv) in THF at −55 °C (30 min) and then at room temperature (1.5 h) gave the conjugate addition products. [d] Yields are based upon isolated purified products unless otherwise noted. [e] Yield determined by NMR using tetrachloroethane as internal standard. [f] 2.5 equiv of TMSCl was employed. [g] Trace amounts of the α-silylated nitrile were obtained.

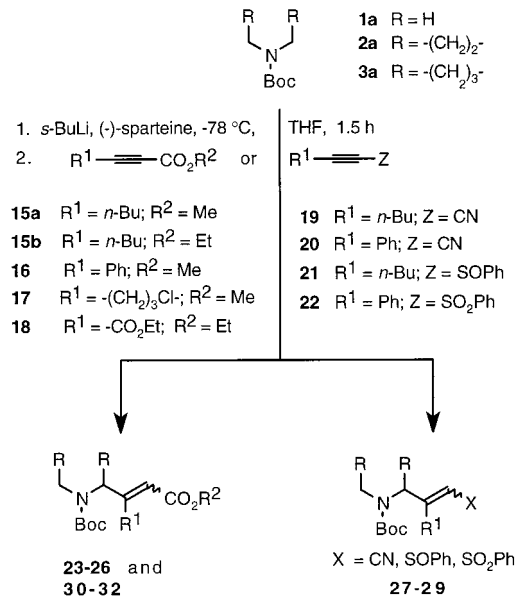
RCuCNLi prepared from **2a** gave significantly lower yields than the 2RLi + CuCN reagent (entry 10 vs 9).

In an effort to increase the yields of conjugate adducts with alkyl-substituted alkenyl esters, the corresponding thiol esters were examined. Anticipating competitive acylation[14] and conjugate addition pathways, both the *n*-butyl and *tert*-butyl thiol esters were studied. Surprisingly, both butylthio derivatives gave good to excellent yields of conjugate adducts with the cuprates derived from **1a** and **2a** with no acylation products being observed (entries 3−6, and 12−16). The thiol esters offered little advantage in the reactions with the acyclic α-alkyl-substituted substrate (entry 20 vs 19) but facilitated the reaction with the 1-cyclohexene derivative (entry 22 vs 21). In an effort to probe the greater reactivity of the thiol esters, a series of organocopper reagents were examined. The cyanocuprate reagents, RCuCNLi, gave good to excellent yields of conjugate addition products with the thiol esters (entries 4, 6, 13, and 15) and poor yields with esters (entry 10). Utilization of an alkyl copper reagent prepared from **2a** and CuCl·2LiCl gave a modest yield of product (entry 16). Although both cuprate reagents, RCuCNLi and R_2CuLi·LiX, gave comparable yields (5−12% lower for RCuCNLi) with the thiol esters, the RCuCNLi reagent is more efficient in α-aminoalkyl ligand and therefore preferred.

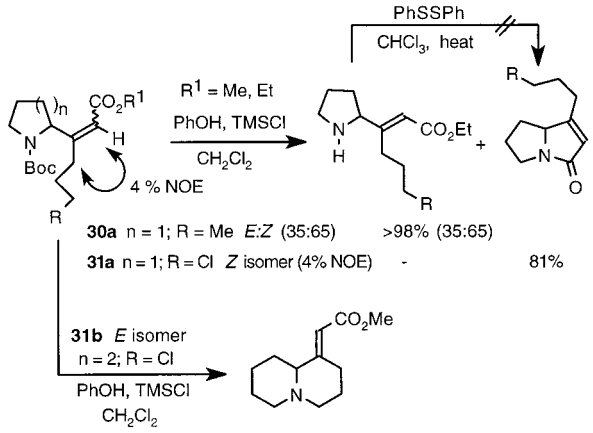
The R_2CuLi·LiCN cuprate reagents prepared from **1a** or **2a** and CuCN·2LiCl also underwent conjugate addition to an imide in excellent to modest yields (Table 1, entries 18 and 17, respectively). These cuprates also gave excellent to good yields of conjugate adducts with acrylonitrile (entries 23 and 26) but the yields diminished greatly with crotononitrile (entry 28). The RCuCNLi reagents prepared from **1a** (entry 24), **2a** (entries 27 and 29), and **3a** (entry 25) gave modest yields of conjugate adducts with either acrylonitrile or crotononitrile. In one instance, the RCuCNLi reagent gave a higher yield than the R_2CuLi·LiCN reagent (entry 28 vs 29). In these reactions, the conjugate adducts were isolated as α-silylnitriles resulting from C-silylation of the nitrile enolate anion with the exception of the piperidine (**3a**)-derived cuprate, which gave the α-silylated nitrile as the minor product (entry 25). These yields could not be improved by the use of Lewis acids such as BF_3·Et_2O or $Sc(OTf)_3$.[15]

α-Aminoalkylcuprates prepared from carbamates **1a**−**3a** gave good to excellent yields of conjugate adducts with α,β-alkynyl esters, nitriles, and a sulfoxide and trace amounts of adduct with a sulfone (Scheme 2, Table 2), the latter result being consistent with the low yields generally observed with cuprates and unsaturated sulfones.[16] In initial studies, a cuprate reagent prepared from 2 equiv of the lithio derivative of **2a** and CuCN·2LiCl gave a good yield of conjugate adduct with ynoate **15b**, while nearly quantitative yields could be achieved with RCuCNLi reagents prepared from **1a** or **2a** under similar conditions (Table 2, entries 13 vs 12, and 3 and 4). Given this generally superior performance of RCuCNLi with **15b** and its efficient use of α-aminoalkyl ligand,

Scheme 2



Scheme 3



this reagent was used to explore a range of α,β-alkynyl substrates. The reaction proved tolerant of β-aryl (entries 5, 9, and 18), β-carboalkoxy (entry 7), and β-(ω-chloroalkyl) (entries 6 and 15−17) substituents. In one experiment, deprotonation of **2a** was performed in the absence of TMEDA and conjugate addition of the resulting cuprate gave a yield comparable to that obtained with **1a** deprotonated in the presence of TMEDA (entry 18 vs 5).

The product enoate obtained from the **2a**-derived cuprate and **15b** was isolated as a 65:35 mixture of *Z*:*E* geometrical isomers, which was confirmed by amine deprotection [PhOH (30 equiv), TMSCl (10 equiv), CH_2Cl_2][17] to quantitatively afford a lactam and (*E*)-ethyl 3-(2-pyrrolidinyl)-2-heptenoate in a 65:35 ratio respectively (Scheme 3). Similarly, the configuration of *Z*-**31a** was confirmed by NOE measurements and by Boc deprotection and cyclization to the pyrrolizinone, while **31b** was cyclized to the quinolizidine (Scheme 3). The *E*:*Z* diastereomeric conjugate adducts from **3a** and **17** (*E*, δ 5.58, *Z* δ 5.69), and **1a** and **19** (*E* δ 5.08, *Z* δ 5.25) were isolated by chromatography. The *Z* diastereomers in the series (Table 2) displayed olefin absorptions downfield (δ 5.25−

(14) (a) Anderson, R. J.; Henrick, C. A.; Rosenblum, L. D. *J. Am. Chem. Soc.* **1974**, *96*, 3654. (b) Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.; Nambiar, K. P.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7131. (c) Collum, D. B.; McDonald, J. H.; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2120.

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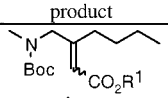
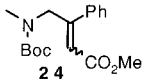
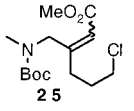
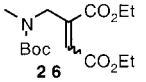
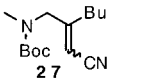
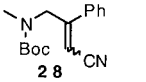
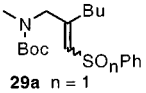
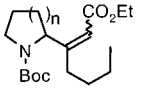
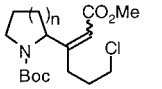
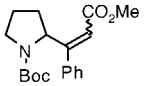
(17) Kaiser, E., Sr.; Picart, F.; Kubiak, T.; Tam, J. P.; Merrifield, R. B. *J. Org. Chem.* **1993**, *58*, 5167.

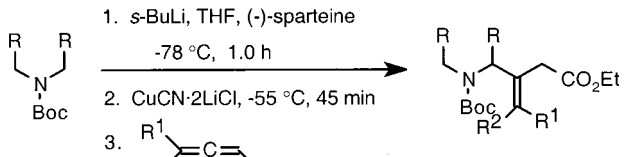
Table 2. Reaction of α-Aminoalkylcuprates with α,β-Alkynyl Esters, Nitriles, Sulfoxides, and Sulfones

entry	Boc[a] amine	n	α,β-unsat substrate	rxn cond[b]	product	% yield[c]	*E*:*Z*[d]
1	**1a**	-	**15a**	A		70	66:34
2	**1a**	-	**15a**	A		82	54:46
3	**1a**	-	**15b**	A		94	50:50[e]
4	**1a**	-	**15b**	A	**23a** R^1 = Et **23b** R^1 = Me	88	35:65
5	**1a**	-	**16**	A	 **24**	55	50:50
6	**1a**	-	**17**	A	 **25**	81	57:43
7	**1a**	-	**18**	A	 **26**	64	65:35
8	**1a**	-	**19**	A	 **27**	85	70:30
9	**1a**	-	**20**	A	 **28**	74	43:57
10	**1a**	1	**21**	A		70	47:53
11	**1a**	2	**22**	A		trace	
					29a n = 1 **b** n = 2		
12	**2a**	1	**15b**	A		95	35:65
13	**2a**	1	**15b**	B		68[f]	
14	**3a**	2	**15b**	A		74	100:0[g]
					30a n = 1 **b** n = 2		
15	**2a**	1	**17**	A		76	35:65
16	**3a**	1	**17**	B		71	79:21
17	**3a**	2	**17**	A		65	64:36
					31a n = 1 **b** n = 2		
18	**2a**		**16**	A	 **32**	60[h]	36:64

[a] The carbamates were deprotonated [*s*-BuLi, THF, TMEDA or (−)-sparteine, −78 °C, 1.25 h (3.5−4 h in Et_2O for Boc-piperidine] and reacted with a Cu(I) salt to form the cuprate reagent. [b] A = RLi + CuCN·2LiCl. B = 2 RLi + CuCN·2LiCl. The alkynoates and TMSCl [neat, 2.5 equiv for B and 5.0 equiv for A] were added to the α-aminoalkylcuprate at −55 to −60 °C and slowly warmed to room temperature. Reactions were run in THF or THF/Et_2O (Boc-piperidine). [c] Based upon products purified and isolated by chromatography unless otherwise noted. [d] The *E*:*Z* ratios were determined from ^{1}H NMR integration ratios of the olefinic proton absorptions. [e] The reaction was run in the presence of *t*-BuOH (1.0 equiv). [f] Yield determined by NMR using tetrachloroethane as internal standard. [g] A single diastereomer was obtained and assigned the *E* configuration on the basis of the olefinic proton absorption. [h] Deprotonation was achieved without addition of TMEDA.

6.76) relative to those of the *E* diastereomers (δ 5.08−6.66).[18] In those instances when both geometric isomers gave nearly identical chemical shifts for the olefinic protons, the assignment of stereochemistry was made from the amino-substituted methylene chemical shifts,

Table 3. Reaction of α-Aminoalkylcuprates with α-Allenyl Esters, RCH=C=CHCO$_2$Et



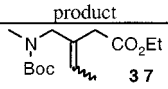
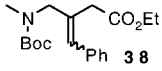
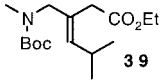
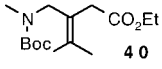
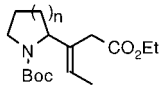
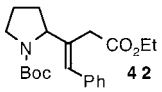
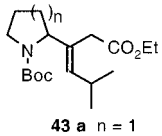
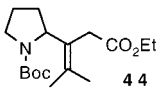
eq. 2

33 R^1 = Me; R^2 = H

34 R^1 = Ph; R^2 = H

35 R^1 = *i*-Pr; R^2 = H

36 R^1 = R^2 = Me

entry	Boc amine	ester	method[a]	product	% yield[b]	*E*:*Z*[c]
1	**1a**	**33**	A		82	91:9
2	**1a**	**33**	B	**37**	74	86:14
3	**1a**	**34**	A	 **38**	48	
4	**1a**	**35**	A	 **39**	65	
5	**1a**	**36**	A	 **40**	42	
6	**2a**	**33**	A		85	
7	**3a**	**33**	A		87	
8	**3a**	**33**	B		81	
				41 a n = 1 **b** n = 2		
9	**2a**	**34**	A	 **42**	45	
10	**2a**	**35**	A		77	
11	**3a**	**35**	B		59	
				43 a n = 1 **b** n = 2		
12	**2a**	**36**	A	 **44**	80	

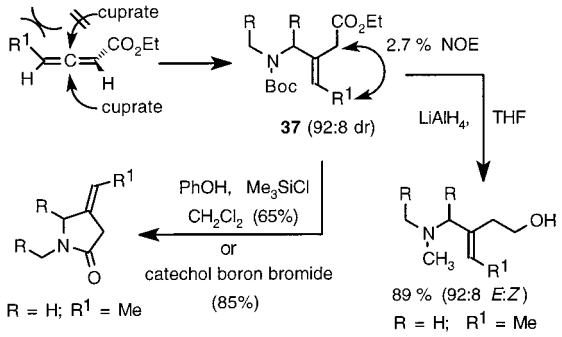
[a] A = Carbamate deprotonation (*s*-BuLi, sparteine or TMEDA, THF, −78 °C) followed by sequential addition of 0.5 equiv of CuCN·2LiCl (−55 °C, 45 min) and allenyl ester [TMSCl (2.5 equiv), −55 °C to rt]. B = Same conditions as in A, except 1.0 equiv CuCN·2LiCl per RLi was employed [TMSCl (5.0 equiv)]. [b] Isolated yields based upon products purified by chromatography. [c] Diastereomeric ratio determined by ^{1}H NMR analysis; >95:5 unless noted.

which displayed dramatic differences. The methylene group *syn* to the carbonyl absorbed significantly further downfield.[18b] Quenching of the reaction at −78 °C with methanol or running the reaction in the presence of 1.0 equiv of *tert*-BuOH did not provide any better stereocontrol in the protonation of the vinyl cuprate.[19] Ratios of *E*:*Z* diastereomers varied as a function of temperature, concentration, and solvent mixtures. Only the piperidine (**3a**)-derived cuprate gave a single geometrical isomer (Table 2, entry 14). In contrast to the γ-amino-α,β-enones, PhOH/TMSCl did not effect isomerization and subse-

(18) (a) Dieter, R. K.; Silks, L. A., III; Fishpaugh, J. R.; Kastner, M. E. *J. Am. Chem. Soc.* **1985**, *107*, 4679. (b) Piers, E.; Chong, J. M.; Morton, H. E. *Tetrahedron* **1989**, *45*, 363. (c) Dieter, R. K.; Yu, H. *Org. Lett.* **2000**, *2*, 2283.

(19) (a) Klein, J.; Levene, R. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1971. (b) Piers, E.; Wong, T.; Ellis, K. A. *Can. J. Chem.* **1992**, *70*, 2058.

Scheme 4



quent cyclization[18c] of the *E* diastereomer and experimental conditions for the conversion of the *E* isomer to the lactam derivatives were not found.[20]

α-Aminoalkylcuprates also reacted with allenyl esters to give conjugate adducts in good overall yields (eq 2, Table 3). Although slightly lower yields were obtained with RCuCNLi than with the reagent prepared from 2RLi + CuCN·2LiCl (entries 1 and 7 vs 2 and 8, respectively) the former reagent is more efficient in the α-aminoalkyl ligand. Modest yields of conjugate adducts were obtained with allenyl esters containing a γ-phenyl substituent (entries 3 and 9) or a γ,γ-disubstitution pattern (entry 5), although the increased reactivity of the pyrrolidinylcuprate derived from **2a** gave good yields with a γ,γ-disubstitution pattern (entry 12).

The conjugate addition reactions to the allenyl esters proceeded stereoselectively to afford the *E* olefins. The stereoselectivity of these additions was confirmed by NOE experiments on **37** and by reduction of **37** to the homo allylic alcohol, which permitted analysis of the *E*:*Z* diastereomer ratio that was obscured in the NMR spectra of **37** by the presence of rotomers arising from hindered rotation about the carbamate N−C bond (Scheme 4). Treatment of these allylic carbamates with PhOH/TMSCl or catechol boron bromide effected carbamate deprotection and cyclization to 4-alkylidine pyrrolidinones and pyrrolizidinones with regio- and stereocontrol of the olefin position and geometry (Scheme 4).[21]

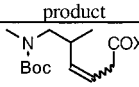
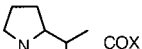
The addition of α-aminoalkylcuprates to ethyl or *n*-propylthiol sorbate was examined to explore the competition between 1,4- and 1,6-additions for these cuprate reagents.[22] Like cuprate reagents in general, the α-aminoalkylcuprate preferred to add in a 1,6-fashion and this pattern was not altered for the thiol esters (Table 4). The resultant nonconjugated alkenyl esters were obtained as a mixture of *E* and *Z* diastereomers. Attempted addition of the cuprate derived from **1** to a benzothiazole derivative gave little conjugate addition.[23] Upon quenching with either methanol or NH_4Cl a yellow precipitate was obtained, suggesting decomposition of the benzothioazole derivative.

Discussion

The copper(I) salt often plays a significant role in the chemistry of the resultant organocopper or cuprate reagent. Salts such as CuCN and CuBr·SMe_2 have been promoted as particularly effective reagent precursors.[24] Cuprate reagents prepared from CuCN and either 1 or 2 equiv of an alkyllithium reagent (i.e., RCuCNLi or R_2CuLi·LiCN) often display superior attributes with regard to chemical yields, suggesting an important role of the cyanide anion in the composition, reactivity, or stability of the cuprate complex. A higher order cuprate (i.e., $R_2CuCNLi_2$) was invoked to explain the superior qualities of the latter reagent and the structure of this reagent prepared from 2RLi + CuCN has been the subject of considerable interest centering around the location of the cyanide ion.[26] Nevertheless, in organocopper (i.e., RCu/TMSI) conjugate additions to lactones and enoates, CuI affords yields comparable to or better than CuCN-derived cuprate reagents.[11f] Similarly, in the CuI/TMSI-promoted 1,4-additions of copper acetylides to α,β-enones and enals (68−89% yields), replacement of CuI with CuBr, CuCN, or CuOTf results in greatly diminished yields (1−25%).[25] Although THF soluble CuCN·2LiCl has been extensively used by Knochel in the copper-promoted reactions of organozinc reagents,[2] this source of Cu(I) has not been widely used in the generation of cuprates from alkyllithium or Grignard reagents.[27] In initial studies, the conjugate addition reactions of α-aminoalkylcuprates to α,β-enoates failed when solid CuCN was employed. We subsequently discovered that use of THF-soluble CuCN·2LiCl resulted in the first successful examples of this reaction reliably forming the 1,4-addition products in modest to excellent yields.

The success of these conjugate addition reactions required the activating influence of TMSCl[28] and initially appeared to also require the use of LiCl-solubilized CuCN

Table 4. Conjugate Addition of α-Aminoalkylcuprates with α,β−γ,δ-Dienoates

entry	Boc[a] amine	dienoate X	rxn cond[b]	product	% yield[c] (dr)[d]
1	**1a**	Et	A	 **45a** X = OEt **45b** X = *n*-PrS	67 (25:75)
2	**1a**	*n*-PrS	B		54 (20:80)
3	**1a**	*n*-PrS	C		52 (25:75)
4	**2a**	Et	A	 **46a** X = OEt **46b** X = *n*-PrS	trace
5	**2a**	*n*-PrS	B		56 (40:60)

[a] The carbamates were deprotonated [*s*-BuLi, THF, TMEDA (entries 2, 3, 5) or (−)-sparteine (entries 1, 4), −78 °C, 1.25 h] and reacted with a Cu(I) salt to form the cuprate reagent. [b] A = 2RLi + CuCN·2LiCl. B = RLi + CuCN·2LiCl. C = RLi + CuCl·2LiCl. The dienoates and TMSCl [neat, 5.0 equiv] were added to the α-aminoalkylcuprate at −55 to −60 °C, and slowly warmed to room temperature. Reactions were run in THF. [c] Based upon products purified and isolated by chromatography unless otherwise noted. [d] The diastereomeric ratios (dr) were determined from GC−mass selector spectrometry via ion currents. Assignment of *E* and *Z* isomers could not be established from ^{1}H NMR spectroscopy.

(20) Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T. *Synthesis* **1990**, 1123.

(21) For a preliminary account of this work see: Dieter, R. K.; Lu, K. *Tetrahderon Lett.* **1999**, *40*, 4011.

(22) For a review see: Krause, N.; Gerold, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 187.

(23) For use of benzothiazole-2-thiol derivatives for control of allylic substitution see: (a) Caló, V.; Fiandanese, V.; Nacci, A.; Scilimati, A. *Tetrahedron* **1994**, *50*, 7283. (b) Dieter, R. K.; Velu, S. E.; Nice, L. E. *Synlett* **1997**, 1114.

(24) Bertz, S. H.; Gibson, C. P.; Dabbagh, G. *Tetrahedron Lett.* **1987** *28*, 4251.

(25) Eriksson, M.; Iliefski, T.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1997**, *62*, 182.

(26) (a) Bertz, S. H.; Miao, G.; Eriksson, M. *J. Chem. Soc., Chem. Commun.* **1996**, 815. (b) Snyder, J. P.; Bertz, S. H. *J. Org. Chem.* **1995**, *60*, 4312. (c) Barnhart, T. M.; Huang, H.; Penner-Hahn, J. E. *J. Org. Chem.* **1995**, *60*, 4310. (d) Lipshutz, B. H.; James, B. *J. Org. Chem.* **1994**, *59*, 7585. (e) Krause, N. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 79.

(27) Backvall, J.-E.; Persson, E. S. M.; Bombrun, A. *J. Org. Chem.* **1994**, *59*, 4126. (b) Schlosser, M.; Bossert, H. *Tetrahedron* **1991**, *47*, 6287.

for the preparation of the cuprate reagents. Recently, a cuprate thermal stability study indicated that good yields of enoate conjugate adducts can also be obtained with the use of solid CuCN.[29a] The yields ranged from 59% (cuprate formation at −50 °C) to >98% (cuprate formation at 0 °C) for both the R_2CuLi and RCuCNLi (R = *N*-Boc pyrrolidinyl, ester = methyl crotonate) reagents and were dependent upon the temperature at which the cuprate was allowed to form. The reliable use of THF-soluble CuCN·2LiCl, initial failure of solid CuCN, and successful use of solid CuCN with a strict temperature protocol in these enoate conjugate addition reactions arises from a complex interplay of several competing reactions. From our own observations[4,29] and indications in the literature,[30] the lithio carbamates are more thermally unstable than the corresponding cuprate reagents. Significant decomposition of the *N*-Boc α-lithiopyrrolidine occurs at −50 °C.[29c] The interplay between the rate of lithio carbamate decomposition and cuprate formation will have a direct bearing on the observed yield of conjugate adducts. The apparent rise in yields for the conjugate addition reactions of α-aminoalkylcuprates prepared from CuCN·2LiCl with carboxylic acid derivatives appears to reflect a subtle balance between the temperature of cuprate formation and the rate of α-lithio carbamate decomposition. The use of CuCN·2LiCl permits the formation of the cuprate reagent at −78 °C, while the use of solid CuCN requires warming of the solution for complete cuprate formation subjecting the reaction mixture to all the vagaries of temperature fluctuation. This would account for the variation in chemical yields from experiment to experiment. The successful use of insoluble CuCN for cuprate preparation suggests that the excess LiCl is not playing a significant role as an external source of lithium ions accelerating the conjugate addition reaction by Lewis acid complexation with the carbonyl oxygen.[28,31] This is consistent with the report that cuprate reactivity is greater in conjugate addition reactions in the absence of LiX.[31c]

We have also observed in our studies with α,*β*-enones that use of freshly distilled TMEDA gives generally higher yields of the conjugate adducts than reactions using distilled TMEDA that has been stored for some time. These variations were significantly less dramatic with the use of (−)-sparteine or when TMEDA was used in conjunction with CuCN·2LiCl.[4c] Although the addition of TMEDA to cuprate solutions prepared from α-aminoalkylstannanes reduced the yields of conjugate adducts with α,*β*-enones,[4c] this diamine effect is irreproducible in experiments using CuCN and CuCN·2LiCl and we offer the observation as a cautionary note.

We have no rate data on the conjugate addition of α-aminoalkylcuprates with a variety of α,*β*-unsaturated carbonyl compounds, and the complexity of the influence of additives and reaction conditions makes it difficult to estimate the intrinsic reactivity of these reagents. A mixed homocuprate, RCuMeLi [R = *N*-Boc-*N*-methyl-(aminomethyl)], derived from **1a** transfers the α-aminoalkyl and methyl ligands in comparable yields.[4c,32] Additionally, the higher yields of conjugate adducts obtained with the *N*-Boc pyrrolidinylcuprates [vs *N*-Boc-*N*-methyl-(aminomethyl)cuprates] suggests that the α-aminoalkyl ligand is comparable in reactivity to the corresponding alkyl ligands. Nevertheless, our experience and the failure of these cuprates to transfer the α-aminoalkyl ligand to lactones, indicates a somewhat lower reactivity with certain substrates than the simple dialkylcuprates. It is possible that the carbamate moiety can play the same role as the *ortho*-substituted *β*-aryl enoates containing three oxygen atoms in the side chain which retard the rate of reaction with lithium dialkylcuprates.[33] Either steric hindrance or coordination of the lithium ion to the carbamate moiety of the α-aminoalkylcuprate could account for the diminished reactivity observed with less reactive substrates such as lactones.

In an effort to circumvent the deleterious effects of α-alkyl substitution, the corresponding thiol ester functionality was examined with the expectation that the lower LUMO energies of these substrates might enhance their reactivity with cuprate reagents.[34] Although the increased yields obtained with the thiol ester derivatives could arise from coordination of the cuprate and copper reagents to the sulfur atom thereby facilitating the conjugate addition reactions, it is more likely that electronic factors inherent in the thiol ester functionality are involved. The carbonyl group in thiol esters is more "ketone-like" and hence more reactive with cuprate reagents.[18b,35] Calculated resonance energies for thiol esters are significantly smaller than those for esters (i.e., 5.5 vs 13.5 kcal/mol, respectively), although the carbonyl oxygen is slightly more negatively charged (e.g., −0.250 vs −0.231, respectively).[35a] In addition, the lower electronegativity of S vs O should give rise to a weaker C=O bond in thiol esters than in esters.[35b] These yields involving esters, thiol esters, and imides are intriguing, since the imides have particularly high LUMO energies in comparison to the esters or thiol esters.[34] These results are suggestive of the crucial role that lithium cation coordination to the unsaturated carbonyl moiety plays in these conjugate addition reactions. The increased reactivity of the thiol esters is also consistent with this interpretation (i.e., greater negative charge on the carbonyl oxygen), although the thiol esters are also more akin to a ketonic carbonyl than an ester carbonyl.[35] This

(28) For discussions on the role of TMSCl in accelerating cuprate conjugate addition reactions see: (a) Frantz, D. E.; Singleton, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 3288 and references therein. (b) Bertz, S. H.; Miao, G.; Rossiter, B. E.; Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11023.

(29) (a) Dieter, R. K.; Topping, C., unpublished results. (b) Dieter, R. K.; Li, S. *J. Org. Chem.* **1997**, *62*, 7726. (c) Chlorotrimethylsilane quenching of *N*-Boc α-lithiopyrrolidine after aging at a given temperature for 30 min gave *N*-Boc 2-trimethylsilylpyrrolidine [−78 °C (94%), −50 °C (71%), 0 °C (1−2%)]. Li, S. M.S. Thesis, Clemson University, Clemson, SC, 1996.

(30) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.

(31) For the importance of lithium ion carbonyl oxygen coordination in cuprate conjugate addition reactions see: (a) Ouannes, C.; Dressaire, G.; Langlois, Y. *Tetrahedron Lett.* **1977**, 815. (b) House, H. O.; Wilkins, J. M. *J. Org. Chem.* **1978**, *43*, 2443. (c) Krauss, S. R.; Smith, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 141. (d) Vellekoop, A. S.; Smith, R. A. J. *J. Am. Chem. Soc.* **1994**, *116*, 2902. For a review see: (e) Smith, R. A. J.; Vellekoop, A. S. *Advances in Detailed Reaction Mechanisms*; Coxon, J. M., Ed.; JAI Press: Grenwich, CT, 1994; Vol. 3, p 79.

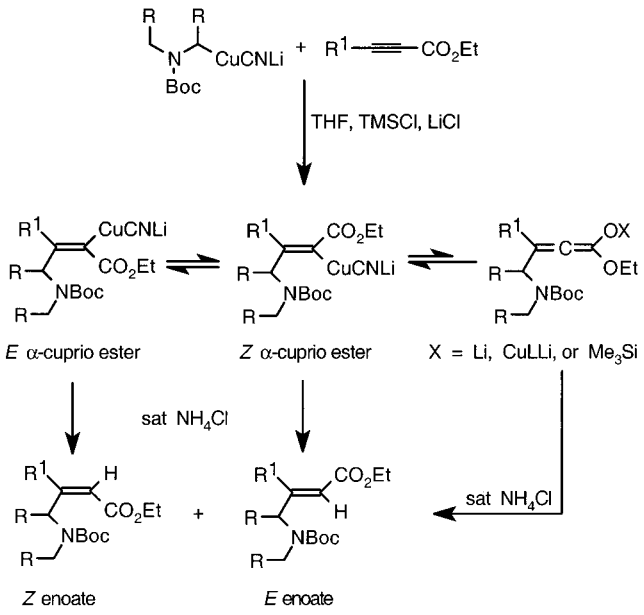
(32) Dieter, R. K.; Dieter, J. W.; Alexander, C. W.; Bhinderwala, N. S. *J. Am. Chem. Soc.* **1996**, *61*, 2930.

(33) Hallnemo, G.; Ullenius, C. *Tetrahedron Lett.* **1986**, *27*, 395.

(34) AM1 calculations obtained from the MacSpartan program (Wavefunction, Inc., 18401 Von Karman Ave., #370, Irvine, CA 92715) gave the following relative ordering of LUMO energies: thiol esters < esters < imides. The calculated magnitude of the LUMO energies displayed no clear correlation with the observed chemical yields.

(35) (a) Janssen, M. J. In *The Chemistry of Carboxylic Acids and Esters*; Patai, S., Ed.; Wiley: Hungary, 1969; Chapter 15, p 705. (b) For C=O bond strengths in RCOX as a function of the electronegativity of X see: Wiberg, K. B. *J. Chem. Educ.* **1996**, *73*, 1089 and references therein.

Scheme 5



would not explain the diminished reactivity of the α,*β*-unsaturated nitriles which give poor yields when carrying a *β*-alkyl substituent. Silylation of the nitrile enolate on carbon reflects the relative weakness of the N−Si bond strength in comparison to the O−Si bond strength. The absence of a silylated product in the piperidine reaction (Table 1, entry 25) may reflect steric hindrance to C-silylation and hydrolysis of the resultant *N*-silyl ketenimine during the workup procedure.

The α,*β*-ynoates gave slightly higher yields of conjugate adducts with the RCuCNLi reagent than with the R_2CuLi·LiCN reagent, in contrast to the α-alkoxyalkylcuprates.[36] Currently, these additions are viewed as involving a carbocupration reaction affording an α-cuprio ester in equilibrium with an allenyl enolate (Scheme 5).[37] It is this temperature and lithium salt (i.e., LiX) dependent isomerization that accounts for the *E*:*Z* mixture of diastereomers obtained in the reactions of cuprates with α,*β*-ynoates. The initial *syn* carbocupration affords the *Z* α-cuprio ester and quenching of this intermediate at low temperature stereoselectively affords the *E* diastereomer in the reactions of simple lithium dialkylcuprates with ynoates.[37] Upon warming, the *Z* α-cuprio ester isomerizes to the *E* α-cuprio ester via an intermediate allenyl enolate. Protonation of the *E* α-cuprio ester stereoselectively affords the *Z* enoate diastereomer and the ratio of *E*:*Z* diastereomers reflects the equilibrium *E*:*Z* mixture of alkenyl cuprate intermediates (i.e., α-cuprio esters). Trapping of these alkenylcuprates with trimethylsilylchoride affords ketene acetals arising from O-silylation of the allenolate. Formation of this product reflects the HSAB principle[37c] or the outcome of a charge controlled reaction[38] rather than the equilibrium mixture of alkenylcuprates and allenolate intermediates in solution. Simple lithium dialkylcuprates add stereoselectively *syn* to alkynoates in THF and the cyano cuprates, RCuCNLi, also display a greater degree of *syn* selectivity than the corresponding Gilman reagents.[37] Although the RCuCNLi (R = α-aminoalkyl ligand) reagent was used in THF, the reaction conditions employed for the conjugate addition of these reagents to alkynyl esters used excess lithium chloride (i.e., from CuCN·2LiCl) which should favor isomerization of the initially formed *Z* alkenylcuprate (i.e., *syn* addition) while use of TMSCl should lead to formation of the *O*-silyl ketene acetal. Protonation of the latter intermediate upon quenching will occur in a nonstereoselective manner affording a mixture of *E* and *Z* olefinic diastereomers.[37]

The allenyl esters gave better yields with the R_2CuLi·LiCN reagent than with the RCuCNLi, although the differences were small. While good yields of conjugate adducts are obtained with allenyl esters containing a single *γ*-substituent, the yields diminished for a *γ*,*γ*-disubstituted derivative **36** with the cuprate derived from **1a** but remained high for the cuprate derived from the pyrrolidinyl cuprate **2a**. These results reflect a sensitivity to steric factors in these conjugate addition reactions as well as the importance of cuprate reactivity. This steric effect is also seen in the diastereoselectivity of the reaction. Preferential approach of the cuprate reagent away from the *γ*-substituent affords the *E* diastereomer with a selectivity generally greater than 90:10 (Scheme 4). The origin of the modest yields obtained with allenyl ester **34** containing a single *γ*-phenyl substituent is unclear, since steric effects should not play a significant role if the cuprates approach from the side opposite the phenyl substituent and electronically the phenyl ring is not in conjugation with the double bond undergoing attack by the cuprate reagent.

A brief examination of α,*β*−*γ*,*δ*-dienoates reveal that these substrates afford products arising from 1,6-conjugate addition. This reflects the inherent tendency of carbonyl conjugated diene systems.[39] Initial cuprate attack occurs at the C2−C3 double bond to afford a *β*C−Cu adduct, which can either undergo reductive elimination to give the 1,4-addition product or allylic rearrangement and subsequent reductive elimination to give the 1,6-addition product. For most α,*β*−*γ*,*δ*-dienones and dienoates allylic rearrangement is faster than reductive elimination and the 1,6-addition product predominates. This is consistent with the emerging view that the reductive elimination step in conjugate addition reactions is the rate determining step.[40] Efforts to direct the reaction toward 1,4-conjugate addition by use of a thiol ester which could potentially retard allylic rearrangement via intramolecular chelation proved unsuccessful.

Summary

In summary, reaction conditions have been developed for the conjugate addition of α-nitrogen heteroatom functionalized cuprate reagents with the less reactive carboxylic acid derivatives. The conjugate addition reactions of α-aminoalkylcuprates to α,*β*-unsaturated carboxylic acid derivatives proceeds uneventfully when CuCN·2LiCl is used, although higher yields might be

(36) For a comparison of α-alkoxyalkylcopper and cuprate reagents in conjugate additions to ethyl propiolate see: Linderman, R. J.; Griedel, B. D. *J. Org. Chem.* **1991**, *56*, 5491.

(37) (a) Nilsson, K.; Ullenius, C.; Krause, N. *J. Am. Chem. Soc.* **1996**, *118*, 4194. (b) Nilsson, K.; Andersson, T.; Ullenius, C. *J. Organomet. Chem.* **1997**, 591. (c) Nilsson, K.; Andersson, T.; Ullenius, C.; Gerold, A.; Krause, N. *Chem. Eur. J.* **1998**, *4*, 2051. (d) Nakamura, E.; Mori, S.; Nakamura, M.; Morokuma, K. *J. Am. Chem. Soc.* **1997**, *119*, 4887.

(38) Fleming, I. *Frontier Orbitals and Organic Reactions*; John Wiley & Sons: England, 1976; pp 27−32 and 43−47.

(39) Uerdingen, M.; Krause, N. *Tetrahedron* **2000**, *56*, 2799.

(40) (a) Frantz, D.; Singleton, D. A.; Snyder, J. P. *J. Am. Chem. Soc.* **1997**, *119*, 3383. (b) Nakamura, E.; Mori, S.; Morokuma, K. *J. Am. Chem. Soc.* **1997**, *119*, 4900.

achieved with solid CuCN under more stringently controlled reaction conditions. Yields of conjugate adducts from α-aminoalkylcuprates and conjugated alkenes can be improved by utilization of unsaturated thiol esters. These α-aminoalkylcuprates also undergo conjugate additions to α,*β*-alkynyl and allenyl derivatives, with the latter reaction being highly stereoselective. The alkynyl substrates may actually involve a carbocupration rather than a conjugate addition reaction. Although the current reaction conditions do not afford high stereoselectivities with the α,*β*-alkynyl substrates, the evidence for a carbocupration pathway encourages a continued search for more effective cuprate reagents and reaction conditions for stereocontrol of the addition event and subsequent protonation. The method currently fails with lactones and is limited to derivatives lacking an α-alkyl substituent. These conjugate addition reactions of α-aminoalkylcuprates provide flexible routes for the preparation of various *N*-heterocycles and these applications are currently under investigation.

Experimental Section

Materials. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and chlorotrimethylsilane were distilled from CaH_2 under a N_2 atmosphere. BF_3·Et_2O was purified by distillation. (−)-Sparteine was distilled via Kugelrohr distillation at 150 °C, 0.05 mmHg. CuCN, and CuCl were used without further purification. *s*-BuLi (1.5 M in pentane) was purchased from FMC Corp. and titrated using *s*-BuOH and 1,10-phenanthroline monohydrate in THF.

The α,*β*-unsaturated esters were either commerically available or readily prepared via esterification of the commercially available carboxylic acids. Acrylonitrile and crotononitrile were commercially available. Alkynyl nitriles[41] **19** and **20** and allenyl esters[42] **33**−**36** were prepared by established literature procedures. Ethyl sorbate and sorbic acid were commerically available and the thiol ester was prepared from the acid chloride as described below. The alkynyl sufoxide **21** and sulfone **22** were prepared by oxone oxidation[43] of the corresponding sulfide, which in turn was prepared by quenching the lithium acetylide with diphenyl disulfide as described below.

All round-bottom flasks used for the preparation of the organocopper and cuprate reagents were first cleaned with 48% hydrobromic acid, followed by placement into a potassium hydroxide/isopropyl alcohol bath, rinsed with 10% hydrochloric acid and copious amounts of water, followed by rinsing with acetone, and then oven dried (100 °C). All glassware was flamed-dried under house vacuum pressure, purged with argon, and then cooled under a dry nitrogen atmosphere. The LiCl was first dried under high vacuum (0.005 mmHg) with heat (100−110 °C) and stirring for 3 h. Then after it was weighed into a flame-dried flask, it was flamed-dried under vacuum (0.05 mmHg), purged with argon, and then cooled under a dry nitrogen atmosphere.

All copper reactions were conducted under a positive, dry nitrogen atmosphere in anhydrous solvents in flasks fitted with rubber septa. The nitrogen gas was passed through concentrated sulfuric acid, potassium hydroxide, and indicating and nonindicating drierite before being introduced into the reaction flask. Low-temperature baths (−78 °C or warmer) were prepared using shallow thermoflasks with a Neslab CC-60 II cyrocool machine or dry ice/2-propanol slush bath mixtures. 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.

Preparation of α,*β*-Ynoates 15−17. *n*-BuLi in hexane (1.6 N, 6.5 mL) was added dropwise via syringe to a solution of the 1-alkyne (10 mmol) in 30 mL of Et_2O at −30 °C. The reaction mixture was stirred at −30 °C for 30 min, whereupon a solution of methyl chloroformate (10 mmol) in 5 mL of ether was added dropwise via syringe. As the addition proceeded a white solid was formed. The reaction mixture was stirred at −30 °C for 20 min, warmed to room temperature, filtered, and concentrated in vacuo to afford crude alkynyl ester. Kugelrohr distillation gave the pure alkynyl esters in 79−97% yield.

Preparation of α,*β*-Alkynyl Sulfoxide 21 and Sulfone 22. *n*-BuLi in cyclohexane (1.6 N, 5.0 mL, 0.8 equiv) was added dropwise via syringe to a solution of the 1-alkyne (10 mmol) in 25 mL of Et_2O at −30 °C. The reaction mixture was stirred at −30 °C for 30 min, whereupon a solution of diphenyl disulfide (10 mmol) in 5 mL of THF was added dropwise via syringe. The reaction mixture was stirred at −30 °C for 30 min and then warmed to room temperature. The organic phase was washed with water (3 × 5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford crude alkynyl sulfide (95−100%), which was used without further purification.

The crude alkynyl sulfide was oxidized to the sulfoxide **21** or sulfone **22** according to an established procedure.[43]

Preparation of *S*-Propyl 2,4-hexadienoate. Thionyl chloride (10 mL) was added dropwise to sorbic acid (10 g) in 50 mL of ether at room temperature whereupon the mixture was stirred for 5 min and then heated to reflux for 60 min. Concentration in vacuo and Kugelrohr distillation gave the acid chloride (10.5 g, 90%).

Propanethiol (2.0 mmol) was added dropwise via syringe to a suspension of NaH (3.0 mmol) in ether (10 mL) cooled to 0 °C and stirred at this temperature for 20 min. A solution of 2,4-hexadienoyl chloride (2 mmol in 5 mL of Et_2O) was added dropwise via syringe and the reaction mixture was then allowed to warm to room temperature over a 1 h period. The solution was quenched and washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo to afford pure thiol ester upon Kugelrohr distillation (0.28 g, 82%).

General Procedure A for Cuprates Prepared from 2RLi + CuCN·2LiCl. A solution of *N*-Boc protected amine (1 mmol) and (−)-sparteine (1 mmol) in THF (4 mL) under an Ar or N_2 atmosphere was cooled to −78 °C. *s*-BuLi (in cyclohexane, 1 mmol) was added and this mixture was stirred at −78 °C for 1 h. A solution of the complex, CuCN·2LiCl, in THF (prepared by dissolving 0.5 mmol of CuCN and 1 mmol of LiCl in 3 mL THF) was added via syringe to the 2-lithio-*N*-Boc carbamate and the solution was warmed from −78 to −55 °C over a period of 45 min to generate the cuprate reagent. A solution of the electrophile (0.5 mmol) and TMSCl (2.5 mmol) in THF (1 mL) was added to the cuprate reagent and the reaction mixture was stirred at −55 °C for 0.5 h and at room temperature for 1.5 h. The reaction mixture was quenched with saturated NH_4Cl (5 mL), filtered through Celite, extracted with ether (3 × 10 mL), and washed with saturated NH_4Cl (2 × 10 mL) and brine (10 mL). The extract was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the crude product, which was purified by radial chromatography [silica gel, ether/petroleum ether, 10:90 to 50:50, v/v] to afford the pure product.

General Procedure B for Cuprates Prepared from RLi + CuCN·2LiCl. The procedure was identical to that described in General Procedure A, except that 1 equiv of RLi was used per equiv of CuCN·2LiCl.

General Procedure C for Cuprates Prepared from RLi + CuCl·2LiCl (Alkyl Copper). The procedure was identical to that describe in General Procedure A, except that CuCl·2LiCl was used in place of CuCN·2LiCl. The CuCl·2LiCl solution in THF was prepared and transferred in the same manner as CuCN·2LiCl.

Methyl 1-[(1,1-Dimethylethoxy)carbonyl]-2-piperidinepropanoate (6b). General Procedure B was employed (1 mmol). Purification by flash colunm chromatography gave **6b** as a colorless oil (192 mg, 71%): IR (neat) 1742 (s), 1695 (s) cm^{-1}; ^1H NMR δ 1.42 (s, 9H), 1.20−1.75 (m, 7H), 1.95−2.20

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(42) Lang, R. W.; Hansen, H.-J *Org. Synth.* **1984**, *62*, 202.
(43) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.

(m, 1H), 2.20−2.35 (m, 2H), 2.72 (app. t, J = 12.9 Hz, 1H), 3.64 (s, 3H), 3.85−4.05 (br m, 1H), 4.15−4.35 (br s, 1H); ^{13}C NMR δ 19.0, 25.0, 25.5, 28.4, 28.8, 30.9, 38.6, 49.9, 51.5, 79.2, 155.0, 173.9; MS *m*/*z* (relative intensity) EI 271 (M^+, 02), 215 ($M^+ - C_4H_8$, 06), 198 ($M^+ - C_4H_8 - OH$, 07), 184 ($M^+ - CH_2CH_2CO_2Me$, 07), 170 ($M^+ - C_4H_9CO_2$, 28), 128 ($M^+ - C_4H_8 - CH_2CH_2CO_2Me$, 100), 57 ($C_4H_9$, 45). Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.40; N, 5.16. Found: C, 61.92; H, 9.40; N, 5.23.

***S*-Butyl 1-[(1,1-Dimethylethoxy)carbonyl]-*β*-methyl-2-pyrrolidinepropanethiolate (7b).** ^{1}H NMR ($CDCl_3$) δ 0.75−0.89 (m, 6H), 1.16−1.34 (m, 2H), 1.40 (s, 9H), 1.43−1.52, (m, 2H), 1.52−1.88 (m, 4H), 2.00−2.26 (m, 1H), 2.26−2.42 (m, 1H), 2.42−2.67 (m, 1H), 2.78 (t, 2H, J = 7.1 Hz), 3.04−3.22 (m, 1H), 3.21−3.56 (m, 1H), 3.56−3.74 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.3, 16.2, 21.7, 23.4, 27.0, 28.3, 29.5, 31.4, 33.7 (33.9), 46.5 (47.0), 48.3, 61.1, 79.2, 154.8, 198.6. Anal. Calcd for $C_{17}H_{31}NO_3S$: C, 62.0; H, 9.5; N, 4.3. Found: C, 61.89; H, 9.48; N, 4.22.

Methyl 1-[(1,1-Dimethylethoxy)carbonyl]-*β*-methyl-2-piperidinepropanoate (8). Employing General Procedure A, **8** was obtained as a 68:32 mixture of diastereomers (45%): IR (neat) 1742 (s), 1692 (s) cm^{-1}; ^{1}H NMR δ 0.94 [0.86] (d, J = 6.6 Hz, 3H), 1.43 (s, 9H), 1.20−1.80 (m, 6H), 1.90−2.15 (m, 1H), 2.30−2.55 (m, 2H), 2.55−2.80 (m, 1H), 3.64 [3.67] (s, 3H), 3.70−4.10 (br m, 2H) [minor diastereomer]; ^{13}C NMR δ 16.5, 17.5, 18.9 (19.1), 25.4, 25.9, 28.4, 28.8, 38.4, 39.1, 51.4, 79.3, 155.0, (173.0) 174.5 (minor diastereomer); MS *m*/*z* (relative intensity) EI 285 (M^+, 01), 229 ($M^+ - C_4H_9$, 01), 184 ($M^+ - C_4H_9 - CO_2$, 16), 128 ($M^+ - CHMeCH_2CO_2Me$, 08), 57 (C_4H_9, 29).

4-[[(1,1-Dimethylethoxy)carbonyl]methylamino]-3-methyl-2-(trimethylsilyl)butanenitrile (12b). General Procedure B was employed (1 mmol). Purification by chromatography gave **12b** as a colorless oil (108 mg, 38%) present as a 85:15 mixture of diastereomers: IR (neat) 2225 (m), 1702 (s) cm^{-1}; ^{1}H NMR δ 0.19 [0.23] (s, 9H), 1.01 [1.03] (d, J = 6.9 Hz, 3H), 1.44 (s, 9H), 1.85−1.95 (br s, 1H), 1.95−2.25 (m, 1H), 2.86 [2.85] (s, 3H), 2.95−3.15 (br s, 1H), 3.15−3.39 (br s, 1H) [diastereomer]; ^{13}C NMR δ −2.2 [−1.78], 15.6, 22.0, 28.3, 30.3, 35.1, 55.4, 79.9, 120.5, 155.8 [diastereomer]; MS *m*/*z* (relative intensity) EI 284 (M^+, 02), 228 ($M^+ - C_4H_8$), 211 ($M^+ - Si(CH_3)_3$, 08), 184 (228 − CO_2, 14). Anal. Calcd for $C_{14}H_{28}N_2O_2Si$: C, 67.22; H, 9.80; N, 4.13. Found: C, 66.92; H, 9.72: N, 4.25.

1,1-[(Dimethylethoxy)carbonyl]-2-piperidinepropanenitrile (13). General Procedure B was employed (1 mmol). Purification by chromatography gave **13** as a colorless oil (129 mg, 54%): IR (neat) 2260 (w), 1693 (s) cm^{-1}; ^{1}H NMR δ 1.40 (s, 9H), 1.30−1.75 (m, 7H), 2.09−2.20 (m, 1H), 2.29 (t, J = 7.2 Hz, 2H), 2.67 (app. t, J = 12.3 Hz, 1H), 3.90−4.15 (br m, 1H), 4.25−4.45 (m, 1H); ^{13}C NMR δ 14.3, 19.0, 25.3, 26.1, 28.3, 28.6, 38.7, 49.5, 79.9, 119.6, 155.0; MS *m*/*z* (relative intensity) EI 238 (M^+, 02), 184 ($M^+ - CH_2CH_2CN$, 20), 137 ($M^+ - C_4H_9CO_2$, 41), 128 ($M^+ - C_4H_8 - CH_2CH_2CN$, 88), 57 ($C_4H_9$, 100).

1,1-[(Dimethylethoxy)carbonyl]-α-(trimethylsilyl)-2-pyrrolidinepropanenitrile (14a). General Procedure A was employed (0.5 mmol). Purification by chromatography gave **14a** as a colorless oil (115 mg, 78%) existing as a separable mixture of diastereomers. Diastereomer 1 (57 mg): IR (neat) 2215 (m), 1702 (s) cm^{-1}; ^{1}H NMR δ 0.15 (s, 9H), 1.42 (s, 9H), 1.40−1.70 (br m, 1H), 1.70−1.95 (m, 5H), 1.95−2.05 (m, 1H), 3.25−3.40 (br m, 2H), 3.70−3.90 (m, 1H); ^{13}C NMR δ −3.39, 16.4, 22.9, 28.5, 31.2, 32.0, 45.8, 58.4, 79.0, 122.5, 154.5; MS *m*/*z* (relative intensity) EI 296 (M^+, 02), 223 ($M^+ - SiMe_3$, 09). Diastereomer 2 (58 mg): IR (neat) 2230 (m), 1702 (s) cm^{-1}; ^{1}H NMR δ 0.18 (s, 9H), 1.20−1.35 (m, 1H), 1.46 (s, 9H), 1.55−2.15 (m, 6H), 3.20−3.50 (m, 2H), 3.80−4.10 (m, 1H); ^{13}C NMR δ −3.4, 15.6, 23.0, 28.5, 29.8, 30.6, 46.3, 56.6, 79.6, 121.5, 154.4; MS *m*/*z* (relative intensity) EI ($M^+ - Si(CH_3)_3$, 09). Anal. Calcd for $C_{15}H_{28}N_2O_2Si$: C, 60.77; H, 9.52; N, 9.45. Found: C, 60.71; H, 9.59; N, 9.44.

Methyl 3-[[(1,1-Dimethylethoxy)carbonyl]methylaminomethyl]-2-heptenoate (23b, R^1 = Me). General Procedure B was employed (1 mmol). Purification by flash column chromatography gave **23** as a colorless oil (199 mg, 70%) as a 66:34 *E*:*Z* mixture of stereoisomers: IR (neat) 1726 (s), 1702 (s) cm^{-1}; ^{1}H NMR δ 0.85−0.95 (m, 3H), 1.25−1.45 (m, 4H), 1.43 (s, 9H), 2.09 [2.51] (t, J = 7.5 Hz, 2H), 2.76 (2.74, rotomer) [2.84] (s, 3H), 3.69 (s, 3H), [3.90] 4.54 (4.55, rotomer) (s, 2H), [5.60] 5.78 (s, 1H) [*E* diastereomer]; ^{13}C NMR δ 13.8, 22.5, 28.3, 29.9 (30.5), 33.7, 34.1, 47.4 (46.2), 51.0, 79.1, (113.3) 117.6, 156.0, 160.1, 166.6 (*E* isomer); MS *m*/*z* (relative intensity) EI 229 ($M^+ - C_4H_8$, 03), 226 ($M^+ - CO_2Me$, 02), 212 ($M^+ - C_4H_9O$, 09), 185 (229 − CO_2, 51).

Methyl 3-[[[(1,1-Dimethylethoxy)carbonyl]methylamino]methyl]-6-chloro-2-hexenoate (25). General Procedure B was employed (1 mmol). Purification by flash column chromatography gave **25** as a colorless oil (248 mg, 81%) existing as a 57:43 *E*:*Z* mixture of diastereomers: IR (neat) 1725 (s), 1702 (s) cm^{-1}; ^{1}H NMR δ [1.41] 1.43 (s, 9H), 1.85−2.05 (m, 2H) [2.20−2.30 (m, 2H)], 2.61 (t, J = 7.8 Hz, 2H), [2.75 (2.73 rotomer)] 2.81 (2.77, rotomer) (s, 3H), [3.49] 3.54 (t, J = 6.6 Hz, 2H), 3.66 (s, 3H), 3.80 (3.90, rotomer) [4.52] (s, 2H), 5.63 [5.82] (s, 1H) [*Z* isomer]; ^{13}C NMR δ 28.3, 30.3, 31.3, 34.3, 44.7, 51.1, 55.2, 80.0, 116.0, 118.5, 157.3, 162.2; MS *m*/*z* (relative intensity) EI 249 ($M^+ - C_4H_8$, 02), 205 (249 − CO_2, 67), 57 (100, C_4H_9). Anal. Calcd for $C_{14}H_{24}ClNO_4$: C, 59.11; H, 9.92; N, 9.85. Found: C, 59.87; H, 7.78; N, 4.57.

Diethyl 2-[[[(1,1-Dimethylethoxy)carbonyl]methylamino]methyl]-1,4-dibutenoic Acid (26). General Procedure B was employed (1 mmol). Purification by flash column chromatography gave **24** as a colorless oil (201 mg, 64%) existing as a 65:35 mixture of *E*:*Z* diatereomers: IR (neat) 1727 (s), 1702 (s) cm^{-1}; ^{1}H NMR δ 1.29 (t, J = 7.2 Hz, 6H), 1.43 (s, 9H), [2.85] 2.86 (br s, 3H), 4.10−4.35 (m, 4H), 4.56 (s, 2H), 6.66 [6.76] (br s, 1H) [*Z* isomer]; ^{13}C NMR δ 14.0, 14.1, 28.2, (33.5) 35.0, (43.3) 45.2, 60.9, 61.5, 79.7, 127.3 (129.0), 145.0, 155.2, 166.2 (165.3) (rotomer or diastereomer); MS *m*/*z* (relative intensity) EI 315 (M^+, 01), 259 ($M^+ - C_4H_8$, 13), 214 ($M^+ - C_4H_9CO_2$, 68), 57 (C_4H_9, 87).

2-[[[(1,1-Dimethylethoxy)carbonyl]methylamino]methyl]-1-hexenylsulfinylbenzene (29a). General Procedure B was employed (1 mmol). Purification by flash column chromatography gave **29a** as a colorless oil (245 mg, 70%) existing as a 47:53 *E*:*Z* mixture of diastereomers: IR (neat) 3085 (w), 1702 (s), 1387 (s) cm^{-1}; ^{1}H NMR δ 0.80−0.95 (m, 3H), 1.26 [1.39] (s, 9H), 1.20−1.50 (m, 4H), 2.40−2.60 (m, 2H), 2.77 (s, 3H), 3.80 [3.87] (s, 2H), 6.02 [6.07] (s, 1H), 7.40−7.95 (m, 5H) [*Z* isomer]; ^{13}C NMR δ 13.7, 22.8, 28.0, 28.9, 30.6 (30.3), 34.6, 54.3, 80.1, 124.5, 124.8, 127.0, 129.1, 133.1, 142.2, 156.2 (156.9) [155.0 (155.5)] (rotomer) [*E* isomer]; MS *m*/*z* (relative intensity) EI 294 ($M^+ - 57$, 03), 77 (C_6H_5, 11).

Ethyl 3-[(1,1-Dimethylethoxy)carbonyl]-2-piperidinyl]-2-heptenoate (30b). General Procedure B was employed (1 mmol). Purification by flash column chromatography gave **30b** as a colorless oil (250 mg, 74%) existing as a single diastereomer: IR (neat) 1712 (s), 1702 (s) cm^{-1}; ^{1}H NMR δ 0.90 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 1.36 (s, 9H), 1.20−1.90 (m, 10H), 2.05−2.15 (m, 2H), 3.00−3.15 (m, 1H), 3.90−4.02 (m, 1H), 4.12 (q, J = 6.6 Hz, 2H), 5.58 (s, 1H), 5.52−5.62 (m, 1H); ^{13}C NMR δ 13.9, 14.3, 19.2, 22.7, 22.8, 27.7, 28.2, 29.9, 31.9, 39.8, 54.0, 59.5, 79.2, 113.7, 155.8, 166.0, 167.0; MS *m*/*z* (relative intensity) EI 282 ($M^+ - C_4H_9$, 17), 238 (282 − CO_2, 32), 57 (C_4H_9, 100). Anal. Calcd for $C_{19}H_{33}NO_4$: C, 67.22; H, 9.80; N, 4.13. Found: C, 66.96; H, 9.88; N, 4.11.

***(E)*-Ethyl 3-(2-pyrrolidinyl)-2-heptenoate:** ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3H, J = 7.2 Hz), 1.28 (t, 3H, J = 7.2 Hz), 1.33−1.56 (m, 5H), 1.63−1.91 (m, 3H), 1.91−2.14 (m, 1H), 2.14−2.36 (m, 1H), 2.76−2.90 (m, 1H), 2.90−3.02 (m, 1H), 3.02−3.17 (m, 1H), 3.56−3.78 (m, 1H), 4.11 (q, 2H, J = 7.2 Hz), 5.96 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.8, 14.2, 23.2, 25.3, 30.8, 31.5, 40.7, 46.0, 59.4, 63.7, 113.2, 166.1, 166.9.

1-Butyl-5,6,7,7a-tetrahydro-3*H*-pyrrolizin-3-one: ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H, J = 7.2 Hz), 1.08−1.30 (m, H), 1.30−1.46 (m, 2H), 1.46−1.62 (m, 2H), 1.98−2.13 (m, 1H), 2.13−2.24 (m, 1H), 2.24−2.41 (m, 3H), 3.17−3.31 (m, 1H), 3.38−3.52 (m, 1H), 4.05−4.17 (m, 1H), 5.68 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.4, 28.9, 29.2, 29.3, 29.5, 42.1, 69.0, 121.7,

166.5, 176.7; MS *m/z* (relative intensity) EI 179 (M^+, 39), 136 (100), 122 (19), 109 (39), 94 (39), 67 (20.7), 53 (26).

Methyl 3-[[(1,1-Dimethylethoxy)carbonyl]-2-pyrrolidinyl]-6-chloro-2-hexenoate 31a. General Procedure B was employed (1 mmol). Purification by flash column chromatography gave a colorless oil (251 mg, 70%) existing as a 35:65 mixture of the *E* and *Z* isomers, which could be separated and isolated. *E* isomer: IR (neat) 1725 (s), 1702 (s), 1659 (s) cm^{-1}; ^1H NMR δ 1.38 (1.44) (s, 9H), 1.15−1.85 (m, 3H), 1.85−2.35 (m, 4H), 2.90−3.20 (m, 1H), 3.25−3.55 (m, 2H), 3.50−3.65 (m, 2H) 3.67 (s, 3H), 4.20−4.45 (m, 1H), 5.65 (s, 1H) (rotomer); ^{13}C NMR δ 23.3, 28.0, 28.4, 31.4, 31.8, 45.0, 46.9, 51.0, 62.1, 79.9, 113.5, 154.1, 162.7, 166.7; MS *m/z* (relative intensity) EI 331 (M^+, 01), 275 ($M^+ - C_4H_8$, 06), 231 (275 − CO_2, 24), 57 (C_4H_9, 88). *Z* isomer: IR 1720 (s), 1692 (s), 1460 (s) cm^{-1}; ^1H NMR δ 1.35 (1.42) (s, 9H), 1.45−1.65 (m, 1H), 1.65−2.05 (m, 4H), 2.05−2.50 (m, 3H), 3.20−3.40 (m, 1H), 3.54 (t, J = 6.3 Hz, 2H), 3.67 [3.65] (s, 3H), 3.50−3.80 (m, 1H), 5.54 (t, J = 7.8 Hz, 1H), 5.64 (s, 1H); ^{13}C NMR δ 24.3 (24.7), 28.2, 28.4, (30.4) 30.7, 32.4, 44.2 (44.3), 47.6 (47.8), 51.0, 58.1 (58.3), 79.6, 114.5 (117.7), 154.6, 163.9, 166.3 (rotomer); MS *m/z* (relative intensity) EI 331 (M^+, 01), 274 ($M^+ - C_4H_9$, 05), 230 (274 − CO_2, 83).

1-(3-Chloropropyl)-5,6,7,7a-tetrahydro-3*H*-pyrrolizin-3-one. To a CH_2Cl_2 solution of **31b** (*Z* isomer) were added PhOH (10 equiv) and TMSCl (3.0 equiv) and the mixture was stirred at room temperature for 30 min. The reaction mixtue was diluted with 40 mL of ether, washed with 10% aqueous sodium hydroxide (3 × 10 mL) and brine, dried over $MgSO_4$, and concentrated in vacuo to give crude product. Purification by column chromatography (silica gel, ether/petroleum ether, 1:1 v/v) gave pure material: ^1H NMR δ 1.90−2.35 (m, 6H), 2.40−2.55 (m, 2H), 3.20−3.40 (m, 1H), 3.40−3.50 (m, 1 H), 3.55 (t, J = 7.5 Hz, 2H), 4.05−4.20 (m, 1H), 5.90 (s, 1H); ^{13}C 26.4, 28.6, 29.4, 29.9, 42.1, 43.9, 69.6, 121.9, 165.6, 176.7; MS *m/z* (relative intensity) EI 199 (M^+, 14), 164 (M^+ − Cl, 09), 136 ($M^+ - CH_2CH_2Cl$, 100), 122 (136 − CH_2, 16).

General Procedure D. Conjugate Addition of α-Aminoalkylcuprates to α,β-Allenyl Esters. To a stirred solution of the carbamate (1.0 mmol) in THF (3−4 mL) under nitrogen at room temperature was added TMEDA or sparteine (1.0 mmol). The mixture was cooled to −78 °C and 1.0 mL *s*-BuLi (1.1 M in cyclohexane) was added by syringe. The solution was stirred at −78 °C (1 h) and then warmed to −55 °C, whereupon a solution of CuCN·2LiCl (1.0 mmol in 2 mL THF) was added dropwise and the reaction mixture was stirred for 45 min at −55 °C. A solution of α,β-allenyl ester (1 mmol) in TMSCl (5.0 mmol, 0.64 mL) was added by syringe, and the reaction mixture was stirred for an additional 30 min and then warmed to room temperature over 2 or 3 h. The reaction was quenched with saturated NH_4Cl (3 mL) and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Crude products were purified by chromatography (silica gel, 10% or 15% ether/petroleum ether).

Ethyl 3-[[[(1,1-Dimethylethoxy)carbonyl]methylamino]-methyl]-3-pentenoate (37). General Procedure A was employed (0.5 mmol). Purification by flash column chromatography gave **37** as a colorless oil (111 mg, 82%) existing as a 91:9 *E*:*Z* mixture of diastereomers: IR (neat) 1736 (s), 1702 (s) cm^{-1}; ^1H NMR δ 1.21 (t, J = 6.9 Hz, 3H), 1.40 (s, 9H), 1.62 [1.67] (d, J = 6.6 Hz, 3H), 2.69 [2.81] (s, 3H), [2.90] 2.98 (s, 2H), 3.79 [3.94] (s, 2H), 4.08 (q, J = 7.2 Hz, 2H), 5.49 (q, J = 6.6 Hz, 1H) [*Z*-isomer]; ^{13}C NMR δ 13.4, 14.1, 28.3, 33.2 (br), 54.4, 54.9, 60.5, 79.3, 125.6, 129.1, 155.6, 170.9; MS *m/z* (relative intensity) EI 215 (06, $M^+ - C_4H_8$), 198 (07, $M^+ - CO_2Et$), 171 (30, 215 − CO_2), 156 (22, 171 − CH_3), 57 (100, C_4H_9). Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.23; N, 5.16. Found: C, 62.19; H, 9.23; N, 5.10.

Ethyl 3-[[[(1,1-Dimethylethoxy)carbonyl]methylamino]-methyl]-5-methyl-3-hexenoate (39). General Procedure A was employed (0.5 mmol). Purification by flash column chromatography gave **39** as a colorless oil (97 mg, 65%): IR (neat) 1736 (s), 1694 (s) cm^{-1}; ^1H NMR δ 0.94 (d, J = 6.6 Hz, 6H), 1.23 (t, J = 7.2 Hz, 3H), 1.42 (s, 9H), 2.45−2.60 (m, 1H), 2.72 (br s, 3H), 2.99 (s, 2H), 3.78 (br s, 2H), 4.10 (q, J = 7.2 Hz, 2H), 5.21 (d, J = 9.6 Hz, 1H); ^{13}C NMR δ 14.1, 22.7, 27.4, 28.3, 33.1, 33.8 (br), 54.9 (br), 60.5, 79.3, 125.5, 138.8, 155.8, 171.1; MS *m/z* (relative intensity) EI 299 (M^+, 01), 243 (02, $M^+ - C_4H_8$), 226 (05, $M^+ - CO_2Et$), 199 (08, 243 − CO_2), 156 (100, 199 − C_3H_7), 57 (33, C_4H_9). Anal. Calcd for $C_{16}H_{29}NO_4$: C, 64.19; H, 9.76; N, 4.68. Found: C, 64.38; H, 9.66; N, 4.62.

Ethyl 1-[(1,1-Dimethylethoxy)carbonyl]-β-ethylidene-2-pyrrolidinepropanoate (41a). General Procedure A was employed (0.5 mmol). Purification by flash column chromatography gave **41a** as a colorless oil (126 mg, 85%): IR (neat) 1739 (s), 1700 (s) cm^{-1}; ^1H NMR δ 1.23 (t, J = 7.2 Hz, 3H), 1.40 (s, 9H), 1.63 (d, J = 6.9 Hz, 3H), 1.70−2.05 (m, 4H), 2.94 (v br s, 2H), 3.05−3.45 (m, 2H), 4.10 (q, J = 7.2 Hz, 2 H), 4.20−4.40 (br s, 1H), 5.38 (q, J = 6.9 Hz,1H); ^{13}C NMR δ 13.5, 14.1, 22.8 (br), 28.4, 31.2 (br), 33.9, 46.7 (br), 60.5, 62.7, 79.0, 122.4, 133.2, 154.5, 171.4; MS *m/z* (relative intensity) EI 297 (M^+, 02), 240 ($M^+ - C_4H_9$, 06), 224 (10), 196 (240 − CO_2, 39), 57 (C_4H_9, 43). Anal. Calcd for $C_{16}H_{27}NO_4$: C, 64.62; H, 9.15; N, 4.71. Found: C, 64.51; H, 9.30; N, 4.84.

Ethyl 1-[(1,1-Dimethylethoxy)carbonyl]-β-ethylidene-2-piperidinepropanoate (41b). General Procedure A was employed (0.5 mmol). Purification by flash column chromatography gave **41b** as a colorless oil (135 mg, 87%): IR (neat) 1740 (s), 1695 (s) cm^{-1}; ^1H NMR δ 1.24 (t, J = 7.2 Hz, 3H), 1.44 (s, 9H), 1.35−1.65 (m, 5H), 1.68 (dd, J = 6.6 Hz, J = 2.1 Hz, 3H), 1.90−2.05 (m, 1H), 2.65 (dt, J = 2.4 Hz, J = 12.8 Hz, 1H), 3.00 (center AB quartet, J_{AB} = 16.2 Hz, $\Delta\upsilon_{AB}$ = 12.8 Hz, δ_A = 2.98, δ_B = 3.02, 2H), 3.80−3.95 (m, 1H), 4.10 (q, J = 7.2 Hz, 2H), 4.71 (br s, 1H), 5.50−5.60 (m, 1H); ^{13}C NMR δ 13.8, 14.2, 19.7, 25.5, 26.0, 28.4, 33.9, 39.9, 54.6, 60.4, 79.2, 124.3, 130.9, 155.3, 171.1; MS *m/z* (relative intensity) EI 255 ($M^+ - C_4H_8$, 05), 211 (255 − CO_2, 19). Anal. Calcd for $C_{17}H_{29}NO_4$: C, 65.57; H, 9.39; N, 4.50. Found: C, 65.46; H, 9.39; N, 4.38.

Ethyl 1-[(1,1-Dimethylethoxy)carbonyl]-β-[(1-methyl)-ethylidene]-2-pyrrolidinepropanoate (44). General Procedure A was employed (1 mmol). Purification by flash column chromatography gave **44** as a colorless oil (124 mg, 80%): IR (neat) 1730 (s), 1697 (s) cm^{-1}; ^1H NMR δ 1.22 (t, J = 7.2 Hz, 3H), 1.37 (s, 9H), 1.68−1.94 (m, 3H), 1.65 (s, 3H), 1.78 (s, 3H), 1.95−2.15 (m, 1H), 2.83−3.10 (m, 2H), 3.17−3.31 (m, 1H), 3.50−3.70 (br, 1H), 4.08 (q, J = 6.9 Hz, 2H), 4.50−4.70 (br, 1H); ^{13}C NMR δ 14.2, 20.0, 21.7, 24.0, 28.3, 31.3, 33.1, 48.0, 58.7, 60.3, 78.8, 127.1, 130.0, 154.7, 172.4; MS *m/z* (relative intensity) EI 311 (02, M^+), 254 (05, $M^+ - C_4H_9$), 238 (06, $M^+ - CO_2Et$), 210 (26, 254 − CO_2), 57 (100, C_4H_9).

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **4**, **5b**, **5c**, **6a**, **7a**−**d**, **9**, **23a**, **30a**, (*E*)-ethyl 3-(2-pyrrolidinyl)-2-heptenoate, and 1-butyl-5,6,7,7a-tetrahydro-3*H*-pyrrolizin-3-one are available in the Supporting Information for the preliminary communication [Dieter, R. K.; Velu, S. E. *J. Org. Chem.* **1997**, *62*, 3798]. ^1H and ^{13}C NMR spectra for **13**, **23b**, **26**, **27** (*trans*), **27** (*cis*), **28**, **29a**, **30a**, **31a** (*trans*), **31a** (*cis*), **31b** (*trans*), **31b** (*cis*), **32**, **38**, **40**, **42**, **44**, **45a**, and 1-(3-chloropropyl)-5,6,7,7a-tetrahydro-3*H*-pyrrolizin-3-one. Data reduction (IR, ^1H and ^{13}C NMR, mass spectrum) for compounds **4**, **5b**, **5c**, **6a**, **7a**, **7c**, **7d**, **9**, **12a**, **23a**, **24**, **27**, **28**, **30a**, **31b**, **32**, **38**, **40**, **42**, **43a**, **43b**, **45a**, **45b**, **46b.** This material is available free of charge via the Internet at http://pubs.acs.org.

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