A Study of Factors Affecting α-(*N*-Carbamoyl)alkylcuprate Chemistry

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The effect of Cu(I) salt (i.e., CuCN, CuCN·2LiCl, CuI), cuprate reagent, sec-butyllithium quality, solvent, and temperature upon the chemical yields obtained in the reactions of α -(*N*-carbamoyl)alkylcuprates [i.e., N-Boc-protected α -aminoalkylcuprates] with (E)1-iodo-1-hexene, 5,5-dimethyl-2-cyclohexenone, methylvinyl ketone, crotonate esters, and an acid chloride has been examined. Cuprate conjugate addition and vinylation reactions can succeed with low-quality sec-butyllithium, presumably containing insoluble lithium hydride and lithium alkoxide impurities, although yields are significantly lower than those obtained with high-quality s-BuLi. α -(N-Carbamoyl)alkylcuprates prepared from high-quality sec-butyllithium are thermally stable for 2-3 h at room temperature and are equally effective when prepared from either insoluble CuCN or THF-soluble CuCN·2LiCl. Use of the latter reagent permits rapid cuprate formation at -78 °C, thereby avoiding the higher temperatures required for cuprate formation from THF-insoluble CuCN that are problematic with solutions containing thermally unstable α -lithiocarbamates.

Introduction

Although they effect a wide range of transformations and are widely employed in synthesis, organocopper reagents have a well-earned reputation for capriciousness and sensitivity to reaction conditions.¹ They are incompatible with air, moisture, and oxidants and often display thermal instability in the same temperature region in which the desired transformation occurs.² Reactivity, chemical yields, and regio- and stereoselectivity of organocopper-mediated reactions are dependent upon solvent, additives (e.g., Lewis acids, TMSCl, TMSCl/HMPA, etc.),^{1,3} co-metal (e.g., Li, Mg, Zn), and the Cu(I) salt⁴ used in reagent preparation, as well as the particular reagent employed (e.g., Gilman reagents, mixed homocuprates, heterocuprates, organocopper reagents). The copper(I)

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salt often plays a significant role in the chemistry of the resultant organocopper and cuprate reagents, and CuCN and CuBr·SMe₂ have been promoted as the best Cu(I) precursors.⁴ Organocopper reagents prepared from CuCN and either 1 or 2 equiv of an alkyllithium reagent often display superior attributes with regard to chemical yields, suggesting an important role of the cyanide anion.^{1a} The structure of the latter reagent has been the subject of considerable controversy centering around the location of the cyanide ion.⁵ Although THF-soluble CuCN·2LiCl has been extensively used by Knochel in the copperpromoted reactions of organozinc reagents,⁶ this source of Cu(I) has not been widely used in the generation of cuprates from alkyllithium or Grignard reagents.⁷ The use of CuCN·2LiCl appeared to be crucial for the conjugate addition⁸ and coupling reactions⁹ of α -(*N*-carbamoyl)alkylcuprates with α,β -unsaturated carboxylic acid derivative and vinyl iodides, respectively. This plethora of effects generally necessitates an empirical development of optimal conditions for any particular reaction.

Reactivity can be a major problem in organocuprate chemistry. 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 less reactive enoate substrates. Cuprates prepared from CuCN (2RLi + CuCN),¹⁰ cuprous

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thiophenoxides,¹¹ and copper(I) trimethylsilylacetylide¹² 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. Gilman reagents effect high-yield conjugate addition reactions with mono- β -alkyl-substituted enoates, enamides, and enecarbamates in ether in the presence of TMSCl.¹³ Alkylcopper compounds also participate with enoates in conjugate addition reactions in synthetically useful yields in the presence of additives such as BF₃·Et₂O and chloro- or iodotrimethylsilane.¹⁴

During the course of our developmental work on α -(*N*carbamoyl)alkylcuprates, we experienced considerable difficulty across the range of characteristic cuprate reactions. Conjugate addition reactions of α -(N-carbamoyl)alkylcuprates prepared from CuCN to enones15b,d appeared sensitive to diamine additives, solvent, and the quality of the s-BuLi employed in the deprotonation of *N-tert*-butoxycarbonyl (Boc)-protected amines.¹⁶ Additionally, conjugate addition reactions with carboxylic acid derivatives⁸ and vinylation reactions with vinyl iodides⁹ were only successful when CuCN·2LiCl was employed. Having developed the first examples of N-protected α -aminoalkylcuprate (i.e., α -cuprio formamidines, carbamates, and azo compounds) participation in conjugate addition reactions^{8,15} and of α -(*N*-carbamoyl)alkylcuprates in substitution reactions with acid chlorides,^{17a} vinyl triflates,^{17b} vinyl iodides,⁹ allylic substrates,^{17c} and propargylic^{17d} substrates, we now had the opportunity to examine the influence of various reaction parameters upon the reactions of these cuprates containing an α -heteroatomalkyl ligand. We now report a study of the factors affecting α -(*N*-carbamoyl)alkylcuprate chemistry including the influence of s-BuLi quality, Cu(I) salt employed, cuprate thermal stability, and additives (e.g., TMSCl, diamines, LiCl, s-BuOLi, etc.).

Results

During the early work on α -(*N*-carbamoyl)alkylcuprate conjugate additions to α , β -enones, the reaction often failed or gave capricious yields when insoluble CuCN was used in conjunction with TMEDA employed to assist carbamate deprotonation (eq 1).^{15b,d} Subsequently, it was discovered that reliable and reproducible yields could be

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obtained by use of (-)-sparteine or freshly distilled TMEDA, although the yields were significantly lower than those obtained from cuprates prepared via the intermediate α -(*N*-carbamoyl)alkylstannanes. Ultimately, the use of CuCN·2LiCl for cuprate formation reproducibly gave high chemical yields comparable to those obtained via the stannane protocol (eq 1). More recently, the use of freshly distilled (-)-sparteine and careful manipulation of reaction temperatures during cuprate preparation and reaction afforded high chemical yields in the reactions of α -(*N*-carbamoyl)alkylcuprates prepared from insoluble CuCN with enones (eq 1), enoates, and vinyl iodides that are comparable to those obtained with THF-soluble CuCN·2LiCl or via the α -(*N*-carbamoyl)alkylstannane procedure. In these reactions, addition of solid CuCN (-78 °C) to the α -(N-carbamoyl)alkyllithium reagent was followed by stirring at -78 °C for 30 min, removal of the cold bath permitting the cold flask to stand at ambient air temperature for 10–15 min, and then cooling the flask to -78 °C before addition of the electrophile. The chemical yields of enone conjugate adducts also appeared to vary with the physical appearance of the s-BuLi employed in the carbamate deprotonations.¹⁶



ⁿBu₄NF added to cleave silvl enol ethers

Given the capriciousness of these reactions and the accumulated empirical observations required to obtain reliable and reproducible results, we undertook a study to examine the thermal stability of α -(*N*-carbamoyl)-alkylcuprates and factors such as temperature, Cu(I) salt, *s*-BuLi quality, and additives (e.g., alkoxide impurities in the *s*-BuLi) that might affect the reliability of the reactions.

The effect of *s*-BuLi quality was examined using the conjugate addition reaction with cyclohexenone and the vinylation reaction with *trans*-1-iodo-1-hexene (eq 2). A few examples from a preliminary study using an acid chloride are also included. Commercial samples of *s*-BuLi range in appearance from clear colorless solutions to those having varying amounts of particulates, assumed to be LiH.¹⁸ Thermal and chemical (i.e., reaction with oxygen, H₂O, or CO₂) decomposition of *s*-BuLi leads to the formation of LiH, *s*-BuOLi, LiOH, Li₂O, and *s*-BuCO₂-Li, all of which could have a deleterious effect upon α -(*N*-carbamoyl)alkylcuprate formation and reactivity. The rate of *s*-BuLi decomposition is dependent upon temper-

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 Table 1. Effect of s-BuLi Quality on the Reactions of Organocopper Reagents Prepared from Carbamate 1 and n Equiv of CuCl·2LiCl or CuCN·2LiCl with Cyclohexenone (5 equiv of TMSCl), 4-MeOC₆H₄COCl, or (E)-1-Iodo-1-hexene to Afford, Respectively, 3, 5, or 6a (Eq 2)



	<i>s</i> -BuLi		total		CuX·2L	liCl			rxn ^e		% yield pr	oduct ^g
entry	source ^a	RLi $M^{b,c}$	$base^{c}$ (M)	$appearance^d$	<i>n</i> equiv	Х	additive	electrophile	cond	solvent ^f	NMR IS ^h	isolated ⁱ
1	FMC			filtered	1.0	Cl		acid chloride	А	THF	91-100	88
2					1.0	CN		cyclohexenone	Α	Et ₂ O/THF		54
3				particulates				acid chloride	Α	THF		50
4				clear sample				acid chloride	Α	THF	100	
5					1.0	CN		cyclohexenone	Α	Et ₂ O/THF		72
6	Aldrich			filtered	1.0	Cl		acid chloride	Α	THF	94	
7					1.0	CN		cyclohexenone	Α	Et ₂ O/THF		62
8					1.0	CN	<i>s</i> -BuOH 0.25 ^{<i>j</i>}	cyclohexenone	Α	Et ₂ O/THF		42
9					1.0	CN	<i>s</i> -BuOH 1.0 ^{<i>j</i>}	cyclohexenone	Α	Et ₂ O/THF		60
10				particulates	1.0	CN		cyclohexenone	Α	Et ₂ O/THF		57
11	FMC A	1.1	1.6	particulates	0.5	CN		1-iodohexene	В	THF		80
12									Α	Et ₂ O/THF	93	89
13									С	Et ₂ O/THF	70	
14	FMC A	1.1	1.3	filtered, clear	0.5	CN		1-iodohexene	В	THF		84
15	FMC A	1.1	1.3	filtered, clear	0.5	CN		1-iodohexane	Α	Et ₂ O/THF	67 - 80	67 - 73
16	FMC B	1.7	1.7	clear	0.5	CN		1-iodohexene	D	THF	94 - 100	
17	CT A	0.7	0.7	clear	0.5	CN		1-iodohexene	D	THF	92	
18	CT B	1.5	1.5	clear	0.5	CN		1-iodohexene	D	THF	78 (71) ^k	
19	CT B	1.5	1.5	clear	0.5	CN	<i>s</i> -BuOH 0.3 ^j	1-iodohexene	D	THF	92	
20	CT B	1.5	1.5	clear	0.5	CN	<i>s</i> -BuOH 0.6 ^{<i>j</i>}	1-iodohexene	D	THF	98	
21	CT B	1.5	1.5	clear	1.0	CN	<i>s</i> -BuOH 1.0 ^j	1-iodohexene	D	THF	$\le 5 - 33$	

^{*a*} FMC = milky white material with particulates. FMC A = material containing solid particulates and approximately 2 years old at time of usage. FMC B = new material freshly acquired at time of usage and clear. ^{*b*} M determined by Eastham procedure using *s*-BuOH and 1,10-phenanthrolein as indicator. ^(M) M determined by Gilman double titration using dibromoethane. ^{*d*} Appearance of material used in carbamate deprotonation. ^{*e*} Reaction conditions include the following: (i) deprotonation, (ii) cuprate formation, and (iii) reaction with electrophile. A = [(i) *s*-BuLi, (-)-sparteine, THF or Et₂O, -78 °C, 1 h; (ii) -78 to -50 °C, 30-40 min; (iii) -50 °C to rt (5 equiv of TMSCI with 2-cyclohexenone), 2–5 h]; B = (i) *s*-BuLi, (-)-sparteine, THF or Et₂O, -78 °C, 1 h; (ii) -78 °C, 30 min; (iii) -50 °C (80 min; (iii) -50 °C (60 min), rt (30 min); C = (i) *s*-BuLi, (-)-sparteine, THF or Et₂O, -78 °C, 30 min; (ii) -50 °C (30 min and then quench; D = (i) *s*-BuLi, (-)-sparteine, THF or Et₂O, -78 °C, 45 min; (ii) -50 °C (45 min), rt (30 min). ^{*f*} Deprotonations performed in Et₂O resulted in a 1:2 Et₂O/THF solvent mixture via addition of THF solutions of CuCN-2LiCl and then electrophile. ^{*s*} Yields tetrachloroethane. ^{*I*} Isolated yields of products purified by column chromatography. ^{*j*} *s*-BuOH was added to the carbamate solution and mmol *s*-BuLi = mmol carbamate + mmol *s*-BuOH. ^{*k*} Yield obtained in the absence of (-)-sparteine otherwise used to assist deprotonation.

ature and amounts of s-BuOLi present in solution.¹⁸ In a set of preliminary studies, old s-BuLi (approximately 0.3 to 2.5 years) containing particulates was filtered through Celite (flame dried under vacuum prior to use), and both the filtered and unfiltered material was used for deprotonation of the Boc-protected amine (eq 2, Table 1). Formation of the α -(*N*-carbamoyl)alkylcuprate derived from Boc-protected pyrrolidine (1) using filtered or unfiltered *s*-BuLi and CuX·2LiCl (X = Cl, CN), followed by reaction with 4-methoxybenzovl chloride (entries 1, 6 vs 3, 88-94% vs 50%), 2-cyclohexenone (entries 2, 7 vs 10, 54-62% vs 57%), or 1-iodo-1-hexene (entries 14-15 vs 11-13, 67-80% vs 70-93%) generally gave comparable product yields with the filtered and unfiltered s-BuLi, respectively. The acylation reaction displayed significantly better yields (38-44% higher) when filtered s-BuLi was employed compared to the other two transformations. The conjugate addition and acylation reactions employed the cyanocuprate reagent, RCuCNLi, and the observed yields of the better set (i.e., filtered or unfiltered) are only slightly lower (6-15%) than the optimized yields obtained with high-quality s-BuLi (entries 4-5).^{15d,17a} A more careful study was performed with the vinylation reaction using several sources of *s*-BuLi (Table 1, entries 11-18) including old material (FMC A, filtered and unfiltered), high-quality commercial material (FMC B), and material prepared in our laboratory (CT A & B). The samples of *s*-BuLi used in carbamate deprotonation were titrated according to the modified Gilman double-titration procedure to give a measure of both total base and active *s*-BuLi.^{1a,19} Watson–Eastham titrations gave molarity values for *s*-BuLi that were identical to those obtained using the Gilman doubletitration method.^{1a,20} Filtration of FMC A removed half of the nonalkyllithium base, and both filtered and unfiltered samples gave good yields (entries 11-15, 67-89%) of product, while *s*-BuLi containing no extraneous

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bases (FMC B, CT A & B) gave the desired product in nearly quantitative yield for two of the three samples (entries 16–17) and somewhat lower yield for the third (CT B, entry 18). A diminished yield (7% decrease) was obtained when the deprotonation was performed in the absence of the diamine (–)-sparteine (entry 18). This third *s*-BuLi sample (CT B) did give nearly quantitative yields in subsequent experiments probing the effect of added *s*-BuOLi (entries 19–20).

The effect of s-BuOLi was examined by addition of s-BuOH to the carbamate solution followed by sufficient s-BuLi to deprotonate the alcohol and carbamate.²¹ While the conjugate addition reaction appeared unaffected by the addition of *s*-BuOLi (Table 1, entries 8-9 vs 7) the vield in the vinylation reaction dropped dramatically with one equivalent of *s*-BuOLi (\leq 5–33%, four experiments), although it remained largely unaffected when up to 0.6 equiv of s-BuOLi was added (entries 19-21). Nevertheless, over three experiments considerable variation in product yield was observed when 0.3 (98%, 97%, 60% yield of 6a) or 0.6 (92%, 77%, 38% yields of 6a) equiv of s-BuLi was present in the reaction mixture. In the presence of 1.0 equiv of s-BuOLi, yields of 6a increased with increasing amounts of CuCN·2LiCl [equivalents (% yield): 1.15 (8%), 1.34 (13-15%), 1.39 (42-45%)]. Similarly, the dialkylcuprate prepared from 1 in glassware washed with alcoholic KOH solutions and rinsed three times with cold water (prior to oven drying) gave slightly lower yields of 6a than KOH washed glassware rinsed with 10% aqueous HCl, water, and oven dried (90 vs 99%).

The thermal stabilities of pyrrolidine-derived α -(Ncarbamoyl)alkylcuprates were probed by formation of the cuprate reagents with CuCN·2LiCl or CuCN at -78 °C followed by aging of the reagent at a given temperature for 30 min^{2b} and then cooling the solutions to -50 °C and quenching the reagents with either 1-iodo-1-hexene or methyl vinyl ketone (Table 2). The reagent (2RLi + CuCN·2LiCl) prepared via deprotonation of N-Boc-pyrrolidine (1) with FMC A (filtered) gave comparable yields of **6a** when aged at -40 (75-79%) or 0 °C (80-81%) for 30 min but began to show reduced yields when aged at 20 °C (66%) that diminished to 53% after 2 h at room temperature. Utilization of s-BuLi containing no extraneous base (FMC B) gave nearly quantitative yields of 6a after the cuprate reagent was aged for 60 min at 25 °C, although the yield dropped to 36% after 3 h. The cyanocuprate reagent, RCuCNLi, prepared via filtered FMC A gave very low yields of vinylation product when the reaction was quenched at -50 °C [aging temperature °C (% yield): -40 (17%), 0 (10%), 25 (08)] and modest yields when the solution was allowed to warm to room temperature [aging temperature °C (% yield): -40 (40%), 0 (38%), 25 (40)]. High yields of the vinylation product 6a (84%) could be obtained when the cuprate reagent was prepared from high quality s-BuLi (FMC B), aged at -40°C for 30 min, and allowing the reaction mixture to warm to room temperature after addition of the vinyl iodide. The N-Boc piperidine derived cuprate, R₂CuLi·LiCN, gave 82% for unaged reagent and appeared to decompose more rapidly than the pyrrolidinyl cuprate (cuprate aged 1 h, 45% **6b**). The *N*-Boc-piperidine was deprotonated in

Table 2. Reactivity and Thermal Stability of α-(N-carbamoyl)alkylcuprates Prepared from CuCN or CuCN·2LiCl and Lithiated N-Boc-pyrrolidine or N-Boc-piperidine As Measured by Reaction with Methyl Vinyl Ketone (MVK) To Afford 7 (Eq 3)

	1. (-)-sparteine, <i>s</i> -BuLi, THF	
/()n	-78 °C, 30-60 min (4 , 4 h)	(3)
	2. (0.5 or 1 equiv) CuCN (45 min.)	$\int (h)^n$
ĊO ₂ ^t Bu	CuCN·2LiCl, -78 °C, 30-45 min.	NN
1 n = 1	3. Methyl vinyl ketone or MVK/TMSCI	CO ₂ ^t Bu
4 n = 2	-50 °C, 30 min.	7a n = 1
	4. sat NH₄Cl, -50 °C	b n = 2

entry	compd	Cu source	RLi:Cu ^a	TMSCl (equiv)	cuprate aged	% yield ^{b,c}
1	1	CuCN·2LiCl	1:1	0		<5
2	1	CuCN	1:1	0		<5
3	1	CuCN·2LiCl	2:1	0		68 - 72
4	1	CuCN	2:1	0		58 - 85
5	1	CuCN·2LiCl	1:1	5		88
6	1	CuCN	1:1	5		84
7	1	CuCN·2LiCl	1:1	5	20 °C, 2 h	67
8	1	CuCN	1:1	5	20 °C, 2 h	81
9	1	CuCN·2LiCl	2:1	5		90
10	1	CuCN	2:1	5		92
11	1	CuCN·2LiCl	2:1	5	20 °C, 2 h	96^d
12	1	CuCN	2:1	5	20 °C, 2 h	> 98 ^d
13	4	CuCN·2LiCl	2:1	5		$> 98^{e-g}$
14	4	CuCN·2LiCl	2:1	5	20 °C, 1 h	$75^{e,h}$
15	4	CuCN·2LiCl	2:1	5	20 °C, 2 h	71 ^{e,h}

^{*a*} Deprotonation [(–)-sparteine, *s*-BuLi, THF, –78 °C, 30–60 min] and cuprate formation [–78 °C, 30–45 min] employed uniform conditions. Deprotonation employed FMC B [clear, 1.7 M RLi. 1.7 M total base] unless noted. ^{*b*} MVK was added at –50 °C, and the reaction stirred for 30 min and then quenched with saturated NH₄Cl at –50 °C. ^{*c*} Yields determined by NMR internal standard using 1,3,5-tribromobenzene. Yields reported as a range for multiple experiments. ^{*d*} *s*-BuLi was prepared [1.5 M RLi, 1.5 M total base, CT B]. ^{*e*} Deprotonation was effected in Et₂O [(–)-sparteine, *s*-BuLi, THF, –78 °C, 4 h] and MVK was added at –50 °C [–50 °C to rt overnight]. ^{*f*} Clear colorless solution of *s*-BuLi (1.1M active RLi, 1.2 M total base) was used. ^{*s*} Yield based upon material isolated by column chromatography. ^{*h*} Clear colorless solution of *s*-BuLi (1.3 M active RLi, 1.35 M total base) was used.

Et₂O [1.25 equiv *s*-BuLi, -78 °C, TMEDA (2.3 equiv), 4 h] and was facilitated by excess TMEDA.

The thermal stabilities of 2-pyrrolidinyl- and 2-piperidinylcuprates were also measured using methyl vinyl ketone in the conjugate addition reaction to permit a cleaner examination of the cyanocuprate reagent RCuCN-Li. Although the RCuCNLi reagent prepared from lithiated 1 and either CuCN or CuCN·2LiCl gave very low yields of conjugate adduct with methyl vinyl ketone in the absence of TMSCl (Table 2, entries 1-2), the reagent prepared from 2RLi and either Cu(I) salt gave comparable yields of conjugate adduct in both cases (entries 3-4, 58-85%). The RCuCNLi reagent gave very good yields in the presence of TMSCl (entries 5-6) even after aging for 2 h at room temperature (entries 7-8), although the reagent prepared from CuCN·2LiCl gave a lower yield (14% decrease) after aging. Nearly quantitative yields of conjugate adduct were obtained with the pyrrolidinyl cuprate prepared from 2RLi and either Cu(I) salt in the presence of TMSCl (entries 9-10) even after the cuprate was aged for 2 h at room temperature (entries 11-12). In the presence of TMSCl, the piperidinylcuprate gave a quantitative yield of adduct (entry 13) that appeared to decrease significantly upon aging (entries 14–15) consistent with the earlier result using the vinyl

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Table 3. Effects of Cu(I) Salts in the Reactions of Cuprates Derived from *N*-Boc-Protected *N*,*N*-Dimethylamine and CuX·2LiCl with Methyl Vinyl Ketone or 5,5-Dimethyl-2-cyclohexenone (Eq 4)^a



entry	CuX·2LiCl	equiv ^b	product	% yield ^c
1	Cl	1.0	9	56-58
2	Br	1.0	9	67-70
3	Ι	1.0	9	57 - 60
4	CN	1.0	9	63 - 74
5	Cl	0.5	9	90^d
6	Br	0.5	9	52 - 60
7	Ι	0.5	9	80-84
8	CN	0.5	9	61^d
9	Cl	1.0	10	82 - 95
10	Br	1.0	10	76
11	Ι	1.0	10	$68 - 79^{e}$
12	Ι	1.0	10	91-94 ^f
13	CN	1.0	10	70-90
14	CN	1.0	-	81-82g

^{*a*} Reaction conditions are shown in eq 4. ^{*b*} Stoichiometry of 0.5 equiv corresponds to 2RLi + CuX·2LiCl and 1.0 to RLi + CuX·2LiCl. ^{*c*} Yields were determined via ¹H NMR spectroscopy using tetrachloroethane as the internal standard. A range represents determinations from several absorption peaks. ^{*d*} Isolated yield. ^{*e*} Purified CuI was employed. ^{*f*} Nonpurified CuI was utilized. Product was isolated in 85% yield. ^{*g*} Reaction was performed with the cuprate derived from *N*-Boc-pyrrolidine (**1**) and dimedone.

iodide. Lithiation of N-Boc-protected piperidine (**4**), however, is more difficult to achieve than with N-Boc protected pyrrolidine (**1**) and shows greater variation from experiment to experiment.

In an effort to obtain crystals of an α -(*N*-carbamoyl)alkylcuprate reagent, pentane was added to Et₂O or THF solutions of the pyrrolidinylcuprate (i.e., R₂CuLi·LiCN) resulting in precipitation of solids at -50 °C. In one case, the solution was allowed to warm to room temperature and left standing overnight to afford a suspension of brown solids. Addition of (*E*)-1-iodo-1-hexene to this suspension afforded **6a** in 80% yield, indicating considerable thermal stability of the cuprate reagent in this THF/ pentane solvent system.

Reaction of the cuprate derived from Boc-protected N,N-dimethylamine (8) with methyl vinyl ketone or dimedone was used to examine the effect of the Cu(I) salt [i.e., $CuX \cdot 2LiCl$ (X = Cl, Br, I, CN)] solubilized by LiCl (eq 4, Table 3). Although the yields in this study are uniformly lower for methyl vinyl ketone than the optimized yields shown in Table 2 and show greater variation, the results indicate that the anionic component of the Cu(I) salt (i.e., Cl, Br, I, CN) has no large effect upon the yield of conjugate adduct for either the RCuCNLi reagent (Table 3, entries 1-4) or the reagent prepared from 2 RLi + CuX·2LiCl (entries 5-8). One experiment using optimized reaction conditions with CuCl gave a very high yield of conjugate adduct (entry 5). Conjugate addition reactions to dimedone with the RCuCNLi reagent gave similar results but in uniformly higher yields

(entries 9–14). It is noteworthy that use of CuI purified by treatment with KI^{1b} resulted in lower yields (entry 11 vs 12) consistent with earlier observations.²²

Given the effect of multiple variables upon the success of these α -(*N*-carbamoyl)alkylcuprate reactions, we reexamined the use of solid CuCN taking careful precautions to form the cuprate reagent from 1. When the solid CuCN was added to a solution of lithiated 1 and the solution was stirred at -78 °C for 45 min a good yield of the vinylation product was obtained and higher yields could be achieved if the solution was briefly warmed to room temperature (Table 4, entries 1-2). Similarly high yields could be achieved with cyclohexenone (entry 3) and methyl crotonate (entries 5-7) with the dialkylcuprate reagent and also with the RCuCNLi reagent in the latter reaction (entry 7). Again, a lower yield was obtained when the solution was maintained between -78 and -50°C (entry 4) indicative of incomplete cuprate formation. The use of commercially available undistilled (-)sparteine appeared to have no deleterious effect upon the methyl crotonate conjugate addition reaction. The use of CuI proved to be significantly less effective than CuCN (entry 8) in the conjugate addition reaction assisted by TMSCl. This is in marked contrast to the use of CuI· 2LiCl (Table 3, entries 3, 7, 11-12) with enones. The use of TMSI in THF is problematic since the principal reaction pathway involves TMSI cleavage of THF. Interestingly, the diastereomeric ratios of the conjugate adduct are reversed with TMSI compared with those obtained with TMSCl.

Since our initial success in the reactions of α -(Ncarbamoyl)alkylcuprates with α , β -unsaturated carboxylic acid derivatives and vinylation reactions with vinyl iodides involved cuprate reagents prepared from CuCN· 2LiCl, the effect of CuX·2LiX combinations on the conjugate addition of lithium di-*n*-butylcuprate to an α,β enoate was examined. Lithium di-n-butylcuprate was prepared (-78 °C, 45 min, THF) from LiX (X = Cl, Br, I, (CN) solubilized CuX (X = Cl, Br, I, CN) and reacted with β -phenethyl crotonate in the presence, or absence, of TMSCl in order to probe the contributing effects of TMSCl, Cu(I) salt, and lithium halide (eq 6, Table 5). Reaction of lithium di-n-butylcuprate prepared from 2 n-BuLi and insoluble CuCN or CuCl in THF, in the absence of TMSCl, gave β -phenethyl 3-methylheptanoate (13) in low yield (Table 5, entries 1-2), while use of CuCl or CuI resulted in *E* to *Z* isomerization of the starting crotonate along with formation of the tertiary alcohol, 4-butyl-2-octen-4-ol (entries 2-3). Cuprates prepared from insoluble CuCN, CuCl, or CuI gave good to excellent yields of conjugate adduct in the presence of TMSCl (entries 4-6), although CuI gave the lowest yield. The yields of the conjugate adducts were slightly obscured by the tendency of the phenethyl esters to hydrolyze under the workup conditions. The cuprate prepared from CuCN· 2LiCl in the absence of TMSCl gave very low yields of product (entry 7). All combinations of CuX (X = CN, Cl, Br, I) and LiX (X = Cl, Br, I) gave excellent yields of the conjugate addition product in the presence of TMSCl (entries 8-13 and 15-17). Reagents prepared from CuX· 2LiCN (X = CN, I) gave only modest yields of product in the presence of TMSCl (entry 14). Very similar results were obtained for the mixed cuprate [n-BuCuCH₂SiMe₃]-

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Table 4. Reaction of Cuprates Derived from 1 Employing Solid CuCN with (E)-1-Iodo-1-hexene, 2-Cyclohexenone, or Methyl Crotonate To Afford, Respectively, 6a, 3, and 11 (Eq 5)



entry	х	CuX (equiv)	cuprate prepn ^a (T(°C), (min))	$(\mathrm{E}^+)^b$	product	% yield ^c
1	CN	0.5	-78 (45)	vinyl iodide	6a	83
2	CN	0.5	-78 (30), then rt (15)	vinyl iodide	6a	98
3	CN	0.5	-78 (30), then rt (15)	enone ^d	3	95^{e}
4	CN	0.5	-78 (30), then -50 (15)	$enoate^d$	11	59
5	CN	0.5	-78 (30), then rt (10)	$enoate^d$	11	>95
6	CN	0.5	-78 (30), then rt (10)	$enoate^d$	11	$> 95^{f}$
7	CN	1.0	-78 (30), then rt (10)	$enoate^d$	11	>95
8	Ι	0.5	-78 (30), then rt (10)	enoateg	11	<25
9	Ι	0.5	-78 (30), then rt (10)	enoate ^{g, h}	11	no product
10	Ι	0.5	-78 (30), then rt (10)	$enoate^d$	11	35

^a Solid CuX was added to the α -(N-carbamoyl)alkyllithium reagent in THF and the mixture stirred at the indicated temperature for the indicated time. ^b The electrophile was added between -65 and -50 °C and slowly warmed to room temperature. ^c Yields were determined by NMR using 1,3,5-tribromobenzene as an internal standard unless otherwise noted. ^d TMSCl (5 equiv) was employed. ^e Based upon isolated product. f(-)-Sparteine was used directly from the commerical bottle without prior distillation. ^gTMSI (5 equiv) was employed. ^h The reaction was conducted in Et₂O.

Table 5. Conjugate Addition of Lithium n-Butyl(trimethylsilylmethyl)cuprate or Lithium Di-n-butylcuprate Prepared from Various Copper Salts Solubilized with Lithium Salts to β -Phenethyl Crotonate in THF^a

<i>n</i> -BuLi	1. CuX·nLiX, THF -78 °C (5 min), 0 °C (5 min)						
(2 equiv)	2. CO ₂ (CH ₂) ₂	Ph (12)	_{3u}	h L _F	'n		
	TMSCI (5 equiv) -78 ^o C,1 h	1	3	14	4		
				% yield	\mathbf{l}^d		
entry	metal salt(s) ^b	additive ^c	12	13	14		
1	CuCN		83	10	7		
2	CuCl		37	9			
3	CuI		33				
4	CuCN	TMSCl		93	6		
5	CuCl	TMSCl		91	4		
6	CuI	TMSCl	8	77	10		
7	CuCN·2LiCl		90	3			
8	CuCN• LiCl	TMSCl		90	10		
9	CuCN·2LiCl	TMSCl		96	5		
10	CuCN•3LiCl	TMSCl	8	91			
11	CuCN·4LiCl	TMSCl	7	91			
12	CuCN·2LiBr	TMSCl		95	0.3		
13	CuCN·2LiI	TMSCl		96	3		
14	CuCN·2LiCN	TMSCl	49	30	21		
15	CuCl·2LiCl	TMSCl		94	2		
16	CuBr•2LiCl	TMSCl		88	5		
17	CuI·2LiCl	TMSCl		94	3		
18	CuI + TMSMLi	TMSCl	14	83			
19	CuI + TMSMLi		85				
20	CuCl + TMSMLi	TMSCl	20	80			
21	CuCl + TMSMLi		85	5			

^a Upon addition of phenethyl crotonate and TMSCl, the reaction mixture was allowed to warm to room temperature over 2 h. ^b The metal salt was dissolved in THF, and the solution was added to *n*-BuLi/THF at -78 °C. ^{*c*} The additive was mixed with phenethyl crotonate and added to the cuprate solution at -78 °C. ^d Yields are based upoon isolated products purified by silica gel chromatography unless otherwise noted.

Li (entries 18–21). Consistent with the α -(*N*-carbamoyl)alkylcuprates, dialkylcuprate reagents prepared from CuX·2LiX or insoluble CuX react with α , β -enoates in comparable yields in the presence of TMSCl.

Discussion

Organocopper reactions are particularly susceptible to a variety of experimental factors. This combination of factors include the particular reaction type,1 copper(I) salt (e.g., CuI, CuCN, CuBr·SMe₂)⁴ and its purity,^{22,23} cuprate reagent^{1,2b} and its thermal stability,² additives (e.g., Lewis acids, TMSCl, HMPA/TMSCl, etc.),^{1,3} solvent,^{22,24} and the instability of these organometallic reagents to moisture and oxygen. Sometimes the effects are counterintuitive. Small amounts of added water are reported to accelerate conjugate addition reactions,²⁵ and laboratory-purified Cul gives lower yields of conjugate adducts than commercially available CuI of high purity.²² The presence of Cu(II) impurities in the Cu(I) salts can accelerate cuprate decomposition.²³ In addition to issues of cuprate preparation and cuprate thermal and chemical stability, the actual cuprate transformation will be subject to experimental variables. The rate of cuprate conjugate addition reactions will be dependent upon the nature of the transferable ligand, the presence and perhaps nature of the lithium salts normally present in cuprate solutions (e.g., LiI, LiBr, LiCl, or LiCN),²² the solvent,^{22,24} and the presence of additives.^{3,22} The reactions of α -(*N*-carbamoyl)alkylcuprates with a given α , β enone often displayed variable yields^{15d} which were attributed to the quality of the s-BuLi, the Cu(I) salt (i.e., CuCN or CuCN·2LiCl), and/or to reagent thermal stability. Although the current study does not clearly reveal

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^{545.}

the origin(s) of this variability, it does reveal a combination of effects that can cumulatively result in low yields.

While the presence of nonalkyllithium bases in the s-BuLi does not have fatal consequences for the subsequent α -(N-carbamoyl)alkylcuprate vinylation and conjugate addition reactions (Table 1), their presence generally diminishes the overall yield of the cuprate transformations even though equivalent amounts of carbamate and s-BuLi are utilized as determined by titration for the latter reagent. The Watson-Eastham titration^{1b,20} gives an accurate determination of alkyllithium concentration in direct comparison with determinations made by the Gilman double-titration^{1b,19} procedure. The formation of less reactive mixed cuprates [e.g., RCuHLi, RCu(O^sBu)Li^{2a}, R = α -(*N*-carbamoyl)alkyl], diminished reactivity of the cuprates in the presence of extraneous bases, and/or accelerated decomposition of the organolithium or cuprate reagents could account for the diminished yields. Vinylation of pyrrolidinylcuprates in the presence s-BuOLi ranges from nearly quantitative (0.6 equiv of s-BuOLi) to low yielding $(\leq 5-33\%$ with 1 equiv), suggesting that less reactive mixed alkoxycuprate reagents come into play when stoichiometric quantities of extraneous bases are present. This is also consistent with the observations that product yields can be increased in the presence of 1 equiv of s-BuOLi by increasing the amount of CuCN·2LiCl. The effect of extraneous bases upon cuprate reactivity is expected to vary with the particular type of cuprate reaction. Lithium ion-carbonyl oxygen coordination^{3g,24a-c,26} is particularly important in cuprate conjugate addition reactions and is reflected in diminution of reaction rates and product yields in the presence of polar solvents (THF, DME),^{24a-c} additives (e.g., HMPA, TMEDA, DMAP),^{3f,3h,27} or heteroatom functionality in the substrate^{26c} that can function as Lewis bases with lithium ions. Conjugate addition reactions fail when crown ethers are added to cuprate solutions unless additional amounts of LiX salts are added.^{26a} The presence of extraneous bases may sequester lithium ions in aggregates involving the basic species alone or as bases complexed to the lithium ions in a cuprate aggregate in a manner analogous to polar solvents and additives. The crude yield data in Table 1 are consistent with a greater sensitivity of the conjugate addition reaction as compared to the vinylation reaction to the presence of extraneous bases, although the mixed alkoxy(alkyl)cuprate did give a far better yield in the conjugate addition reaction (i.e., 60% vs \leq 5-33%). It should be noted that both the presence of TMSCl^{3g} and the use of CuCN·LiCl in the conjugate addition reactions tabulated in Table 1 compensate for the competition^{26b} between enone oxygen and base for lithium ions. This in part could account for the greater variability and capriciousness obtained with cuprates prepared from THF insoluble CuCN and poorer quality s-BuLi (eq 1).15b,d

Although not dramatic, the quality of the *s*-BuLi does appear to be related to the thermal stability of these

cuprate solutions. Cuprates prepared from s-BuLi containing no extraneous bases show little to no decomposition after 2 h at room temperature (Table 2, entries 5-8and 9-12) for both the RCuCNLi and R₂CuLi·LiCN reagents. The rate of decomposition for the cuprate solutions appears to be faster when s-BuLi containing extraneous bases is employed. It is unclear whether this declining reactivity of the cuprate solutions reflects cuprate or α -(*N*-carbamoyl)alkyllithium decomposition. Our studies^{4,28} and the observations of others²⁹ have pointed to the thermal instability of α -(N-carbamoyl)alkyllithium reagents. The known autocatalytic effect of s-BuOLi upon s-BuLi decomposition¹⁸ suggests that extraneous s-BuOLi could accentuate the thermal instability of α -(*N*-carbamoyl)alkyllithium reagents. The extent of α -(*N*-carbamoyl)alkyllithium decomposition would be dependent upon the temperature and rate at which cuprate formation occurs (vide infra). The influence of solvent upon the thermal stability of these cuprate solutions may reflect the solvent influence on a cupratealkyllithium equilibrium.³⁰ The long-term stability of heterogeneous cuprate (12 h, room temperature) containing mixtures obtained by addition of pentane to THF solutions of α -(*N*-carbamoyl)alkylcuprates may arise from the particulate nature of the copper species or from the absence of equilibrium amounts of free alkyllithium components. In this scenario, polar solvents such as THF which favor equilibrium of the cuprate with free alkyllithium should be more problematic than Et₂O, Et₂O/ THF, or THF/pentane combinations. Cuprate/alkyllithium equilibrium was not observed by NMR measurements in Et₂O and in THF solutions containing LiX salts where the dynamic exchange of ligands was too fast to observe on the NMR time scale even at low temperatures.³⁰ Nevertheless, minor amounts of byproducts arising from 1,2-nucleophilic additions to enones^{16b,29} or transmetalation of vinyl halides were not readily apparent in the α -(*N*-carbamoyl)alkyllithium reactions indicating either little or no free α -(*N*-carbamoyl)alkyllithium reagent in these solutions or noncompetitive rates for these pathways due to concentration effects.

The conjugate addition reactivity of α -(*N*-carbamovl)alkylcuprates prepared with high quality s-BuLi was probed with a very reactive methyl vinyl ketone substrate (Table 2). In the absence of TMSCl, the RCuCNLi reagent failed to add to methyl vinyl ketone while the inherently more reactive R₂CuLi·LiCN reagent gave modest to good yields of the 1,4-adduct. Both reagents gave good to excellent yields of the 1,4-adduct in the presence of TMSCl. The inherent reactivity of the cuprates was independent of the mode of preparation since similar yields were obtained when either solid CuCN or CuCN. 2LiCl was employed. Although enone oxygen-lithium ion complexation plays a crucial role in cuprate conjugate addition reactions, the presence of soluble lithium chloride from CuCN·2LiCl does not result in higher yields.²⁶ This is consistent with the observation that cuprate reactivity is greater in conjugate addition reactions in

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the absence of LiX.^{26b} Kinetic isotope effects^{3g} probed by NMR indicate that the large TMSCl induced rate acceleration arises from oxygen silylation of a cuprateenone d– π^* complex and in THF the silylation contribution overwhelms the more modest lithium ion contribution. The TMSCl rate acceleration is not observed in Et₂O and the absence of oxygen silylation in a rate determining step is confirmed by the kinetic isotope studies.^{3f.g}

Although generally not essential for α -(N-carbamoyl)alkylcuprate reactivity (Tables 2 & 4), the use of THF soluble CuX·2LiCl appears to remove some of the capriciousness of these reactions. Utilization of THF soluble CuX·2LiCl permits rapid cuprate formation at -78 °C while use of insoluble CuCN generally requires warming of the THF solution to -50 to -40 °C for some extended period of time or to room temperature for shorter periods of time in order to ensure complete cuprate formation. Excellent yields were obtained with insoluble CuCN when the cold bath (-50 to -40 °C) was removed and the reaction flask was allowed to stand in ambient air (25 °C) for 15 min before cooling back down to -78 °C during the cuprate formation stage. Slow cuprate formation and cuprate formation at higher temperatures will increase the likelihood of decomposition of the less thermally stable α -lithio carbamates. The general variability in product yields with time and temperature formats for cuprate preparation, substrate addition, and subsequent reaction profile (e.g., stir at -40 to -50 °C for a period of time before warming to room temperature vs gradual warming of the reaction mixture from -40 to room temperature) seem consistent with both the rate of cuprate formation and an α -(N-carbamoyl)alkylcuprate/ α -(N-carbamoyl)alkyllithium equilibrium³⁰ that can result in decomposition of the thermally less stable alkyllithium reagent. Reaction rates will vary considerably for each reaction type (i.e., 1,4-addition, vinyl substitution, etc.) and for each substrate-cuprate pair for a given transformation. Slower α -(*N*-carbamoyl)alkylcuprate transformations will benefit from long reaction times at moderately low temperatures (e.g., -50 to -30°C) rather than rapid warming to room temperature. The use of CuCN·2LiCl introduces two opposing effects. By solubilizing the CuCN, the presence of lithium chloride significantly increases the rate of cuprate formation at -78 °C even as the added LiCl facilitates the dynamic exchange of the ligands on copper presumably through the intermediacy of alkyllithium species.³⁰ There is, however, a dramatic difference between solid CuI (25% yield of 11) and CuI·2LiCl (57-94% yields of 9 and 10) that is not understood.

We have also observed in our studies with α,β -enones that reactions using freshly distilled TMEDA give generally higher yields of the conjugate adducts than 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.^{15d} Although the use of CuCN·2LiCl also appeared to minimize the effect of diamine purity [i.e., TMEDA or (–)-sparteine], the capriciousness of any potential diamine effect made it difficult to disentangle it from other factors. While we cannot document the deleterious effects of impurities in the diamines employed to assist in carbamate deprotonation, we would recommend purification by distillation prior to use in α -(*N*- carbamoyl)alkylcuprate reactions coupled with use of CuCN \cdot 2LiCl.

During the course of our efforts to unravel the apparent beneficial use of CuCN·2LiCl for α -(*N*-carbamoyl)alkylcuprate preparation, we examined the reaction of *n*-Bu₂-CuLi prepared from a variety of CuX·nLiX with cinnamyl esters to see if the phenomenon was general (Table 5). The reactivity of *n*-Bu₂CuLi with enoates in THF appears to be largely governed by the presence of TMSCl,^{3g} and previous observations⁴ about reactivity differences for cuprates prepared from CuI, CuBr, or CuCl in the absence of TMSCl raise interesting questions. All combinations of CuX and LiX, with the exception of LiCN, give comparable yields of the conjugate addition product. The difficulty of preparing pure LiCN and the failure of lithium cyanide generated in situ by addition of butyllithium to trimethylsilylcyanide to solubilize CuCN at low temperatures complicates any interpretation of the results obtained with LiCN. This study suggests that variation in chemical yield as a function of CuX reflects the rate and extent of cuprate formation since all soluble combinations of CuX·LiX give comparable results. Nevertheless, the nature of the halide counterion plays a significant role in the extent of asymmetric conjugate additions of chiral amidocuprates³¹ and in allylic substitution reactions.³² The variation in the conjugate addition yields obtained with CuX·2LiCl may reflect subtle influences of the halide counterion that are clearly not well understood.^{3f} Although the trimethylsilylmethyl ligand is an effective nontransferable ligand,³³ it does not appear to greatly accelerate the conjugate addition reaction.³⁴

The successful use of insoluble CuCN in α -(*N*-carbamoyl)alkylcuprate vinylation and enoate conjugate addition reactions (Table 4) suggests that the excess LiCl is not playing a significant role in either reaction. It does not appear that lithium chloride is functioning as an external source of lithium ions and accelerating the conjugate addition reaction by Lewis acid complexation with the carbonyl oxygen. Similarly, the success of the vinylation reaction with solid CuCN suggests that soluble chloride ions are not facilitating the reductive elimination step as has been suggested for the action of TMSCl^{3f} and the behavior of CuX (X = Cl, Br, I) in allylic substitution³² reactions.

Finally, the difficulty of executing α -(*N*-carbamoyl)alkylcuprate transformations raised questions about their inherent reactivity. In a previous study, the α -(*N*carbamoyl)alkyl and methyl ligands of a mixed cuprate reagent, RCuMeLi (R derived from **8**), were transferred with nearly equal facility (i.e., 51% for R and 41% for Me) upon reaction with 2-cyclohexenone.^{15d} Additionally, the higher yields of conjugate adducts obtained with *N*-Boc pyrrolidinylcuprates as compared to *N*-Boc-*N*methyl(aminomethyl)cuprates with ester substrates suggests that the α -(*N*-carbamoyl)alkyl ligand is comparable in reactivity to the corresponding alkyl ligands.⁸ Nevertheless, α -(*N*-carbamoyl)alkylcuprate fail to transfer the α -(*N*-carbamoyl)alkyl ligand in some cases (e.g., α , β -

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unsaturated lactones) where simple lithium dialkylcuprates succeed.

Summary

In summary, α -(*N*-carbamoyl)alkylcuprate reactions afford good yields of products in conjugate addition, vinylation, and acylation reactions even with poor quality s-BuLi and with either relatively insoluble CuCN or THFsoluble CuCN·2LiCl. Excellent product yields can be achieved by utilizing high quality s-BuLi and THF soluble CuCN·2LiCl which ensures rapid cuprate formation at -78 °C. Insoluble CuCN also affords excellent product yields if extended time periods are used for cuprate formation at -78 °C (≥ 45 min) or the reaction flask is allowed to stand at ambient air temperature for short periods of time (10-15 min) before cooling back to -78 °C. Lower quality s-BuLi (i.e., containing LiH and lithium alkoxide impurities) appears to increase the rate of cuprate and/or α -(*N*-cabamoyl)alkyllithium decomposition and high quality s-BuLi can be easily prepared with FMC's Lithium Powder-Stabi-Li-ze. The α-(N-carbamoyl)alkylcuprates examined display good thermal stabilities (i.e., up to 71–98% yields after aging the cuprates for 2 h at room temperature) when prepared under optimal conditions in marked contrast to the α -(Ncabamoyl)alkyllithium reagents. Difficulties in executing the transformations appear to revolve around the thermal instabilities of the lithium reagents which can be minimized with the protocols described above. With these caveats in mind, the reactions of α -(*N*-carbamoyl)alkylcuprates are reliable and should prove to be useful reagents for synthetic endeavors.

Experimental Section

All glassware was flame dried under vacuum or an atmosphere of argon prior to use. Sparteine, TMEDA, and vinyl iodides were distilled under reduced (Kugelruhr) pressure prior to use. THF and Et_2O were distilled from Na/benzophenone under an atmosphere of N₂ immediately prior to use. LiCl was flame dried under vacuum immediately prior to use.

Preparation of s-Butyllithium. The preparation must be carried out under an atmosphere of argon as lithium metal reacts with nitrogen. Finely powdered lithium metal (7.8 g, 1.12 mmol, FMC's Stabi-Li-ze) was added cautiously to degassed dry cyclohexane (200 mL) in a large argon-purged three- or four-neck round-bottomed flask fitted with a mechanical stirrer, a dry ice condenser, a pressure-equalizing addition funnel, and a thermometer to directly measure the reaction temperature. A petroleum ether/dry ice cold bath was prepared to control reaction temperature if necessary. The suspension was stirred vigorously for 5 min and warmed to 40 °C using a heat gun. The pressure-equalizing addition funnel was charged with dry s-BuCl (43 mL, 0.40 mol). Approximately 7% of the s-BuCl was added with vigorous stirring and the reaction mixture warmed (if necessary) in order to attain a temperature of 52 ± 3 °C. The remainder of the s-BuCl was then added dropwise with constant supervision over 45–60 min at such a rate that the reaction temperature was maintained at 52 \pm 3 °C. It is essential to keep the reaction temperature below 60 °C [NOTE: Beware of unpredictable initiation period.] After complete addition of s-BuCl the reaction mixture was allowed to cool to room temperature with stirring. The cool solution was transferred by cannular into a Schlenk apparatus to allow filtration through a pad of vacuum/flame dried Celite while maintaining an argon atmosphere. A further extraction of the residual solids was carried out with additional dry cyclohexane. The product was obtained as a clear, colorless solution and the s-BuLi content was found

to be 1.51 M (total base content 1.54 M) by Gilman double titration. A larger scale reaction based on 1.9 mol Li and 0.8 mol *s*-BuCl gave 370 mL of clear colorless product (1.7 M).

The solution may be stored (frozen) at -20 °C for several months with little degradation or loss of activity. If desired, pentane (10% by volume) may be added to lower the freezing point of the solution.

Procedure for Gilman Double Titration. A 1 mL portion of the organometallic reagent was added (cautiously) to water (about 10 mL) and a few drops of phenolphthalein solution were added as an indicator. This purple (due to base) solution was titrated with standardized 0.1 M hydrochloric acid [standardized using a NaOH solution, itself standardized using dry potassium hydrogen phthalate as the primary standard] to the persistent (after 30 s of swirling) colorless endpoint permitting calculation of the total base content of the organometallic solution.

A second 1 mL portion of the organometallic reagent was added to about 1 mL of dry 1,2-dibromoethane (stored over activated sieves) under an inert, dry, atmosphere and stirred for 15 min at room temperature to ensure complete reaction. Addition of water (10 mL) by syringe followed by stirring for 5 min before opening to the atmosphere afforded a solution which was titrated with the standardized 0.1 M HCl (using phenolphthalein indicator as above) to give the non organometallic base content.

N-Boc-2-[(E)-1-hexenyl]pyrrolidine (6a). (–)-Sparteine (0.23 mL, 1.0 mmol) was added to a solution of N-Bocpyrrolidine (1) (171 mg, 1.0 mmol) in THF (3 mL) at room temperature and mixed until homogeneous. After the mixture was cooled to -78 °C, s-BuLi (1.1 mmol) was added in one portion and the reaction mixture stirred at -78 °C for 30 min. Meanwhile, a solution of CuCN·2LiCl in THF was prepared from CuCN (46 mg, 0.5 mmol), LiCl (50-60 mg, 1.15-1.4 mmol), and THF (3 mL) under an inert atmosphere. This copper solution was added by syringe to the reaction mixture and the solution stirred at -78 °C for 30 min. After warming to -50 °C, neat 1-iodohex-1-ene (106 mg, 0.5 mmol) was added, and the mixture stirred at -50 °C for 30 min before quenching with saturated aqueous NH₄Cl at -50 °C. The reaction mixture was diluted with Et₂O and filtered through a pad of flash silica and washed with saturated aqueous NH_4Cl (×2). The aqueous washings were extracted with Et₂O and the combined organic extracts dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to yield the crude product 6a as a pale yellow oil (typical yield 80-90%) as determined by isolation (column chromotography) or by ¹H NMR measurements using an internal standard: IR (neat) 1702 (vs), 970 (w), 885 (w) cm^{-1} ; ¹H NMR δ 0.90 (t, 3 H), 1.03-1.41 (m, 4 H), 1.43 (s, 9 H), 1.59-1.79 (m, 1 H), 1.79-1.85 (m, 2H), 1.85-2.11 (m, 3H), 3.37 (br s, 2 H), 4.20 [4.41] (br s, 1 H) [rotamer], 5.34 (br s, 1 H), 5.43 (br s, 1 H); $^{13}\mathrm{C}$ NMR δ 13.7, 21.9, 22.8 (br), 28.2, 31.3, 31.6, 32.2 (br), 45.9 (br), 58.3 (br), 78.7, 130.0 (2 C), 154.7; mass spectrum *m*/*z* (intensity) EI 197 $(25, M^+ - C_4H_8), 196 (15, M^+ - C_4H_9), 180 (17, M^+ - C_4H_9O),$ 152 (6, $M^+ - C_4 H_9 CO_2$). Anal. Calcd for $C_{15} H_{27} NO_2$: C, 71.15; H, 10.67. Found: C, 70.88; H, 10.60.

N-Boc-2-[(E)-1-hexenyl]piperidine (6b). Freshly distilled TMEDA (0.35 mL, 2.3 mmol) was added to a solution of Bocprotected pyrrolidine (4) (185 mg, 1.0 mmol) in Et₂O (3 mL) at room temperature and the solution mixed until homogeneous. After the mixture was cooled to -78 °C, s-BuLi (1.2 mmol) was added in one portion and the reaction mixture stirred at -78 °C for 4 h. A solution of CuCN·2LiCl in THF was prepared from CuCN (46 mg, 0.5 mmol), LiCl (50-60 mg, 1.15-1.40 mmol), and THF (3 mL) under an inert atmosphere. This copper solution was added by syringe to the reaction mixture and the solution stirred at -78 to -65 °C over 1 h. Neat 1-iodo-1-hexene (106 mg, 0.5 mmol) was added and the reaction mixture stirred overnight at -65 °C to room temperature before quenching with saturated aqueous NH4Cl. Workup procedure involved dilution with Et₂O and filtration through a pad of silica before washing with saturated aqueous NH_4Cl (×2). Aqueous washings were extracted with further Et₂O and the combined organic portions dried (anhydrous MgSO₄) and concentrated under reduced pressure to yield the crude product as a pale yellow oil. Chemical yield (82%) of the desired product (**6b**) was determined by ¹H NMR spectroscopy using an internal standard: IR (neat) 1702 (vs), 1679 (shoulder), 978 (w), 876 (w) cm⁻¹; ¹H NMR δ 0.73–0.93 (m, 3 H), 1.13–1.80 (m, 9 H), 1.38 (s, 9 H), 1.89–2.07 (m, 2 H), 2.75 (t, J = 12.8 Hz, 1 H), 3.28 (br s, 1 H), 3.84 (d, J = 12.0 Hz, 1 H), 4.66 (br s, 1H), 5.27–5.45 (m, 2H); ¹³C NMR δ 13.9, 19.5, 22.1, 25.6, 28.5, 29.4, 31.5, 32.1, 39.6, 51.9, 79.1, 128.1, 131.9, 155.4; mass spectrum, *m*/*z* (relative intensity) EI 211 (20, M⁺ – C₄H₈), 194 (17, M⁺ – C₄H₉O), 166 (21, M⁺ – C₄H₉CO₂). Anal. Calcd for C1₆H₂₉NO₂: C, 71.91; H, 10.86; N, 5.24. Found: C, 72.07; H, 11.03; N, 5.09.

Methyl 1-[(1,1-Dimethylethoxy)carbonyl]- β -methyl-2pyrrolidinepropanoate (11). (–)-Sparteine (0.15 mL, 0.65 mmol) was added to a solution of *N*-Boc-pyrrolidine (1) (86 mg, 0.5 mmol) in THF (3 mL) at room temperature and mixed until homogeneous. After the mixture was cooled to -78 °C, *s*-BuLi (1.1 mmol) was added in one portion and the reaction mixture stirred at -78 °C for 60 min. With the reaction mixture under an argon atmosphere, solid CuCN (46 mg, 0.5 mmol) was quickly added in one portion. The reaction mixture was stirred at -78 °C for 30 min. The cold bath was then removed, and the flask was allowed to stand at ambient air temperature for 15 min after which the flask was immersed in the -78 °C cold bath. After 15 min at ambient temperature, clear nearly colorless to pale yellow solutions were obtained. Methyl crotonate (51 μ L, 0.5 mmol) and TMSCl (0.32 mL, 2.5 mmol) were added as a neat mixture via syringe, and the reaction mixture was stirred overnight at -78 °C to room temperature before quenching with saturated aqueous NH₄Cl. Workup procedure involved dilution with Et₂O and filtration through a pad of silica before washing with saturated aqueous NH₄Cl (×2). Aqueous washings were extracted with further Et₂O and the combined organic portions dried (anhydrous MgSO₄) and concentrated under reduced pressure to yield the crude product as a colorless to pale yellow oil in nearly quantitative yields. Spectral data for the corresponding ethyl ester can be found in ref 8c.

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