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Acylation of α-(*N*-carbamoyl)alkylcuprates and alkyl- or aryl(halo)cuprates

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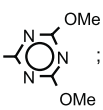
Abstract—α-(*N*-Carbamoyl)alkylcuprates [$R_2CuLi{\cdot}LiX$ or $RCuXLi$ (X=CN, Cl)] when prepared from THF soluble $CuX{\cdot}2LiCl$ (X=Cl, CN) undergo a reliable and generally high yield reaction with aroyl, alkanoyl, and alkenoyl chlorides to provide a rapid and efficient synthesis of α-carbamoyl ketones. Cuprates prepared from acyclic, cyclic, and a functionalized carbamate can be utilized. Although yields are a function of cuprate reagent and substrate structure, nearly quantitative yields can be obtained with reagents generated from 2RLi+CuCN·2LiCl. The use of reagents generated from CuCl·2LiCl are more efficient in the α-(*N*-carbamoyl)alkyl ligand, although yields are slightly lower. Acylation of alkyl(chloro)cuprates generated from one equivalent of CuCl·2LiCl and organolithium or Grignard reagents provides an efficient and high yield procedure for ketone synthesis.

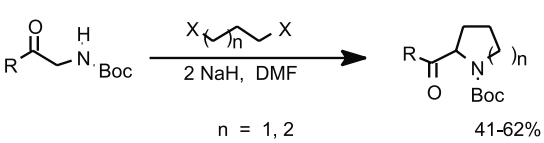
1. Introduction

The chemistry and reactivity of organometallic reagents has often been probed by reaction with acid chlorides and the long history of the reaction mirrors the development of organometallic chemistry.[1] Gilman first reported the acylation of an organocopper reagent[2] in 1936 and this was followed by Whitesides utilization of lithium dialkylcuprates[3] in 1967. Shortly thereafter, Posner and Riviere developed the reaction for the preparation of ketones.[4] Despite its apparent simplicity, successful high yield acylation of organocuprates often required the use of 2–3 equiv. of the copper reagents, although improvements were achieved by use of mixed phenylthio heteroatom cuprates containing a non-transferable ligand.[5] Several groups have recently reported that organocopper species prepared from Grignard or organolithium reagents and 1 equiv. of CuX·2LiX undergo efficient acylation with acid chlorides in good to excellent yields.[6–8] In this full account, we report on the acylation of α-(*N*-carbamoyl)alkylcuprates which provides a rapid synthetic entry to protected α-amino ketones.[8]

α-Amino ketones[9] and their nitrogen protected derivatives are important intermediates for the synthesis of nitrogen heterocycles,[10] physiologically active ethanolamine derivatives[11,12] and peptidyl compounds.[13] Although numerous synthetic routes to these compounds exist, the aziridination of enol ethers[14] and the reaction of α-amino acids and their derivatives (Weinreb amides,[10b,c,15] thiol esters,[10a,16] esters,[17] imidazolides[18] and esters derived from 2-chloro-4,6-dimethoxy[1,3,5]triazine[19]) with organometallic reagents provide particularly convenient procedures (Eq. (1)). The former route offers opportunities for catalytic asymmetric aziridination[14c] while the latter routes can exploit the chiral pool. 2-Acylpyrrolidines and piperidines have been prepared by bis-alkylation of *N*-Boc α-amino ketones with dihalides (Eq. (2)).[11] They have also been prepared by the reaction of α-aminoalkyllithium reagents with aldehydes followed by oxidation with the Dess–Martin reagent.[20] The present method reverses the nucleophile/electrophile components used in the coupling process reacting carbon nucleophiles containing an α-carbamoyl group with acid chlorides.

P = Boc; X = NMe(OMe); RM = $Me_3SiC{\equiv}CMgBr$ 60 % [10c]
P = Cbz; X = SEt; RM = $IZn(CH_2)_3CO_2Et/PdCl_2(PPh_3)_2$ 64 % [16]
P = Boc; X = S(2-pyridyl); RM = Me_2CuLi 70 % [10a]
P = Cbz; X =  ; RM = EtMgBr/CuI 95 % [19]

(1)



n = 1, 2 41-62% [11]

(2)

Keywords: acylation; deprotonation; aryl cuprates; α-(*N*-carbamoyl)alkylcuprates.

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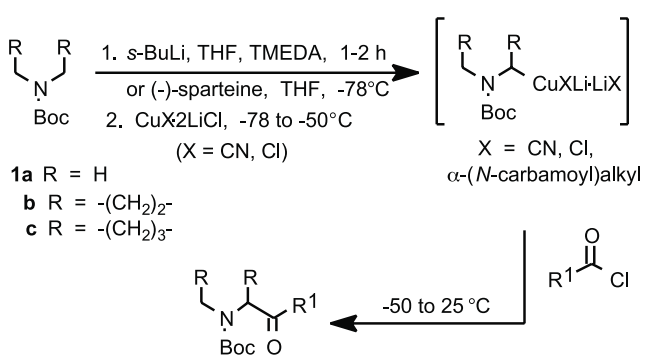
2. Results and discussion

The α-(*N*-carbamoyl)alkylcuprates were prepared by sequential deprotonation[21] of carbamates **1a–c** followed by addition of a THF solution of CuX·2LiCl (X=CN, Cl). Solid CuCN was employed in the initial efforts to effect acylation of α-(*N*-carbamoyl)alkylcuprates and variable and capricious yields of α-carbamoyl ketones were obtained.[22] The dialkylcuprate or alkylcyanocuprate (i.e. RCuCNLi) derived from **1a** gave poor to modest yields upon reaction with benzoyl (25 and 40%, respectively) or propionyl chloride (R_2CuLi, 46%) while the dialkylcuprate derived from **1b** fared better (57–77%) with propionyl chloride. A subsequent investigation of α-(*N*-carbamoyl)alkylcuprate preparation and reactivity found that good yields of vinylation products could be obtained if a careful and rigid warming and cooling protocol was followed to insure complete formation of the cuprate reagent.[23] Utilization of THF soluble CuX·2LiCl permits rapid cuprate formation at −78°C thereby avoiding the necessity of using higher reaction temperatures with the thermally unstable α-lithio carbamates.[23] This study also showed that commercial samples of *s*-BuLi containing particulates (presumably LiH) are not lethal to the reaction, although yields are diminished. Treatment of the cuprate solutions in THF with the acid chlorides [neat addition, −78 to 25°C, 4 h] followed by quenching with saturated ammonium chloride afforded the corresponding α-carbamoyl ketones (Scheme 1).

Reaction of α-(*N*-carbamoyl)alkylcuprates with alkanoyl acid chlorides afforded α-carbamoyl ketones in variable yields depending upon the cuprate reagent and substrate structure (Table 1). The highest yields were obtained with lithium dialkylcuprates (e.g. R_2CuLi) and diminished with utilization of alkylcyanocuprate reagents (i.e. RCuCNLi, Table 1, entries 1 vs 2, 12 vs 11, 17 and 18 vs 19). The reagent prepared from CuCl (1.0 equiv.) generally gave higher yields than the cyanocuprate reagent (3 vs 2, 20 vs 19), although the dialkylcuprates gave slightly higher yields, in one instance, when prepared from CuCN rather than CuCl (entries 24 vs 25). Although copper reagents prepared from CuCl (1.0 equiv.) gave good yields of α-carbamoyl ketones (i.e. 62–96%), higher yields were again obtained with dialkylcuprates derived from CuCl (entries 25 vs. 26). These results suggest that the use of one equivalent of CuCl gives rise to a chlorocuprate reagent (i.e. RCuClLi) that is more reactive than the cyanocuprate reagent RCuCNLi.[23] This is consistent with the observation that the coupling of allylic substrates with organocuprates



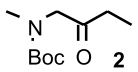
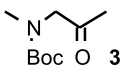
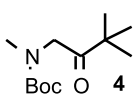
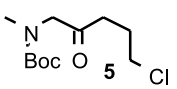
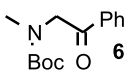
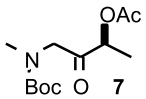
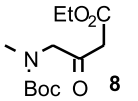
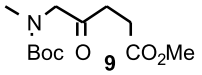
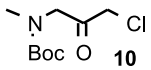
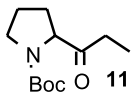
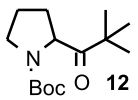
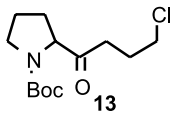
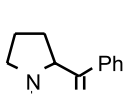
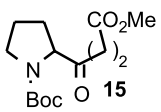
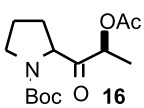
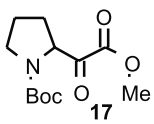
Scheme 1. Acylation of α-(*N*-carbamoyl)alkycuprates

increase in the series CuCl>CuBr>CuI and has been attributed to a rate acceleration in the reductive elimination with increasing electronegativity of the ligands on the transition metal.[24] Recent mechanistic investigations suggest that reductive elimination is the rate determining step in conjugate addition reactions.[25] Nevertheless, this difference between CuCl and CuCN was not observed in the reactions of simple alkyl or aryl cuprates with acid chlorides (vide infra, Table 3).

Cuprates derived from **1a** and **1b** give comparable yields of α-carbamoyl ketones with simple alkanoyl chlorides (entries 1–3 vs 17–20, 5, 6 vs 21, 7, 8 vs 22, 23, and 9, 10 vs 24–26), although those derived from **1a** give low to modest yields with acid chlorides containing electron withdrawing substitutents at the α-position and/or easily enolizable substrates (entries 11, 12 vs 28 and 13 and 16). Functionalized ketones **5** and **13** were obtained in modest yields as previously reported, although the structures were incorrectly drawn in the preliminary communication.[8] The notoriously difficult α-chloro acetyl chloride[26] derived ketone (**10**) is obtain in modest yield with the **1a** derived cuprate reagent (entry 16). The cuprates derived from **1b** give good yields with a variety of functionalized alkanoyl acid chlorides (entries 17–29), although a low yield was obtained with the easily enolizable ethyl 3-chloro-3-oxopropionate (entry 30). These results are consistent with the generally lower reactivity of primary alkylcuprate reagents compared to secondary alkylcuprate reagents. A cuprate reagent derived from **1c** gave a modest yield of α-carbamoyl ketone when reacted with pivaloyl chloride (entry 31) and may reflect either the difficulty of deprotonating *N*-Boc piperidine[21] or the increased steric factors in piperdinylcuprate reagents. Acylation of the cuprate derived from **1b** with methyl 4-chloro-4-oxobutyrate gave **15** in good yields (entry 27) which could provide a potential route to indolizidinones. Conditions for the cyclization of **15** or the *N*-Boc deprotected pyrrolidinium salts to the indolizidine carbon skeleton, however, were not found. The salts were readily obtained by treatment of **15** with PhOH/TMSCl (25%), CF_3COOH (80%) or CF_3SO_2H (85%) in CH_2Cl_2. The reaction with ethyl oxalyl chloride provides a simple synthesis of β-*N*-carbamoyl-α-keto esters (i.e. **17**) employed in the preparation of α-diketones of interest as enzyme inhibitors.[27] The current methodology could potentially lead to the α-diketones directly via acylation of α-(*N*-carbamoyl)alkylcuprates with α-keto acid chlorides.

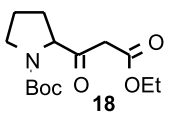
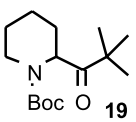
The reaction of organocuprate reagents with alkenoyl chlorides is potentially fraught with chemoselectivity problems since the product α,β-enones can undergo conjugate addition reactions with the cuprate reagent.[4b,26,28] The reaction of α-(*N*-carbamoyl)alkylcuprates derived from **1a**, **b** with alkenoyl chlorides gave modest to good yields of α′-carbamoyl-α,β-enones (Table 2). Slightly lower yields of α-carbamoyl ketones were obtained from the primary alkylcuprate derived from **1a** than from the secondary alkylcuprate derived from **1b** (entries 1, 2 vs 6, and 3 vs 8). Again, the dialkylcuprate reagents gave higher yields than monoalkylcuprate reagents (entries 5 vs 6 and 7 vs 8). β,β-Di-unsubstituted alkenoyl chlorides or thiol esters gave very low yields of

Table 1. Acylation of α-(*N*-carbomoyl)alkyl copper and cuprate reagents

Entry	Boc[a] amine	acid chloride RCOCl	CuX·2LiCl X (equiv.)[b]	Product	%[c] yield
1	**1a**	Et	CN (0.5)		98[d]
2	**1a**		CN (1.0)		55
3	**1a**		Cl (1.0)	**2**	85[d]
4	**1a**	Me[d]	CN (1.0)	 **3**	81[e]
5	**1a**	^{t}Bu	Cl (1.0)		96[f]
6	**1a**	^{t}Bu	Cl (1.0)	 **4**	95
7	**1a**	$Cl(CH_2)_3$–	Cl (1.0)		68[f]
8	**1a**	$Cl(CH_2)_3$-	Cl (1.0)	 **5**	63
9	**1a**	Ph	CN (0.5)	 **6**	100
10	**1a**		Cl (1.0)		73[d]
11	**1a**		CN (1.0)		25
12	**1a**		CN (0.5)	 **7**	44
13	**1a**	EtO_2CCH_2–	CN (1.0)	 **8**	31
14	**1a**	$MeO_2C(CH_2)_2$–	CN (1.0)		42
15	**1a**		CN (0.5)	 **9**	42
16	**1a**	$ClCH_2$	Cl (1.0)	 **10**	41
17	**1b**	Et	CN (0.5)		100
18	**1b**		CN (0.5)		91[f]
19	**1b**		CN (1.0)		55
20	**1b**		Cl (1.0)	 **11**	70[d]
21	**1b**	^{t}Bu	Cl (1.0)	 **12**	88
22	**1b**	$Cl(CH_2)_3$	Cl (1.0)		62
23	**1b**	$Cl(CH_2)_3$	Cl (1.0)	 **13**	52[f]
24	**1b**	Ph	CN (0.5)		100
25	**1b**		Cl (0.5)		89–93
26	**1b**		Cl (1.0)	 **14**	62[d]–65
27	**1b**	$MeO_2C(CH_2)_2$	Cl (1.0)	 **15**	74
28	**1b**		CN (1.0)	 **16**	77
29	**1b**	MeO_2C	Cl (1.0)	 **17**	76

(*continued on next page*)

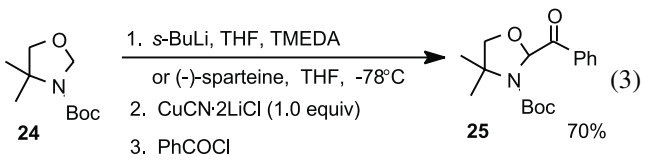
Table 1 (*continued*)

Entry	Boc[a] amine	acid chloride RCOCl	CuX·2LiCl X (equiv.)[b]	Product	%[c] yield
30	**1b**	CH_2CO_2Et	CN (1.0)	 **18**	18
31	**1c**	^{t}Bu	CN (1.0)	 **19**	45

[a] The carbamate was deprotonated [*sec*-BuLi, THF, (−)-sparteine unless noted, −78°C, 1–2 h] and added to the Cu(I) salt at −50°C unless noted.
[b] Equivalents of Cu(I) relative to RLi.
[c] Yields are based upon purified isolated products unless otherwise noted.
[d] Cuprate was formed at −78°C followed by addition of acid chloride after 15–20 min. at −78°C.
[e] Acyl bromide was employed.
[f] TMEDA was used to facilitate deprotonation.

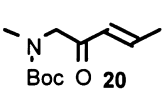
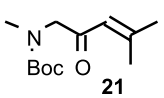
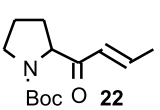
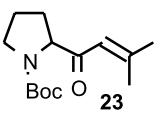
α′-carbamoyl-α,β-enones. Reaction of the alkylcyanocuprate (i.e. RCuCNLi) derived from **1b** with methacryloyl chloride gave low yields of the ketone (14%) while reaction of the R_2CuLi reagent with the corresponding phenylthiol ester gave only the homocoupling product of the 2-pyrrolidinyl ligand (28%). The procedure could also not be usefully extended to α,β-alkynoyl chlorides as the α′-carbamoyl-α,β-ynones were obtained in low yields. TLC analysis indicated the formation of many products and the failure of these reactions appears to reflect the greater reactivity of the product alkynones under the reaction conditions.

Extension of the method to more complex carbamates and acid chlorides was briefly examined. α-(*N*-carbamoyl)alkylcuprates were not acylated by chloroformates (e.g. ethyl or phenyl) or anhydrides (e.g. succinic or maleic). Cuprates derived from *N*-Boc 1,2,3,6-tetrahydropyridine or 1,2,3,4-tetrahydropyridine were not successfully acylated with propionyl chloride reflecting the problematic nature of allylic cuprate reagents[29] and the difficulty of deprotonating *N*-Boc encarbamates.[30] Although Martin[30] found that employing the *N*-2,4,6-triisopropylbenzenesulfonyl (Trs) protecting group for 2,3-dihydropyrrole permitted facile deprotonation and cuprate formation, we were unable to effect acylation of the cuprate reagent. A cuprate reagent derived from a *N*-Boc protected 4,4-dimethyloxazolidine was successfully acylated with benzoyl chloride in 70% yield (Eq. (3)). The acylation of α-(*N*-carbamoyl)alkylcuprates derived from scalemic oxazolidines would provide a rapid access to 2-acyloxazolidines[31a] which have been employed in an asymmetric synthesis of scalemic α-hydroxy aldehydes.[31]



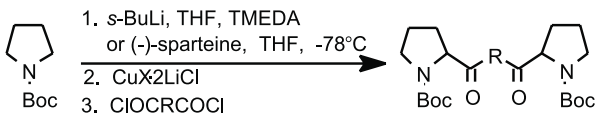
(3)

Table 2. Acylation of α-(*N*-carbamoyl)alkylcuprate reagents with α,β-alkenoyl chlorides

Entry	Boc amine[a]	Acid chloride RCOCl	CuX·2LiCl X (equiv.)[b]	Product	%[c] Yield
1	**1a**	MeCH=CH	Cl (1.0)	 **20**	55
2	**1a**	MeCH=CH	Cl (1.0)		50[d]
3	**1a**	Me_2C=CH	Cl (1.0)	 **21**	46–53
4	**1b**	MeCH=CH	CN (0.5)	 **22**	70–84
5	**1b**	MeCH=CH	Cl (0.5)		84–91
6	**1b**	MeCH=CH	Cl (1.0)		60
7	**1b**	Me_2C=CH	CN (0.5)	 **23**	99
8	**1b**	Me_2C=CH	Cl (1.0)		50–57
9	**1b**	Me_2C=CH	Cl (1.0)		75[e]

[a] The carbamate was deprotonated [*sec*-BuLi, THF, (−)-sparteine unless noted, −78°C, 1–2 h] and added to the Cu(I) salt at −50°C unless noted.
[b] Equivalents of Cu(I) relative to RLi.
[c] Yields are based upon purified isolated products unless otherwise noted.
[d] Cuprate was formed at −78°C followed by addition of acid chloride after 15–20 min at −78°C.
[e] TMEDA was used to facilitate deprotonation.

The reaction of α-(*N*-carbamoyl)alkylcuprates with bis-acid chlorides was briefly examined since the resultant *N*-heterocycles linked by various spacers could provide monomer precursors for novel polymers. The reaction of the cuprate derived from **1b** with terephthaloyl chloride afforded the diketone in modest yields (i.e. 45%) that decreased with increasing reaction times (i.e. 30–34%) (Eq. (4)). Slightly higher yields could be achieved using 1 equiv. of CuBr·LiBr[6,7] or CuCl·2LiCl. A significant amount (20–30%) of starting carbamate **1b** was generally recovered. The corresponding bis phenylthiol ester of terephthalic acid gave comparable yields of **26a** with various cuprates [RCuCNLi (60%), R_2CuLi·LiCN (66%), RCuBrLi (53%)] derived from CuCN·2LiCl or CuBr·2LiCl. Utilization of oxyal chloride or succinoyl chloride afford complex mixtures containing numerous by-products as indicated by many spots upon TLC analysis. A maximum yield of **26b** (21%) was obtained with succinoyl chloride and the dialkylcuprate (i.e. R_2CuLi) derived from **1b** along with significant amounts (15%) of the **1b** homodimer. The yields of **26b** were lower when the bis phenylthiol ester of succinic acid was employed.



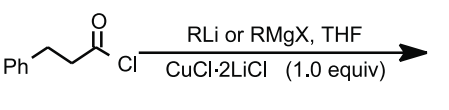
(4)

R	CuX·2LiY	product	% yield
$-C_6H_4-$	CuCN·2LiCl	**26a**	45
	CuBr·2LiBr		60
	CuCl·2LiCl		57
$-(CH_2)_2-$	CuCN·2LiCl	**26b**	7
	CuBr·2LiBr		15
	CuBr·2LiCl		8

During the early development of α-(*N*-carbamoyl)alkylcuprate chemistry, a difference in chemical yields was sometimes observed that was attributed to a differential influence of the diamines employed to facilitate deprotonation of the starting carbamates.[23] A brief examination of the question was undertaken. Under the reaction conditions where CuX·2LiCl was used for cuprate formation, no significant difference in chemical yields could be discerned when either freshly distilled or older TMEDA or (−)-sparteine was employed (Table 1, entries 5 vs 6, 7 vs 8, 18 vs 17 and 23 vs 22).

Enantioselective acylation was briefly examined since pyrrolidinylcuprates (e.g. R_2CuLi·LiCN) are configurationally stable under certain reaction conditions.[32] Earlier efforts to effect asymmetric acylation with acid chlorides were repeatedly unsuccessful and a series of substrates were examined in an effort to achieve some selectivity. The reactions of a thiol ester, acyl cyanide, and acyl iodide [e.g. PhCOX (X=CN, SPh, I)] with the scalemic lithium di-2-pyrrolidinylcuprate reagent gave good chemical yields (72–100%) but no enantioselectivity. Thus, the acylation and conjugate addition reactions of α-(*N*-carbamoyl)alkylcuprates give low to no eantionselectivity in marked contrast to the high asymmetric induction observed in the vinylation reactions.[32] Although the product *N*-Boc protected α-amino ketones can undergo racemization, the failure of the acylation reactions to give any enantiomeric excess is not understood.

The necessity of generally employing 2–3 equiv. of lithium dialkylcuprates for good yields in acylation reactions[5,33] and the reduced reactivity of phenylthio mixed cuprates[33] prompted a brief examination of alkyl(chloro)cuprates derived from CuCl·2LiCl and organolithium or Grignard reagents (Eq. (5)). Excellent yields of ketones were obtained with either the lithium or magnesium aryl or alkyl(chloro)-cuprates. The lowest yield was obtained with the *tert*-butylcuprate and compares very favorably with the lithium *tert*-butyl(phenylthio)cuprate offered as the most effective reagent for acylation of *tert*-butylcuprates.[5] This procedure is highly efficient since the alkyl ligand is completely utilized and only one equivalent of cuprate reagent is required. In contrast to simple alkyl or aryl ligands, magnesium α-(*N*-carbamoyl)alkylcuprates were less effective than their lithium counterparts. Treatment of α-lithio carbamates derived from **1a**, **b** with $MgBr_2$ (generated in situ from Mg and 1,2-dibromoethane) followed by 1.0 equiv. of CuCl·2LiCl afforded the magnesium cuprates that gave modest yields of α-carbamoyl ketones upon acylation with propionyl chloride (i.e. 39% from **1a** and 60% from **1b**). This reflects both the lower reactivity of magnesium cuprates and of α-(*N*-carbamoyl)alkylcuprates. The latter appear to be slightly lower in reactivity than the corresponding simple alkylcuprate reagents.



(5)

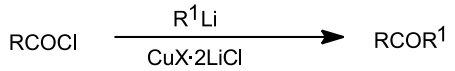
R	product	RLi	RMgX
n–Bu	**27a**	90	96
t–Bu	**27b**	72	–
s–Bu	**27c**	82	89
Ph	**27d**	90	87

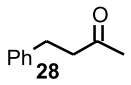
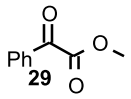
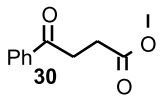
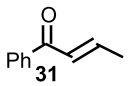
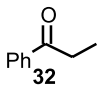
Cuprate reagents can be prepared from a variety of Cu(I) salts and CuCN and $CuBr{\cdot}SMe_2$ have been promoted as the most effective cuprate precursors.[34] Chemical yields and selectivity are often times a function of the Cu(I) salt employed in cuprate formation.[34] As we had previously observed[23] in the conjugate addition and vinylation reactions of α-(*N*-carbamoyl)alkylcuprates little significant difference is observed for various Cu(I) salts when they are used in the THF soluble CuX·2LiCl form (Table 3). Both the less reactive MeCuXLi or more reactive PhCuXLi gave comparable yields of ketones with acid chlorides (entries 1–6). The only exception appeared to involve alkenoyl chlorides where the cyanocuprate reagent gave higher yields (entries 8 vs 9).

3. Summary

α-(*N*-Carbamoyl)alkylcuprates prepared at −78°C with

Table 3. Acylation of alkyl and arylcuprates with CuX·2LiCl (1.0 equiv.)



Entry	R	R^1	X	Product	% Yield
1	$Ph(CH_2)_2-$	Me	Cl		35
2			Br		30
3			I		30
4			CN		40
5	MeOCOCO–	Ph	Cl		72
6			CN		79
7	$MeO_2C(CH_2)_2-$	Ph	Cl		61
8	MeCH=CH-	Ph	Cl		25
9			CN		40
10	Et	Ph	Cl		78

THF soluble CuX·2LiCl (X=CN, Cl) are readily acylated in high yields with a variety of alkanoyl, aroyl, and alkenoyl chlorides to afford *N*-Boc protected α-amino ketones. α-Heteroatom or α-carboalkoxy substituents in the acid chloride result in diminished yields of protected α-amino ketones. The procedure fails for alkynoyl chlorides and generally low yields are obtained with β,β-di-unsubstituted alkenoyl chlorides and bis acid chlorides. The free primary or secondary amino ketones are generally unstable and the method provides a short and reliable route to α-amino ketones in protected form. Reaction of lithium or magnesium alkyl(chloro)cuprates (i.e. RCuClLi) prepared from THF soluble CuCl·2LiCl provides excellent yields of ketones employing one equivalent of the reagent. This protocol is efficient in alkyl ligand and provides a practical and useful alternative to lithium dialkylcuprates prepared from other Cu(I) salts. The latter reagents generally require 2–3 equiv. of reagent for good to excellent chemical yields.

4. Experimental

4.1. General

^1H NMR and ^{13}C NMR spectra were recorded using a Brucker AC 300 (300 MHz) or JEOL 500 MHz spectrometer in deuterated chloroform. Gas chromatography-mass spectroscopy (GC–MS) was performed using Hewlett–Packard 5890A gas chromatograph coupled to a Hewlett–Packard 5970B mass selective detector at 70 eV. Infrared spectra were recorded on either a Magna 550 FT-IR or a Nicolet 5DX spectrometer by using thin film of neat liquid sample. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel plates with F-254 indicator. Visualization was accomplished by UV light (254 nm), saturated ethanol solution of phosphomolybdic acid or *p*-anisaldehyde, or iodine. Preparative thin-layer chromatography was performed on 20 cm×20 cm Merck silica gel plates visualized by UV light (254 nm). Column chromatography (gravity or flash) was performed by using silica gel (60–200 meshes or 200–400 meshes) and the eluent as indicated in the text. Elemental analyses were done by Atlantic Microlab, Inc. Norcross, Georgia, USA via supplying samples which were purified by preparative TLC or by MPLC.

The benzyl carbamate derived from the methyl ester of proline displays a barrier to rotation [$\delta G^{\ddagger}$=17.1–17.4 kcal/mol] that is relatively insensitive to solvent.[35] A $\delta G^{\ddagger}$=17.4 kcal/mol corresponds to a coalescence temperature of 87.3°C while a value of $\delta G^{\ddagger}$=16.7 corresponds to 61.4°C for coalescence.[36] Compounds containing the *N*-Boc carbamate functionality generally display absorptions in the ^1H and ^{13}C NMR spectra attributable to rotomers arising from restricted rotation about the C–N bond. Additional absorptions due to rotamers are indicated within parentheses.

4.2. Materials

Reaction flasks used in organocopper and cuprate experiments were cleaned with 48% hydrobromic acid, rinsed with copious amount of water, washed with acetone and then dried in an oven (180°C) overnight. All copper reactions were conducted under a positive, dry nitrogen atmosphere in anhydrous solvents in flasks fitted with rubber septa secured with parafilm. Flask to flask transfers of air sensitive intermediates or starting materials were made using double-tipped needles (cannula) under a positive argon pressure maintained by double layered balloons filled with argon. All reagents were obtained from commercial sources and used without further purification unless mentioned elsewhere. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium and benzophenone (dark blue-purple color) under a nitrogen atmosphere. Products **14**,[11] **27a**,[37] **27b**,[38] **27c**,[39] **27d**,[40] **31**[41] and the methyl ester corresponding to **18**[42] are reported in the literature while compounds **28–30** are commercially available.

4.3. General procedure A (2RLi+CuCN)

A solution of *N*-Boc-carbamate (1.0 mmol) in 3.0 mL of diethyl ether was cooled to −78°C and treated with (−)-sparteine (0.25 mL, 1.1 mmol) and *sec*-BuLi (0.91 mL, 1.1 mmol). The mixture was stirred for 1 h between −78°C and −60°C then transferred to a suspension of CuCN (0.045 g, 0.50 mmol) in 3.0 mL THF at −60°C via cannula. The reaction mixture was slowly warmed to −50°C over 30 min and then treated with the acid chloride (0.50 mmol) in THF (2.0 mL) via cannula. The mixture was stirred at −50°C for 10–15 min and then quickly warmed to 0°C, stirred for an additional 10 min and then quenched with H_2O (2.0 mL) and filtered through celite. The mixture was extracted with diethyl ether (3×15 mL) and the combined extracts were washed with saturated aqueous NH_4Cl (5.0 mL), dried over $MgSO_4$ and then concentrated in vacuo.

4.4. General procedure B (RLi+CuCN·2LiCl)

A solution of *N*-Boc-carbamate (0.50 mmol) in 3 mL of THF was cooled to −78°C and treated with sparteine (0.12 mL, 0.55 mmol) and *sec*-BuLi (0.46 mL, 0.55 mmol). The mixture was stirred for 1 h at −78°C. To the solution was added a premixed homogenous solution of CuCN (0.044 g, 0.50 mmol) and LiCl (0.042 g, 1.0 mmol) in 4.0 mL THF via cannula. The reaction mixture was stirred at −78°C for 30–40 min and then treated with the acid chloride (0.50 mmol) in THF (2.0 mL) via cannula. The mixture was stirred at −78°C for 35 min, quickly warmed to room temperature, stirred for 30 min, quenched with H_2O (2.0 mL) and then filtered through celite. The mixture was extracted with diethyl ether (3×15 mL) and the combined extracts were washed with saturated aqueous NH_4Cl (5.0 mL), dried over $MgSO_4$ and concentrated in vacuo.

4.5. General procedure C (RLi+CuCl·2LiCl)

A solution of *N*-Boc-carbamate (0.54 mmol) in 3.0 mL of THF was cooled to −78°C and treated with (−)-sparteine (0.138 mL, 0.597 mmol) and *sec*-BuLi (0.52 mL, 0.60 mmol). The mixture was stirred for 1 h at −78°C. To the solution was added a premixed homogenous solution of CuCl (0.052 g, 0.58 mmol) and LiCl (0.048 g, 1.2 mol) in 4 mL THF via cannula. The reaction mixture was stirred at −78°C over 10 min and then treated with the acid chloride (0.08 mL, 0.60 mmol) in THF (2.0 mL) via cannula. The mixture was then quickly warmed to room temperature and stirred for an additional 10–15 min, quenched with H_2O (2.0 mL) and then filtered through celite. The mixture was extracted with diethyl ether (3×15 mL) and the combined extracts were washed with saturated aqueous NH_4Cl (5.0 mL), dried over $MgSO_4$ and concentrated in vacuo.

4.6. General procedure D (2RLi+CuCN·2LiCl)

A solution of *N*-Boc-carbamate (1.0 mmol) in 3.0 mL of THF was cooled to −78°C and treated with sparteine (0.25 mL, 1.1 mmol) and *sec*-BuLi (0.91 mL, 1.1 mmol). The mixture was stirred for 1 h at −78°C. To the solution was added a premixed homogeneous solution of CuCN (0.045 g, 0.50 mmol) and LiCl (0.042 g, 1.0 mmol) in 4.0 mL of THF via cannula. The reaction mixture was slowly warmed to −55°C over 60 min and then treated with the acid chloride (0.10 mL, 1.1 mmol) in THF (2.0 mL) via cannula. The mixture was stirred at −50°C for 10 min and then quickly warmed to room temperature and stirred for an additional 30 min, quenched with H_2O (2.0 mL) and filtered through celite. The mixture was extracted with diethyl ether (3×15 mL) and the combined extracts were washed with saturated aqueous NH_4Cl (5.0 mL), dried over $MgSO_4$ and concentrated in vacuo.

4.6.1. 1,1-Dimethylethyl methyl(2-oxobutyl)carbamate (2). General procedure D was employed (**1a**, 0.115 g, 0.796 mmol). Purification of the crude product by medium pressure liquid chromatography (20% ether/pet. ether) gave 0.079 g (98%) of **2** as a colorless liquid: IR 1702 (s), 1472 (m), 1395 (s), 1251 (m), 1166 (s), 893 (m) cm^{-1}; ^1H NMR for rotamers (minor) δ 0.95–1.10 (m, 3H), 1.35 (1.40) (s, 9H), 2.34 (two overlapping q, J=6.9 Hz, 2H), 2.82 (2.85) (s, 3H), 3.86 (3.95) (s, 2H); ^{13}C NMR for rotamers (minor) δ 7.22 (7.42), (28.1) 28.2, (32.5) 32.5, 35.6, 57.5 (58.2), 79.9, (155.3) 156.0, 207.0; mass spectrum, *m*/*z* (relative intensity) EI 201 (0.3, M^+), 144 (16, $M^+-C_4H_9$), 116 (0.1), 89 (0.7), 88 (9), 57 (100, C_4H_9). Anal. calcd for $C_{10}H_{19}NO_3$: C, 59.70; H, 9.45; N, 6.96. Found: C, 59.45; H, 9.42; N, 6.93.

4.6.2. 1,1-Dimethylethyl methyl(2-oxopropyl)carbamate (3). General procedure B and acetyl bromide were employed (**1a**, 0.15 g, 1.0 mmol). Purification of the crude material by flash column chromatography (20% diethyl ether/pet. ether, v/v) gave **3** (0.14 g, 81 %): IR (neat) 3592 (br, m), 2973 (s), 2936 (s), 2332 (w), 1737 (s), 1711 (s), 1480 (s), 1455 (s), 1396 (s), 1251 (s), 1183 (s), 894 (s), 775 (s), 579 (m), 536 (s) cm^{-1}; ^1H NMR for rotamers (minor) δ 1.37 (1.42) (s, 9H), 2.08 (s, 3H), 2.84 (2.88) (s, 3H), 3.87 (3.96) (s, 2H); ^{13}C NMR for rotamers (minor) δ 26.6 (26.8), 28.2 (28.3), 35.6, 58.4 (59.1), 80.1, 155.3, (156.0), 204.5; mass spectrum *m*/*z* (relative intensity) EI 144 (29), 131 (5), 114 (13), 88 (11), 70 (12), 57 (100). Anal. calcd for $C_9H_{17}NO_3$: C, 57.8; H, 9.10; Found: C, 56.6; H, 9.10.

4.6.3. 1,1-Dimethylethyl methyl(3,3-dimethyl-2-oxobutyl)carbamate (4). General procedure C was employed (**1a**, 0.15 g, 1.0 mmol). Purification of the crude material by medium pressure liquid chromatography (20% ether/pet. ether) gave 0.221 g (96%) [with (−)-sparteine, obtained 95% yield] of **4** as a colorless oil: IR 1702 (s), 1455 (w), 1412 (s), 1378 (w), 1259 (s), 1166 (s), 1055 (w), 885 (s), 791 (m) cm^{-1}; ^1H NMR for rotamers (minor) δ 1.12 (s, 9H), 1.34 (1.41) (s, 9H), 2.78 (2.81) (s, 3H), 4.07 (4.15) (s, 2H); ^{13}C NMR for rotamers (minor) δ 26.2 (26.3), 28.2 (28.3), 35.4 (35.6), 42.8 (42.9), 53.1 (53.7), 79.6, 155.5 (156.1), (209.9) 210.4; mass spectrum, *m*/*z* (relative intensity) EI 172 (6, $M^+-C_4H_9$), 144 (27, $M^+-C_5H_9O$), 130 (0.3, $M^+-C_6H_{11}ON$), 116 (2, $M^+-C_6H_{11}ON$), 100 (11), 88 (10), 70 (0.4), 57 (100, C_4H_9). Anal. calcd for $C_{12}H_{23}NO_3$: C, 62.88; H, 10.04; N, 6.11. Found: C, 62.92; H, 10.03; N, 6.01.

4.6.4. 1,1-Dimethylethyl methyl(5-chloro-2-oxopentyl)-carbamate (5). General procedure B was employed (**1a**, 0.059 g, 0.41 mmol). Purification of the crude product by medium pressure (20% ether/pet. ether) liquid chromatography gave 0.06 g (63%) [with TMEDA, 68% yield] of **5** as a colorless oil: IR 1702 (s), 1659 (w), 1557 (w), 1489 (w), 1463 (w), 1395 (m), 1251 (m), 1174 (s), 893 (m), 783 (m) cm^{-1}; ^1H NMR for rotamers (minor) δ 1.35 (1.41) (s, 9H), 2.01 (p, J=6.6 Hz, 2H), 2.51 (t, J=7.2 Hz, 2H), 2.84 (2.86) (s, 3H), 3.50–3.63 (m, 2H), 3.88 (3.96) (s, 2H); ^{13}C NMR for rotamers (minor) δ 25.9, 28.1 (28.2), 28.3, 35.8 (36.1), 44.1 (44.2), 57.9 (58.6), 80.0, 155.2 (156.0), 205.6; mass spectrum, *m*/*z* (relative intensity) EI 249 (0.3, M^+), 176 (6, $M^+-C_4H_9O$), 150 (0.6), 144 (23), 105 (0.3), 88 (11), 57 (92, C_4H_9), 44 (100). Anal. calcd for $C_{11}H_{20}ClNO_3$: C, 52.90; H, 8.01; N, 5.61; Cl, 14.22. Found: C, 53.04, H, 7.92; N, 5.51; Cl, 14.38.

4.6.5. 1,1-Dimethylethyl methyl(2-phenyl-2-oxoethyl)-carbamate (6). General procedure D was employed (**1a**, 0.10 g, 0.71 mmol). Purification of the crude material by medium pressure liquid chromatography (20% ether/pet. ether) gave 0.089 g (100%) of **6** as a colorless liquid: IR

1710 (s), 1608 (w), 1497 (s), 1463 (s), 1412 (s), 1242 (s), 1166 (s), 1005 (m), 893 (m), 766 (m) cm^{-1}; ^1H NMR for rotamers (minor) δ (1.26) 1.38 (s, 9H), 2.83 (2.86) (s, 3H), 4.48 (4.58) (s, 2H), 7.24–7.55 (m, 3H), 7.81 (7.93) (d, J=7.8 Hz, 2H); ^{13}C NMR for rotamers (minor) δ 28.1 (28.3), 35.5, 55.0 (55.6), 79.9, 127.6 (127.8), 128.2, 128.6 (128.7), 129.9, 133.2 (133.4), 135.1, 155.6 (156.2), 194.7 (195.0); mass spectrum, *m/z* (relative intensity) EI 249 (0.4, M^+), 193 (12, $M^+-C_4H_8$), 150 (1), 144 (46), 105 (83), 77 (32) 57 (100, C_4H_9). Anal. calcd for $C_{14}H_{19}NO_3$: C, 67.47; H, 7.63. Found: C, 67.68; H, 7.66.

4.6.6. (*S*)-1,1-Dimethylethyl methyl(3-acetoxy-2-oxobutyl)carbamate (7). General procedure B was employed (**1a**, 0.15 g, 1.0 mmol). Purification of the crude material by flash column chromatography (20% diethyl ether/pet. ether, v/v) gave **7** (0.065 g, 25 %): IR (neat) 2978 (m), 2945 (m), 2353 (w), 1741 (s) 1693 (s), 1458 (m), 1243 (s), 1153 (s), 885 (m), 776 (m) cm^{-1}; ^1H NMR for rotamers (minor) δ 1.24–1.51 (m, 12H), 2.07 (2.08) (s, 3H), 2.83 (2.84) (s, 3H), 3.99–4.16 (m, 2H), 5.07 (q, J=6.4 Hz, 1H); ^{13}C NMR for rotamers (minor) δ 16.0 (16.1), 20.5, 28.1 (28.2), 35.6, 54.8 (55.4), 72.9 (73.2), 80.1, 155.3 (155.9), 170.2, 203.1 (203.8); mass spectrum *m/z* (relative intensity) EI 223 (2), 203 (6.5), 144 (25.5), 126 (17), 115 (13), 88 (14), 57 (100). Anal. calcd for $C_{12}H_{21}NO_5$: C, 55.59; H, 8.11; N, 5.40. Found: C, 55.55; H, 8.19; N, 5.30.

4.6.7. Ethyl 4-[[(1,1-dimethylethoxy)carbonyl]methylamino]-3-oxobutyrate (8). General procedure B was employed (**1a**, 0.15 g, 1.0 mmol). Purification of the crude material by flash column chromatography (20% diethyl ether/pet. ether, v/v) gave **8** (0.081 g, 31 %): IR (neat) 2979 (m), 2249 (w), 1750 (s), 1725 (s), 1693 (s), 1396 (s), 1157 (s), 740 (s), cm^{-1}; ^1H NMR for rotamers (minor) δ 1.23 (t, J=7.1 Hz, 3H), 1.36 (1.41) (s, 9H), 2.84 (2.86) (s, 3H), 3.38 (3.39) (s, 2H), 3.96–4.22 (m, 4H); ^{13}C NMR for rotamers (minor) δ 14.0, 28.1 (28.2), 35.6, 46.1 (46.3), 58.1 (58.7), 61.4, 80.2 (80.4), 153.2 (156.0), 166.6 (166.8), 198.9 (199.1); mass spectrum *m/z* (relative intensity) EI 259 (0.1, M^+), 203 (18), 186 (11), 158 (11), 144 (29) 114 (10), 88 (22), 57 (100). Anal. calcd for $C_{12}H_{21}N0_5$: C, 55.60; H, 8.10; N, 5.4. Found: C, 55.47; H, 8.30; N, 5.38.

4.6.8. Methyl 5-[[(1,1-dimethylethoxy)carbonyl]methylamino]-4-oxopentanoate (9). General procedure B was employed (**1a**, 0.15 g, 1.0 mmol). Purification of the crude material by flash column chromatography (20% diethyl ether/pet. ether, v/v) gave **9** (0.109 g, 42 %): IR (neat) 2979 (m), 2255 (m), 1733 (vs), 1694 (vs), 1455 (s), 1175 (vs), 912 (vs), 733 (vs), 655 (m) cm^{-1}; ^1H NMR for rotamers (minor) δ 1.36 (1.41) (s, 9H), 2.51–2.83 (m, 4H), 2.84 (2.87) (s, 3H), 3.62 (s, 3H), 3.92 (4.00) (s, 2H); ^{13}C NMR for rotamers (minor) δ 27.4, 28.1 (28.4), 33.8 (33.9), 35.7, 51.7, 57.9 (58.6), 80.1, 155.3 (156.0), 172.8 (173.0), 205.1; mass spectrum *m/z* (relative intensity) EI 203 (16), 186 (11, $M^+-C_3H_50_2$) 172 (20, $M^+-C_4H_70_2$), 88 (17) 57 (100). Anal. calcd for $C_{12}H_{21}NO_3$: C, 55.60; H, 8.11; N, 5.40. Found: C, 55.40, H 8.14; N, 5.38.

4.6.9. 1,1-Dimethylethyl methyl(3-chloro-2-oxopropyl)carbamate (10). General procedure C was employed (**1a**, 0.15 g, 1.0 mmol). Purification of the crude material by flash column chromatography (20% diethyl ether/pet. ether, v/v) gave **10** (0.092 g, 41 %): IR (neat) 2974 (m), 2247 (w), 1739 (s), 1694 (s), 1482 (s), 1455 (s), 1396 (s), 1251 (s), 1166 (s), 918 (s), 732 (s) cm^{-1}; ^1H NMR for rotamers (minor) δ 1.38 (1.43) (s, 9H), 2.88 (2.90), (s, 3H), 3.92–4.22 (m, 4H); ^{13}C NMR for rotamers (minor) δ 28.2 (28.3), 35.8, 45.8 (46.2), 56.0 (56.4), 80.4, 155.1 (156.0), 198.6 (198.8); mass spectrum *m/z* (relative intensity) EI 221 (0.5, M^+), 150 (5), 144 (30), 88 (10), 57 (100). Anal. calcd for $C_9H_{16}ClNO_3$: C, 48.8; H, 7.20; N, 6.30. Found: C, 49.75; H, 7.54; N, 6.67.

4.6.10. *N*-(*tert*-Butoxycarbonyl)-2-(1-oxopropyl)pyrrolidine (11). General procedure B was employed [**1b** (0.085 g, 0.50 mmol), THF (3.0 mL), (−)-sparteine (0.12 mL, 0.55 mmol), *s*-BuLi (0.46 mL, 0.55 mmol), CuCN (0.044 g, 0.50 mmol) and LiCl (0.042 g, 1.0 mmol) in 4.0 mL THF]. Purification of the crude material by medium pressure liquid chromatography (20% ether/pet. ether) gave 0.061 g (55%) of **11** as a colorless liquid: IR 1702 (s), 1472 (w), 1412 (s), 1259 (m), 1174 (m), 1123 (m), 885 (m), 783 (m) cm^{-1}; ^1H NMR for rotamers (minor) δ 1.02–1.16 (m, 3H), 1.40 (1.46) (s, 9H), 1.74–1.96 (m, 3H), 2.08–2.29 (m, 1H), 2.35–2.61 (m, 2H), 3.40–3.61 (m, 2H), 4.25 (4.35) (dd, J=4.5, 8.4 Hz, 1H); ^{13}C NMR for rotamers (minor) δ 7.27 (7.37), 23.5 (24.2), 28.1 (28.2), (28.8) 30.1, 31.4 (32.2), 46.5 (46.7), 64.3 (64.8), 79.5 (79.8), 153.7 (154.4), 210.5; mass spectrum, *m/z* (relative intensity) EI 227 (0.8, M^+), 170 (22, $M^+-C_3H_5O$), 154 (8), 128 (13), 114 (92), 82 (2), 70 (100, C_4H_8N), 57 (80, C_4H_9). Anal. calcd for $C_{12}H_{21}NO_3$: C, 63.43; H, 9.25; N, 6.16. Found: C, 63.22; H, 9.19; N, 6.09.

4.6.11. *N*-(*tert*-Butoxycarbonyl)-2-(2,2-dimethyl-1-oxopropyl)pyrrolidine (12). General procedure C was employed [**1b** (0.13 g, 0.76 mmol), 3.0 mL THF, sparteine (0.18 mL, 0.83 mmol), *sec*-BuLi (0.70 mL, 0.83 mmol), CuCl (0.078 g, 0.79 mmol) and LiCl (0.067 g, 1.6 mmol) in 4.0 mL THF]. Purification of the crude material by medium pressure liquid chromatography (20% ether/pet. ether) gave 0.17 g (88%) of **12** as a colorless oil: IR 1702 (s), 1566 (w), 1472 (w), 1421 (s), 1174 (m), 1131 (w) cm^{-1}; ^1H NMR for rotamers (minor) δ 1.16 (1.17) (s, 9H), 1.35 (1.37) (s, 9H), 1.55–2.00 (m, 3H), 2.00–2.30 (m, 1H), 3.30–3.78 (m, 2H), 4.65–4.78 (m, 1H); ^{13}C NMR for rotamers (minor) δ 22.9 (24.0), 26.8 (27.3), 28.4 (28.5), 29.9 (30.6), 42.9 (43.3), 46.7 (46.9), 59.4 (60.1), 79.1 (79.8), 153.6 (153.9), 213.4 (214.7); mass spectrum, *m/z* (relative intensity) EI 170 (24, $M^+-C_5H_9O$), 156 (0.1), 138 (5), 126 (3), 114 (96), 85 (1), 70 (100), 57 (90, C_4H_9). Anal. calcd for $C_{14}H_{25}NO_3$: C, 65.88; H, 9.80; N, 5.49. Found: C, 65.66; H, 9.70; N, 5.49.

4.6.12. *N*-(*tert*-Butoxycarbonyl)-2-(4-chloro-1-oxobutyl)pyrrolidine (13). General procedure C was employed (**1b**, 0.09 g, 0.53 mmol). Purification of the crude material by medium pressure liquid chromatography (20% ether/pet. ether) gave 0.085 g (62%) [with TMEDA, 52% yield] of **13** as a colorless oil: IR 1702 (s), 1659 (w), 1574 (w), 1421 (s), 1370 (w), 1259 (w), 1174 (m) cm^{-1}; ^1H NMR for rotamers (minor) δ 1.36 (1.41) (s, 9H), 1.72–1.93 (m, 4H), 1.94–2.27 (m, 4H), 2.50–2.77 (m, 2H), 3.50–3.63 (m, 2H), 4.20 (4.30) (dd, J=4.5, 9.3 Hz, 1H); ^{13}C NMR for rotamers (minor) δ 23.6 (24.4), 25.9, (28.2) 28.3, (28.4) 29.9, 34.8 (35.6), 44.2

(44.4), 46.7 (46.8), (64.7) 65.3, (79.8) 80.1, 153.8 (154.4), (209.1) 209.2; mass spectrum, *m/z* (relative intensity) EI 202 (4), 170 (14, $M^+-C_4H_6ClO$), 158 (3), 140 (0.6), 114 (68), 105 (6, C_4H_6ClO), 70 (100, C_4H_8N), 57 (93, C_4H_9).

4.6.13. *N*-(*tert*-Butoxycarbonyl)-2-(1-phenyl-1-oxomethyl)pyrrolidine (14). General procedure D was employed (**1b**, 0.12 g, 0.67 mmol). Purification of the crude material by medium pressure liquid chromatography (20% ether/pet ether) gave 0.091 g (100%) of **14** as a colorless oil: IR 1702 (s), 1651 (sh), 1455 (w), 1404 (s), 1242 (m), 1174 (m), 1123 (m), 1012 (m), 885 (m), 791 (m), 714 (m) cm^{-1}; ^1H NMR for rotamers (minor) δ 1.18 (1.38) (s, 9H), 1.80–1.96 (m, 3H), 2.11–2.38 (m, 1H) 3.38–3.69 (m, 2H), 5.12 (5.26) (dd, J=3.6, 9.0 Hz, 1H), 7.30–7.58 (m, 3H), 7.74–7.88 (m, 2H); ^{13}C NMR for rotamers (minor) δ 23.4 (24.0), 28.0 (28.3), (29.6) 30.7, 46.4 (46.6), (60.9) 61.6, (79.4) 79.6, 127.9 (128.3), (128.4) 128.5, 133.1, (134.9) 135.0, 153.7 (154.3), (198.2) 198.7; mass spectrum, *m/z* (relative intensity) EI 275 (0.1, M^+), 202 (4, $M^+-C_4H_9O$), 170 (29), 158 (9), 114 (88), 105 (47), 70 (100, C_4H_8N), 57 (90, C_4H_9).

4.6.14. Methyl 1-[(1,1-dimethylethoxy)carbonyl]-γ-oxo-2-pyrrolidinebutanoate (15). General procedure C was employed (**1b**, 0.17 g, 1.0 mmol). Purification of the crude material by medium pressure liquid chromatography (20% ether/pet. ether) gave 0.21 g (74%) of **15** as a colorless liquid: IR 1736 (s), 1696 (s), 1650 (w), 1394 (s), 1210 (w), 1170 (m), 1124 (w) cm^{-1}; ^1H NMR for rotamers (minor) δ 1.30 (1.35) (s, 9H), 1.70–1.93 (m, 3H), 1.93–2.18 (m, 1H), 2.37–2.60 (m, 2H), 2.60–2.79 (m, 2H), 3.35–3.50 (m, 2H), 3.55 (3.57) (s, 3H), 4.17 (4.25) (dd, J=5.1, 8.4 Hz, 1H); ^{13}C NMR for rotamers (minor) δ 23.4 (24.2), 27.0, 28.0 (28.1), (28.6) 29.6, 33.0 (33.5), 46.5 (46.7), (51.4) 51.6, (64.5) 65.0, (79.5) 80.0, 153.6 (154.4), 172.8 (173.1), (208.3) 208.4; mass spectrum *m/z* (relative intensity) EI 212 (9, $M^+-C_4H_9O$), 198 (15), 170 (24), 154 (4), 136 (3), 114 (78), 88 (4), 70 (100), 57 (70, C_4H_9). Anal. calcd for $C_{14}H_{23}NO_5$: C, 58.94; H, 8.07. Found: C, 59.01; H, 8.07.

4.6.15. 2-(1-Oxo-3-carbomethoxyprop-1-yl)pyrrolidine, hydrochloride salt. Treatment of **15** (0.14 g, 0.50 mmol) with phenol (1.42 g, 15.0 mmol) and TMSCl (0.64 mL, 5.0 mmol) in CH_2Cl_2 at room temperture for 30 min followed by solvent removal in vacuo afforded a residue that was dissolved in THF, cooled in liquid N_2 and slowly warmed to 25°C. Excess phenol was removed under Kugelrohr distillation and a colorless solid was obtained (0.026 g, 25%): ^1H NMR δ 1.82–2.35 (m, 3H), 2.38–2.68 (m, 2H), 2.73–3.12 (m, 3H), 3.37–3.60 (m, 2H), 3.67 (s, 3H), 4.72–4.92 (m, 1H), 8.52 (br s, 1H), 10.25 (br s, 1H). ^{13}C NMR δ 23.7, 27.2, 28.1, 34.0, 45.9, 51.9, 65.2, 172.7, 203.3. Utilization of trifluoroacetic acid or trifluoromethane sulfonic acid in CH_2Cl_2 afforded the corresponding amine salts in 80 and 85% yields, respectively.

4.6.16. *N*-(*tert*-Butoxycarbonyl)-2-(2-acetoxy-1-oxopropyl)pyrrolidine (16). General procedure B was employed (**1b**, 0.17 g, 1.0 mmol). Purification of the crude material by flash column chromatography (20% diethyl ether/pet. ether, v/v) gave **16** (0.219 g, 77%): IR (neat) 3626 (br,w), 2980 (s), 2250 (w), 1739 (s), 1702 (s), 1404 (s), 1243 (s), 1175 (s), 1106 (s), 1047 (s), 765 (m), 693 (m) cm^{-1}; ^1H NMR for two diastereomers δ 1.27–1.51 (m, 12H), 1.66–2.22 (m, 7H), 3.22–3.55 (m, 2H), 4.41–4.58 (m, 1H), 5.08–5.36 (m, 1H); ^{13}C NMR for two diastereomers plus rotamers (minor) δ 15.9 (16.3, 16.6), 20.5 (20.7), 22.9 (23.2, 23.9, 24.1), 28.3 (28.5), 29.5, 46.5 (46.7), 61.6 (61.8, 62.0, 62.1), 72.3 (72.5, 73.0), 79.5 (79.8, 80.0, 80.2), 153.5 (153.7, 154.2, 154.5), 169.7 (170.1, 170.2), 204.9 (205.8, 206.4, 207.6); mass spectrum *m/z* (relative intensity) EI 212 (3), 197 (5), 170 (53), 114 (100), 70 (98), 57 (69); Anal. calcd for $C_{14}H_{23}NO_5$: C, 58.9; H, 8.1; N, 4.9 Found: C, 58.77; H, 8.13; N, 4.89.

4.6.17. Methyl 1-[(1,1-dimethylethoxy)carbonyl]-α-oxo-2-pyrrolidineacetate (17). General procedure C was employed (**1b**, 0.17 g, 1.0 mmol). Purification of the crude material by medium pressure liquid chromatography (20% ether/pet. ether) gave 0.190 g (76%) of **17** as a colorless oil: IR 1736 (s), 1696 (s), 1591 (m), 1400 (s), 1256 (m), 1164 (s), 1065 (m) cm^{-1}; ^1H NMR for rotamers (minor) δ 1.30 (1.35) (s, 9H), 1.74–2.08 (m, 3H), 2.05–2.40 (m, 1H), 3.45 (t, J=7.5 Hz, 2H), 3.70 (3.81) (s, 3H), 4.71 (4.81) (dd, J=5.7, 8.7 Hz, 1H); ^{13}C NMR for rotamers (minor) δ 23.5 (24.3), 27.8 (28.1), (28.8) 29.9, 46.4 (46.5), 52.7, (62.0) 62.3, (80.0) 80.4, 153.0 (154.2), (160.7) 161.0, (192.3) 193.0; mass spectrum *m/z* (relative intensity) EI 202 (0.6), 170 (14, $M^+-C_3H_3O_3$), 156 (1), 128 (14), 114 (54), 97 (1), 70 (96), 57 (100, C_4H_9). Anal. calcd for $C_{12}H_{19}NO_5$: C, 56.03; H, 7.39. Found: C, 55.86; H, 7.45.

4.6.18. Ethyl 1-[(1,1-dimethylethoxy)carbonyl]-β-oxo-2-pyrrolidinepropanoate (18). General procedure B was employed (**1a**, 0.15 g, 1.0 mmol). Purification of the crude material by flash column chromatography (20% diethyl ether/pet. ether, v/v) gave **18** (0.052 g, 18 %): IR (neat) 2987 (s), 2254 (m), 1755 (s), 1726 (s), 1702 (s), 1404 (s), 1175 (s), 919 (s), 740 (s), 655 (s) cm^{-1}; ^1H NMR for rotamers (minor) δ 1.23 (t, J=7.1 Hz, 3H), 1.38 (1.41) (s, 9H), 1.74–2.24 (m, 4H), 3.32–3.59 (m, 4H), 4.07–4.46 (m, 3H); ^{13}C NMR for rotamers (minor) δ 14.0, 23.7 (24.4), 28.2 (28.3), 29.7, 45.2, 46.7 (46.9), 61.2 (61.3), 65.0 (65.5), 80.1 (80.6), 153.7 (154.8), 166.9 (167.2), 202.6 (203.0); mass spectrum *m/z* (relative intensity) EI 285 (0.1, $M^+-C_3H_5O_2$) 170 (25, M^+-$C_5H_7O_3$), 114 (92), 70 (100), 57 (74). Anal. calcd for $C_{14}H_{23}NO_5$: C, 58.90; H, 8.10; N, 4.90. Found: C, 58.77; H, 8.16; N, 4.70.

4.6.19. *N*-(*tert*-Butoxycarbonyl)-2-(2,2-dimethyl-1-oxopropyl)piperidine (19). General procedure B was employed (**1c**, 0.19 g, 1.0 mmol). Purification of the crude material by flash column chromatography (20% diethyl ether/pet ether, v/v) gave **19** (0.12 g, 45%): IR (neat) 2978 (s), 2366 (w), 2255 (w), 1711 (vs), 1472 (s) 1370 (s), 1249 (s), 1159 (s), 570 (m) cm^{-1}; ^1H NMR δ 1.17 (s, 9H), 1.40 (s, 9H), 1.46–1.96 (m, 5H), 3.19–3.38 (m, 2H), 3.88 (br, 1H), 5.11 (br, 1H); ^{13}C NMR for rotamers (minor) δ 19.3, 24.9, 26.0, 27.1, 28.4, 40.6 (42.2), 43.5, 54.1 (55.6), 79.7, 155.4, 215.9 (216.1); mass spectrum *m/z* (relative intensity) EI 196 (3), 184 (14, $M^+-C_5H_90$), 140 (6), 128 (100), 84 (67, $M^+-C_{10}H_9O_3$), 57 (61). Anal. calcd for $C_{15}H_{27}NO_3$: C, 66.91; H, 10.04, N, 5.20. Found: C, 66.82 H, 10.20 N, 5.31.

4.6.20. 1,1-Dimethylethyl methyl[(*E*)-2-oxo-3-pentenyl]-carbamate (20). General procedure C was employed (**1a**,

0.07 g, 0.48 mmol). Purification of the crude material by medium pressure liquid chromatography (20% ether/pet. ether) gave 0.056 g (55%) [with TMEDA, 57%] of **20** as a colorless oil: IR 1702 (s), 1651 (w), 1455 (w), 1392 (s), 1302 (m), 1251 (m), 1157 (s), 978 (m), 885 (m), 783 (m) cm^{-1}; ^1H NMR for rotamers (minor) δ 1.36 (1.42), (s, 9H), 1.87 (t, J=5.4 Hz, 3H), 2.84 (2.87) (s, 3H), 4.02 (4.13) (s, 2H), 6.12 (two overlapping d, J=15.9 Hz, 1H), 6.91 (dq, J=6.9, 15.6 Hz, 1H); ^{13}C NMR for rotamers (minor) δ 18.4, 28.2 (28.4), 35.5, 56.0 (57.0), 79.9, 128.3 (128.8), 143.6, 155.2 (155.8), (195.1) 195.2; mass spectrum, m/z (relative intensity) EI 157 (9, $M^+-C_4H_8$), 144 (20), 129 (4), 113 (1), 88 (9), 81 (3), 57 (100, C_4H_9), 44 (95).

4.6.21. 1,1-Dimethylethyl methyl(4-methyl-2-oxo-3-pentenyl)carbamate (21). General procedure C was employed (**1a**, 0.059 g, 0.41 mmol). Purification of the crude material by medium pressure liquid chromatography (20% ether/pet. ether) gave 0.048 g (53%) of **21** as a colorless oil: IR 1702 (s), 1642 (w), 1463 (m), 1404 (m), 1251 (m), 1166 (s), 1046 (w), 961 (w), 902 (w), 774 (w) cm^{-1}; ^1H NMR for rotamers (minor) δ 1.33 (1.40) (s, 9H), 1.84 (s, 3H), 2.10 (s, 3H), 2.81 (2.84) (s, 3H), 3.83 (3.95) (s, 2H), 5.97 (s, 1H); ^{13}C NMR for rotamers (minor) δ 20.2, 27.4, 28.1 (28.2), 35.4, 58.6 (59.3), (79.4) 79.7, 119.9 (120.2), 155.6 (156.0), 157.5, 195.7 (195.9); mass spectrum, m/z (relative intensity) EI 227 (0.3, M^+), 199 (1), 171 (7, $M^+-C_4H_8$), 144 (22), 127 (2), 110 (5), 83 (96), 57 (100, C_4H_9). Anal. calcd for $C_{12}H_{21}NO_3$: C, 63.43; H, 9.25. Found: C, 63.54; H, 9.30.

4.6.22. *N*-(*tert*-Butoxycarbonyl)-2-[(*E*)-1-oxo-2-butenyl]-pyrrolidine (22). General procedure D was employed (**1b**, 0.07 g, 0.41 mmol). Purification of the crude material by medium pressure liquid chromatography (20% ether/pet. ether) gave 0.045 g (84%) of **22** as a colorless oil: IR 1702 (s), 1651 (w), 1556 (w), 1463 (w), 1404 (s), 1183 (m), 1131 (m), 987 (w), 893 (w), 783 (w) cm^{-1}; ^1H NMR for rotamers (minor) δ 1.26 (1.31) (s, 9H), 1.69–1.90 (m, 6H), 2.00–2.18 (m, 1H), 3.37–3.52 (m, 2H), 4.26 (4.50) (dd, J=5.1, 8.7 Hz, 1H), 6.14 (br d, J=15.6 Hz, 1H), 6.91 (dq, J=6.9, 15.6 Hz, 1H); ^{13}C NMR for rotamers (minor) δ 18.2, 23.5 (24.0), 28.0 (28.2), (29.0) 30.1, 46.5 (46.7), (63.0) 64.0, (79.4) 79.7, 126.9 (128.0), 143.6 (143.7), 153.8 (154.3), (198.1) 198.5; mass spectrum, m/z (relative intensity) EI 239 (0.1, M^+), 211 (0.2, $M^+-C_2H_4$), 170 (20, $M^+-C_4H_5O$), 166 (4), 122 (8), 114 (77), 94 (2), 70 (100, $-C_4H_8N$), 57 (93, C_4H_9). Anal. calcd for $C_{13}H_{21}NO_3$: C, 65.27; H, 8.78. Found: C, 64.84; H, 8.73.

4.6.23. *N*-(*tert*-Butoxycarbonyl)-2-(3-methyl-1-oxo-2-butenyl)pyrrolidine (23). General procedure D was employed (**1b**, 0.10 g, 0.58 mmol). Purification of the crude product by medium pressure liquid chromatography (20% ether/pet. ether) gave 0.076 g (99%) of **23** as a colorless oil: IR 1702 (s), 1642 (w), 1463 (w), 1412 (s), 1174 (m), 1123 (m) cm^{-1}; ^1H NMR for rotamers (minor) δ 1.30 (1.39) (s, 9H), 1.69–1.93 (m, 4H), 1.84 (1.86) (s, 3H), 2.12 (s, 3H), 3.30–3.58 (m, 2H), 4.10 (4.28) (dd, J=5.4, 8.7 Hz, 1H), 6.03 (6.06) (s, 1H); ^{13}C NMR for rotamers (minor) δ 20.8 (20.9), 23.7 (24.1), 27.8, 28.1 (28.3), (29.0) 30.2, 46.7 (46.8), (65.3) 66.0, (79.4) 76.7, 119.4 (120.4), 154.0 (154.4), 157.4 (157.7), (199.1) 199.8; mass spectrum, m/z (relative intensity) EI 253 (0.4, M^+), 180 (0.4), 170 (29, $M^+-C_5H_7O$), 136 (3), 114 (95), 83 (47), 70 (100, $M^+-C_4H_8N$), 57 (64, C_4H_9). Anal. calcd for $C_{14}H_{23}NO_3$: C, 66.40; H, 9.10; N, 5.53. Found: C, 66.12; H, 9.09; N, 5.39.

4.6.24. *N*-(*tert*-Butoxycarbonyl)-4,4-dimethyl-2-benzoyl-1,3-oxazolidine (25). The general procedure A was employed. A solution of *N*-Boc-4,4-dimethyl-1,3-oxazolidine (0.20 g, 1.0 mmol) in 2.0 mL of dry THF was cooled to −78°C and treated with (−)-sparteine (0.23 mL, 1.0 mmol) and *sec*-BuLi (0.90 mL, 1.1 mmol). The mixture was stirred for 3 h at −78°C. Then a premixed homogenous solution of CuCN (0.089 g, 1.0 mmol) and LiCl (0.085 g, 2.0 mmol) in 2.0 mL dry THF was added to the above solution via cannula. The reaction mixture was stirred for 1 h at −78°C followed by the addition of benzoyl chloride (0.13 mL, 1.1 mmol) via syringe. The mixture was slowly warmed up to room temperature over 4 h. The reaction was quenched with saturated $NaHCO_3$ (aq) and filtered through celite. The mixture was extracted with ether (3×10 mL) and the combined extracts were washed with saturated NH_4Cl (aq), dried over $MgSO_4$, then concentrated in vacuum. The crude material was purified by flash column chromatography (ether/pet. ether, 1/4, v/v) to give 0.21 g (70%) of a white solid: m.p. 103–5°C; IR (CCl_4) 2977 (m), 1715 (s) 1381 (s) 1177 (m), 1062 (m) cm^{-1}; ^1H NMR for rotamers (minor) δ 1.11–1.69 (m, 15H), 3.65–3.91 (m, 2H), 6.17 (6.33) (s, 1H), 7.35–7.70 (m, 3H), 7.94–8.19 (m, 2H); ^{13}C NMR for rotamers (minor) δ 22.9 (23.6), 24.2 (25.2), 28.1 (28.3), 58.6 (59.0), 79.6 (80.2), 80.0 (80.1), 86.6 (87.5), 128.5 (128.6), 128.7, 133.4, 134.4, 150.8 (152.3), 192.5 (193.1); A DEPT experiment revealed methyl absoptions at δ 22.9, 24.2, 28.1, quaternary or carbonyl carbons at 58.6, 80.0, 134.4, 150.8, 192.5, CH carbons at 86.6, 128.5, 128.7, 133.4 and a CH_2 carbon at 79.6.

A homogeneous sample of **25** as indicated by ^1H and ^{13}C NMR and TLC analysis failed to give a satisfactory m/z value for $C_{17}H_{23}NO_4$ (305.1627) or combustion analysis data. Reaction of *N*-Boc-4,4-dimethyl-2-lithio-1,3-oxazolidine with benzaldehyde followed by oxidation of the resultant alcohol with CrO_3 in pyridine gave a sample identical with **25** by IR, ^1H and ^{13}C NMR analysis and by TLC R_f values.

4.6.25. 1,4-Bis[1-oxo-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidino)]benzene (26a). General procedure B was employed. A solution of *N*-Boc-pyrrolidine (0.17 g, 1.0 mmol) in 2.0 mL of dry ether was cooled to−-78°C and treated with (−)-sparteine (0.23 mL, 1.0 mmol) and *sec*-BuLi (0.90 mL, 1.1 mmol). The mixture was stirred for 1 h at −78°C. Then a premixed homogenous solution of CuCN (0.089 g, 1.0 mmol) and LiCl (0.085 g, 2.0 mmol) in 2.0 mL of dry THF was added to the above solution via cannula. The reaction mixture was stirred for 1 h at −78°C followed by the addition of terephthaloyl chloride (0.10 g, 0.50 mmol) in ether (1.0 mL) via syringe. The mixture was slowly warmed up to room temperature over 4 h. The reaction was quenched with saturated $NaHCO_3$ (aq) and filtered through celite. The mixture was extracted with ether (3×10 mL) and the combined extracts were washed with saturated NH_4Cl (aq), dried over $MgSO_4$, then concentrated in vacuum. The crude material was purified by flash column chromatography (ether/pet. ether, 1/1, v/v) to give 0.106 g (45%)

of a colorless oil: IR (neat) 3432 (br, s), 3056 (s), 2978 (s), 2304 (w), 1693 (vs), 1405 (s), 1265 (vs), 1160 (s), 1116 (s), 915 (m), 741 (vs) cm^{-1}; ^1H NMR for diastereomers or rotamers (minor) δ 1.22 (1.24) (s, 9H), 1.44 (s, 9H), 1.77–2.05 (m, 6H), 2.19–2.42 (m, 2H), 3.38–3.77 (m, 4H), 5.11–5.34 (m, 2H), 7.96–8.11 (m, 4H); ^{13}C NMR for diastereomers or rotamers (minor) δ 23.5 (24.2), 28.1 (28.4), 29.6 (30.7), 46.6 (46.8), 61.3 (61.5), 79.9, 128.4 (128.7), 138.5 (138.6), 153.6 (154.4), 198.0 (198.3). High-resolution mass spectrum *m/z* 472.2580 (M^+) (calcd for $C_{26}H_{36}N_2O_6$ 472.2573).

4.6.26. 1,4-Bis(*N*-*tert*-butoxycarbonyl-2-pyrrolidinyl)-1,4-butanedione (26b). General procedure B was employed. The crude material was purified by flash column chromatography (ether/pet. ether, 1/1, v/v) to give 0.0148 g (7%) of a colorless oil: IR (neat) 3502 (w), 3056 (m), 2978 (s), 2925 (m), 2882 (m), 2305 (w), 2254 (w), 1684 (s), 1396 (s), 1265 (s), 1160 (s), 1119 (s), 908 (m), 732 (s) cm^{-1}; ^1H NMR for rotamers or diastereomers (minor) δ 1.39 (1.44) (s, 18H), 1.72–2.30 (m, 8H), 2.55–2.95 (m, 4H), 3.31–3.61 (m, 4H), 4.15–4.41 (m, 2H); ^{13}C NMR for rotamers or diastereomers (minor) δ 23.7 (24.4), 28.3 (28.4), 28.9, 29.9, 31.7 (31.8), 32.1 (32.5), 46.8 (47.0), (64.6, 64.7, 64.8, 64.9) 65.3, 79.7 (79.8), 153.9 (154.7), 208.7 (208.8, 209.2).

4.6.27. 1-Phenyl-3-heptanone (27a). A premixed solution of CuCl (0.049 g, 0.50 mmol) and LiCl (0.042 g, 1.0 mmol) in 4.0 mL of THF was cooled to −78°C and treated with *n*-BuMgCl (0.28 mL, 0.48 mmol). The mixture was slowly warmed to −60°C and then treated with 3-phenyl propionyl chloride (0.08 mL, 0.53 mmol). The mixture was stirred for 5–10 min, quickly warmed to room temperature, quenched with $NaHCO_3$, extracted with ether (3×15 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude material by medium pressure liquid chromatography (5% ether/pet. ether) gave 0.088 g (96%) of pure **27a** as a colorless liquid: IR 1727 (s), 1506 (m), 1472 (m), 1387 (m), 1183 (m), 1089 (m), 766 (m), 714 (m) cm^{-1}; ^1H NMR δ 0.88 (t, J=7.5 Hz, 3H), 1.21–1.40 (m, 2H), 1.50–1.62 (m, 2H), 2.37 (t, J=7.5 Hz, 2H), 2.71 (t, J=7.2 Hz, 2H), 2.90 (t, J=7.2 Hz, 2H), 7.11–7.35 (m, 5H); ^{13}C NMR δ 13.8, 22.2, 25.8, 29.7, 42.6, 44.1, 125.9, 128.2, 128.4, 141.1, 210.2; mass spectrum, *m/z* (relative intensity) EI 190 (23, M^+), 172 (1), 148 (25), 33 (29), 105 (79, $M^+-C_5H_9O$), 91 (100), 85 (38), 57 (60, C_4H_9).

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References

1. Dieter, R. K. *Tetrahedron* **1999**, *55*, 4177.
2. Gilman, H.; Straley, J. M. *Rec. Trav. Chim.* **1936**, *55*, 821.
3. Whitesides, G. M.; Casey, C. P.; San Filippo, Jr. J.; Panek, E. J. *Trans. N.Y. Acad. Sci.* **1967**, *29*, 572.
4. (a) Posner, G. H.; Whitten, C. E. *Tetrahedron Lett.* **1970**, 4647. (b) Jallabert, C.; Luong-Thi, N. T.; Rivière, H. *Bull. Soc. Chim. Fr.* **1970**, 797.
5. Posner, G. H.; Whitten, C. E.; McFarland, P. E. *J. Am. Chem. Soc.* **1972**, *94*, 5106.
6. (a) Babudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron Lett.* **1995**, *36*, 7305. (b) Babudri, F.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron* **1996**, *52*, 13513.
7. Faust, R.; Weber, C.; Fiandanese, V.; Marchese, G.; Punzi, A. *Tetrahedron* **1997**, *53*, 14655.
8. (a) Dieter, R. K.; Sharma, R. R.; Ryan, W. *Tetrahedron Lett.* **1997**, *38*, 783. (b) Structures **11** and **5** were drawn incorrectly in this paper as the smaller homologues i.e. missing one $-(CH_2)-$ unit and are correctly represented by structures **5** and **13**, respectively, in this full report.
9. For a review on α-amino ketone synthesis see: Fisher, L. E.; Muchowski, J. M. *Org. Prep. Proced. Int.* **1990**, *22*, 399.
10. (a) Orlemans, E. O. M.; Verboom, W.; Lammerink, B. H. M.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1989**, *108*, 64. (b) Overhand, M.; Hecht, S. M. *J. Org. Chem.* **1994**, *59*, 4721. (c) Falorni, M.; Giacomelli, G.; Spanedda, A. M. *Tetrahedron: Asymmetry* **1998**, *9*, 3039. (d) Trost, B. M.; Scanlan, T. S. *J. Am. Chem. Soc.* **1989**, *111*, 4988.
11. Guzman, A.; Quintero, C.; Muchowski, J. M. *Can. J. Chem.* **1991**, *69*, 2059.
12. Bonte, J. P.; Piancastelli, M. C.; Lesieur, I.; Lamar, J. C.; Beaughard, M.; Dureng, G. *Eur. J. Med. Chem.* **1990**, *25*, 361.
13. (a) Digenis, G. A.; Agha, B. J.; Tsuji, K.; Kato, M.; Shinogi, M. *J. Med. Chem.* **1986**, *29*, 1468. (b) Fittkau, S.; Jahreis, G.; Peters, K. *J. Prakt. Chem.* **1986**, *328*, 529.
14. (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742. (b) Lociuro, S.; Pellacani, L.; Tardella, P. A. *Tetrahedron Lett.* **1983**, *24*, 593. (c) Adam, W.; Roschmann, K. J.; Saha-Moller, C. R. *Eur. J. Org. Chem.* **2000**, *3*, 557.
15. (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Hamby, J. M.; Hodges, J. C. *Heterocycles* **1993**, *35*, 843. (c) De Luca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 2534.
16. Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189.
17. Barluenga, J.; Baragaña, B.; Concellón, J. M. *J. Org. Chem.* **1995**, *60*, 6696.
18. Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Mazzanti, G.; Ricci, A.; Varchi, G. *Synlett* **1998**, 1013.
19. De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 1519.
20. Tomoyasu, T.; Tomooka, K.; Nakai, T. *Synlett* **1998**, 1147.
21. Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109. and references cited therein.
22. Dieter, R. K.; Dieter, J. W.; Bhinderawala, N. S.; Nice, L. E., unpublished results.
23. Dieter, R. K.; Topping, C. M.; Nice, L. E. *J. Org. Chem.* **2001**, *66*, 2302.
24. Bäckvall, J.-E.; Persson, E. S. M.; Bombrun, A. *J. Org. Chem.* **1994**, *59*, 4126. and Ref. 13 cited therein.
25. (a) Frantz, D.; Singleton, D. A.; Snyder, J. P. *J. Am. Chem. Soc.* **1997**, *119*, 3383. (b) Frantz, D. E.; Singleton, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 3288. (c) Nakamura, E.; Mori, S.; Morokuma, K. *J. Am. Chem. Soc.* **1997**, *119*, 4900.

26. (a) Bajgrowicz, J. A.; El-Hallaou, A.; Jacquier, R.; Pigiere, Ch.; Viallefont, Ph. *Tetrahedron* **1985**, *41*, 1833. (b) Friour, G.; Cahiez, G.; Normant, J. F. *Synthesis* **1984**, 37.
27. Conrow, R.; Portoghese, P. S. *J. Org. Chem.* **1986**, *51*, 938.
28. Gillet, J. P.; Sauvêtre, R.; Normant, J. F. *Synthesis* **1982**, 297.
29. (a) Lipshutz, B. H.; Hackmann, C. *J. Org. Chem.* **1994**, *59*, 7437. (b) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Smith, R. A. J. *J. Am. Chem. Soc.* **1990**, *112*, 4404.
30. Neipp, C. E.; Humphrey, J. M.; Martin, S. F. *J. Org. Chem.* **2001**, *66*, 531.
31. (a) Colombo, L.; Di Giacomo, M.; Brusotti, G.; Delogu, G. *Tetrahedron Lett.* **1994**, *35*, 2063. (b) Gawley, R. E.; Zhang, Q.; McPhail, A. T. *Tetrahedron: Asymmetry* **2000**, *11*, 2093. (c) Gawley, R. E.; Campagna, S. A.; Santiago, M.; Ren, T. *Tetrahedron: Asymmetry* **2002**, *13*, 29.
32. Dieter, R. K.; Topping, C. M.; Chandupatla, K. R.; Lu, K. *J. Am. Chem. Soc.* **2001**, *123*, 5132.
33. Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 7788.
34. Bertz, S. H.; Gibson, C. P.; Dabbagh, G. *Tetrahedron Lett.* **1987**, *28*, 4251.
35. Cox, C.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 2426.
36. Rogers, M. T.; Woodbrey, J. C. *J. Phys. Chem.* **1962**, *66*, 540.
37. Brandänge, S.; Holmgren, E.; Leijonmarck, H.; Rodriguez, B. *Acta. Chem. Scand.* **1995**, *49*, 922.
38. Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2001**, *57*, 4817.
39. Araki, M.; Sakata, S.; Takei, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1777.
40. Pitts, M. R.; Harrison, J. R.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 955.
41. Minami, I.; Takahashi, K.; Shimizu, I.; Kimura, T.; Tsuji, J. *Tetrahedron* **1986**, *42*, 2971.
42. Hanson, G. J.; Baron, J. S.; Lindberg, T. *Tetrahedron Lett.* **1986**, *27*, 3577.