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Reaction of α-(*N*-Carbamoyl)alkylcuprates with Propargyl Substrates: Synthetic Route to α-Amino Allenes and Δ^3-Pyrrolines

R. Karl Dieter,* Ningyi Chen, Huayun Yu, Lois E. Nice, and Vinayak K. Gore

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

dieterr@clemson.edu

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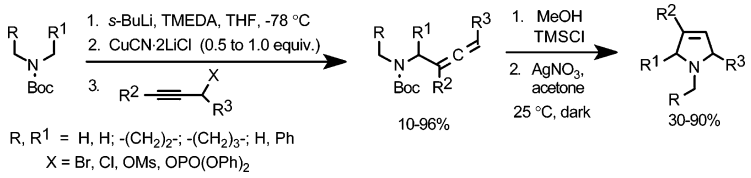

Carbamate deprotonation followed by treatment with CuCN·2LiCl affords α-(*N*-carbamoyl)-alkylcuprates which react with propargyl halides, mesylates, tosylates, phosphates, acetates, and epoxides to give α-(*N*-carbamoyl) allenes via an anti-S_N2' substitution process. Propargyl halides, sulfonates, and phosphates give good yields of carbamoyl allenes, while the acetates afford low yields. Propargyl substrates undergo regiospecific S_N2' substitution in the absence of severe steric hindrance. The α-(*N*-carbamoyl) allenes can be cyclized to 2-oxazolidinones or deprotected to afford the free amines which can be cyclized to Δ^3-pyrrolines with either $AgNO_3$ or $Ru_3(CO)_{12}$.

Introduction

α-Amino allenes and Δ^3-pyrrolines are synthetically useful[1] and biologically[2,3] interesting classes of N-containing compounds. Monoamine oxidase which plays an important role in psychopharmacology[2] is inactivated by α-amino allenes, while Δ^3-pyrrolines also function as MAO inhibitors,[3a−c] NMDA receptor agonists,[3d] k-agonists,[3e] and tumor inhibitors.[3f] Mitochondrial monoamine oxidase exists in two forms (i.e., A and B) and effects the oxidative deamination of transmitter amines (e.g., serotonin, noradrenaline, *β*-phenylethylamine, and dopamine).[2a] MAO-A inhibitors can function as antidepressant agents, while MAO-B inhibitors are selective toward Parkinson's disease. Although α-amino allenes have been prepared[4] via cyclopropyl carbene[5a] fragmentation, retro Diels−Alder reactions,[5b] and nitrogen alkylation with α-mesyloxy[2] (eq 1) or α-halo allenes,[6] the most useful synthetic routes involve conversion of a propargyl substrate into the allene functionality via either an S_N2'- or an S_E2'-substitution event. The amine moiety may be incorporated in the propargyl substrate[2,7] or be part of the nucleophile (S_N2') or electrophile (S_E2') participating in the substitution reaction. Propargyl silanes[8a−c] (eq 2) and stannanes[8d] undergo S_E2'-substitution reactions with imines and/or imminium ions to afford α-amino allenes. The S_E2-reaction of imines or iminium ions with propargyl organometallic reagents may afford either the α-amino allene or the homo propargylamine.[9−11] Although α-methoxy allenyllithium[10] reagents add directly to hy-

(1) For use of pyrrolines in aza sugar synthesis, see: Huwe, C. M.; Blechert, S. *Tetrahedron Lett.* **1995**, *36*, 1621−1624.

(2) (a) Sahlberg, C.; Ross, S. B.; Fagervall, I.; Ask, A.-L.; Claesson, A. *J. Med. Chem.* **1983**, *26*, 1036−1042. (b) Smith, R. A.; White, R. L.; Krantz, A. *J. Med. Chem.* **1988**, *31*, 1558−1566 and references therein.

(3) Pyrrolines as monoamine oxidase inhibitors, see: (a) Williams, C. H.; Lawson, J. *Neurobiology* **1999**, *7*, 225−233. (b) Williams, C. H.; Lawson, J. *Biochem. J.* **1998**, *336*, 63−67. (c) Lee, Y.; Huang, H.; Sayre, L. M. *J. Am. Chem. Soc.* **1996**, *118*, 7241−7242. As NMDA receptor agonists, see: (d) Rondeau, D.; Gill, P.; Chan, M.; Curry, K.; Lubell, W. D. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 771−773. As k-agonists, see: (e) Mou, Q.-Y.; Chen, J.; Zhu, Y.-C.; Zhou, D.-H.; Chi, Z.-Q.; Long, Y.-Q. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2287−2290. As tumor inhibitors, see: (f) Anderson, W. K.; Milowsky, A. S. *J. Med. Chem.* **1987**, *30*, 2144−2147.

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(5) (a) Santelli, C. *Tetrahedron Lett.* **1980**, *21*, 2893−2896. (b) Bertrand, M.; Gras, J.-L.; Galledou, B. S. *Tetrahedron Lett.* **1978**, 2873−2876.

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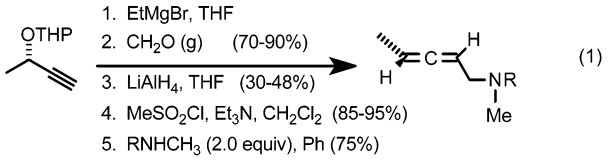
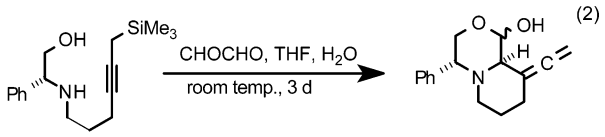
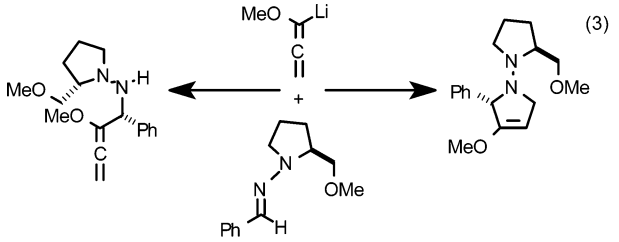
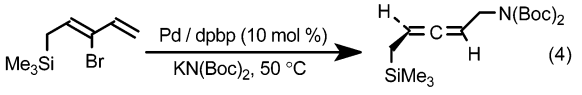
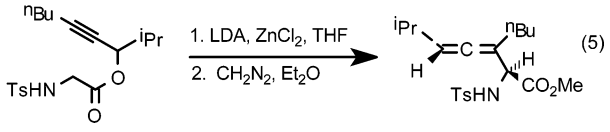
drazones (eq 3), the corresponding α-alkyl or silylmetal reagents (e.g., Zn, Ti, B, Al, Li) react with rearrangement to afford homo propargylamines.[11] The propargyl borane and allenylborane are in rapid equilibrium and generally favor formation of the α-amino allene upon reaction with imines.[11c] Allylic S_N2'-substitution is also involved in the palladium-promoted addition of amide anions to 2-bromo-1,3-dienes,[12] (eq 4) and ester enolate Claisen rearrangements on α-amino propargyl esters incorporates both propargyl rearrangement and α-amino carbanion synthons (eq 5).[6] Reaction of cuprates with δ-amino propargyl ethers,[2a,7d] δ-amino propargyl mesylates,[7c] or alkynyl azirdines[13] also affords α-amino allenes. An early report and our preliminary study suggested that S_N2'-substitution reactions of propargyl substrates with α-aminoalkyl-[14a] or α-(*N*-carbamoyl)alkylcuprates[14b] could provide a general route to α-amino allenes.





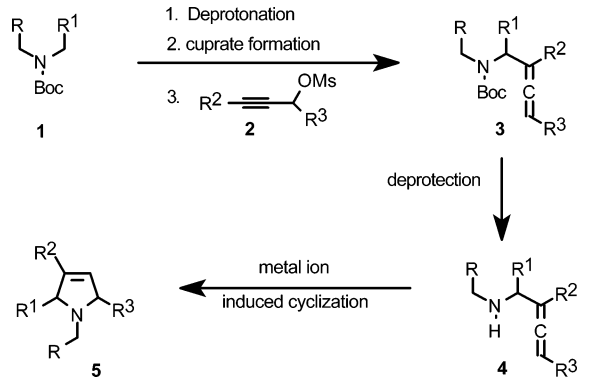






Although recently described synthetic routes to Δ^3-pyrrolines provide versatile opportunities for substitution patterns[3d,10,15a–c] and multiple-component coupling,[15d] transition metal-promoted cyclization of a heteroatom onto an allene moiety remains a powerful strategy for heterocyclic synthesis.[16] Furan formation via silver ion-catalyzed cyclization of α-hydroxy allenes occurs in a highly regio- and stereoselective manner.[17] Silver ion-catalyzed cyclization of a nitrogen functionality onto a proximate olefinic site has been employed for the synthesis of nitrogen heterocycles. Although these cyclizations proceeded cleanly for a range of nitrogen-containing functionality, many of the cyclizations proceeded in an *exo*-cyclic fashion to afford 2-vinyl substituted ring systems.[18] Nevertheless, several recent reports describe silver nitrate-promoted *endo*-cyclization processes involving either a benzyl or an alkylamine functionality,[19a] sulfonamides,[19b] or acyclic amino allenes.[19c] In a preliminary report, we demonstrated that unprotected secondary α-amino allenes undergo $AgNO_3$-promoted cyclization to Δ^3-pyrrolines in good to excellent yields (Scheme 1).[20] Similarly, the vast majority of palladium-promoted cyclizations of nitrogen functionalities onto adjacent double bonds involve nitrogen centers containing electron-withdrawing substituents,[7c,19b,21] although examples of amine participation have been reported.[16] This is significant because strongly basic amines can function as ligands for the palladium catalyst and potentially interfere with the cyclization reaction. Although some 5-*endo*-*trig*-cyclizations have been reported,[19,21] most of these procedures also involve *exo*-cyclizations,[22] raising ques-

SCHEME 1



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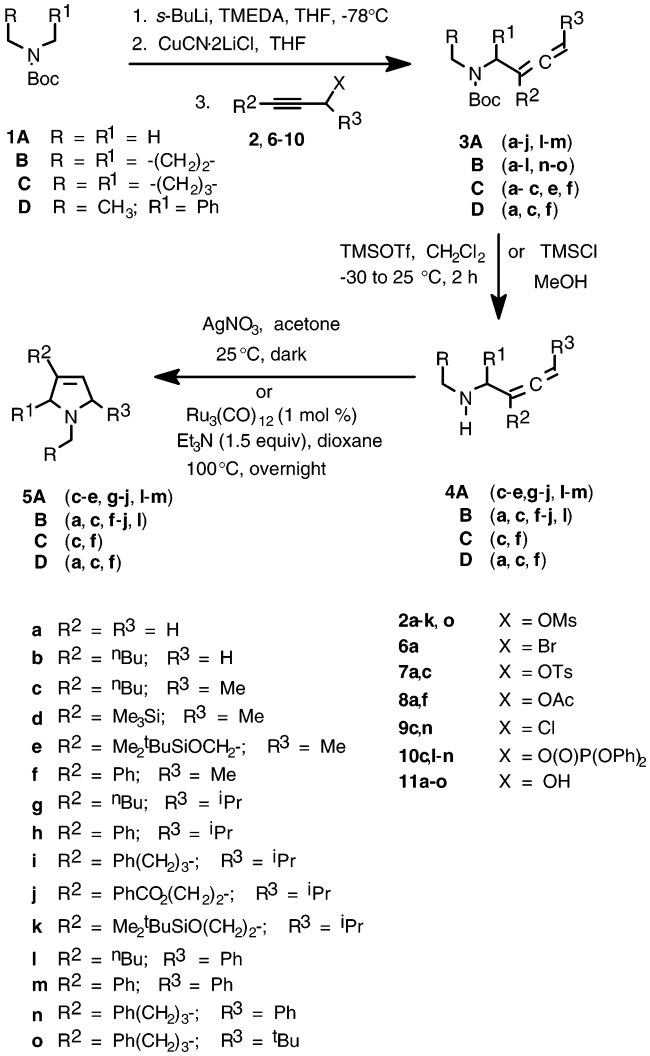
SCHEME 2

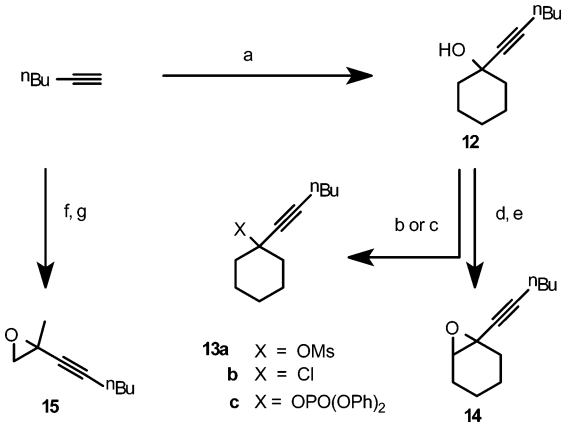


tions about the generality of the *endo*-cyclization process particularly for annulated Δ³-pyrrolines. In this full report, we provide a detailed examination of the scope and limitations of a synthetic route to Δ³-pyrrolines via α-amino allenes available by reaction of α-(*N*-carbamoyl)-alkylcuprates with propargyl substrates (Scheme 1).

Results and Discussion

The key three-step synthetic sequence to Δ³-pyrrolines involves reaction of α-(*N*-carbamoyl)alkylcuprates with propargyl substrates [i.e., mesylates (**2**), tosylates (**7**), phosphates (**10** and **13c**), halides (**6** and **9**), and acetates (**8**)] in an *anti*-S_N2' fashion, followed by *N*-Boc deprotection and cyclization of the amino moiety onto the allene functionality (Schemes 1 and 2). Convenient and rapid access to the propargyl substrates is essential for the utility of the method. The propargyl mesylates **2b**−**k** and **2o**, tosylate **7c**, acetate **8f**, chloride **9c**,**n**, and phosphates **10c**,**l**−**n** (Scheme 2) are readily available from the corresponding propargyl alcohols **11b**−**o**, which in turn

SCHEME 3[a]



[a] (a) (i) ^{n}BuLi, THF, −20 °C, (ii) cyclohexanone (90%); (b) CaCl, CuCl, copper powder, concentrated HCl (87%) for **13b**; (c) (i) LDA, THF, −78 °C, (ii) $(PhO)_2POCl$ for **13c**; (d) pyridine, $POCl_3$, 0 °C 1 h, 25 °C 16 h, 70 °C 2 h (86%); (e) *m*-$ClC_6H_4CO_3H$, CH_2Cl_2, 0−25 °C, 16 h (75%); (f) (i) ^{n}BuLi, THF, −20 °C, (ii) CH_3COCH_2Cl (52%); (g) ^{t}BuOK, THF (93%).

can be prepared by the addition of lithium or magnesium acetylides to aldehydes.[23] Mesylates containing combinations of alkene, alkyne, or arene functionality on both sides of the carbinol carbon were prone to rearrangements and nucleophilic substitution reactions and proved difficult to prepare. Mesylates could not be prepared from secondary alcohols that were both propargylic and benzylic. Phosphates **10c**,**l**−**n**, although unstable to purification, could be used as crude materials in the substitution reaction. Similarly, although the proparyl mesylate **13a** or phosphate **13c** could not be isolated (Scheme 3), phosphate **13c** could be generated in situ [(i) LDA, THF, −78 °C, (ii) $(PhO)_2POCl$, −78 to 25 °C] and used in the cuprate substitution reaction (Scheme 3).

The alkynyl epoxides **14** and **15** were also easily prepared according to established procedures. Dehydration[24] of alcohol **12** followed by chemoselective epoxidation[24b] of the enyne afforded propargyl epoxide **14** (Scheme 3), while addition of 1-lithiohexyne to α-chloro acetone[25a] followed by treatment with base[25b] afforded **15**. The asymmetric epoxidation of conjugated enynes provides a convenient access to scalemic (i.e., enantioenriched) propargyl epoxides necessary for asymmetric variations of the synthetic method.[26]

The α-(*N*-carbamoyl)alkylcuprate reagents were prepared from *N*-Boc (i.e., *tert*-butoxycarbonyl)-protected amines **1A**−**D** by sequential deprotonation [*s*-BuLi, THF, sparteine, or TMEDA, −78 °C (−20 °C for piperidine)][27] and treatment with solid CuCN in the early studies.

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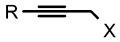
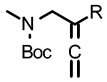
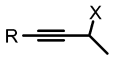
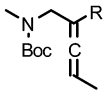
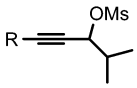
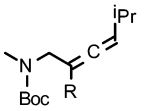
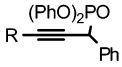
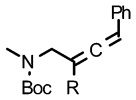
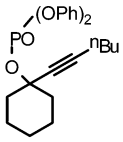
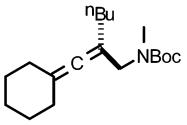
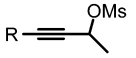
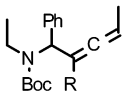
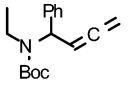
TABLE 1. Reaction of Propargylic Acetates, Bromides, Mesylates, and Phosphates with Acyclic α-(*N*-Carbamoyl)alkylcuprates

entry	carbamate[a]	propargyl substrate	X	R	E+ No.	CuCN equiv[b]	product	product No.	% yield[c] (dr)
1			Br	H	**6 a**	1.0 Cl		**3 A a**	59
2			Br	H	**6 a**	1.0		**3 A a**	76
3	**1A**		Br	H	**6 a**	1.0		**3 A a**	96
4			OMs	Bu	**2 b**	0.5		**3 A b**	67
5			OMs	Bu	**2 b**	1.0		**3 A b**	57-78
6			OMs	Bu	**2 b**	1.0 Cl		**3 A b**	63
7			OMs	Bu	**2 c**	0.5		**3 A c**	47
8			OMs	Bu	**2 c**	1.0		**3 A c**	75-90
9			OMs	Bu	**2 c**	1.0[d]		**3 A c**	56
10				Me_3Si	**2 d**	1.0		**3 A d**	70-76
11				TBDMSO(CH_2)-	**2 e**	1.0		**3 A e**	57
12			OMs	Ph	**2 f**	0.5		**3 A f**	65
13			OMs	Ph	**2 f**	1.0		**3 A f**	68
14			OAc	Ph	**8 f**	1.0		**3 A f**	39
15			OAc	Ph	**8 f**	0.5		**3 A f**	11[e]
16			-	^{n}Bu	**2 g**	1.0		**3 A g**	40 [70]
17			-	Ph	**2 h**	1.0		**3 A h**	70-79
18				Ph(CH_2)$_3$-	**2 i**	1.0		**3 A i**	74
19				$PhCO_2$(CH_2)$_2$-	**2 j**	1.0		**3 A j**	64
20				^{n}Bu	**1 0 l**	1.0		**3 A l**	54 [70]
21				^{n}Bu	**1 0 l**	0.5		**3 A l**	47
22				Ph	**1 0 m**	1.0		**3 A m**	62 [84]
23					**1 3 c**	1.0		**1 6**	65
24					**1 3 c**	1.0		**1 6**	[72]
25			-	^{n}Bu	**2 c**	1.0		**3 D c**	66 (45:55)
26			-	Ph	**2 f**	1.0		**3 D f**	63 (36:64)
	1D								
27			-	-	**6 a**	1.0		**3 D a**	68

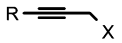
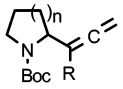
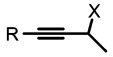
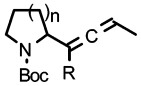
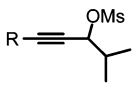
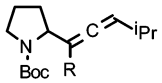
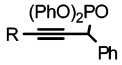
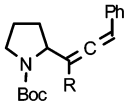
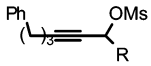
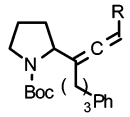
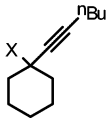
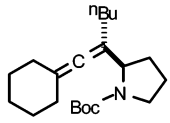
[a] Cuprates were prepared from the carbamates by sequential deprotonation (*s*-BuLi, TMEDA, or sparteine, THF, −78 °C) and addition of CuCN·2LiCl (−55 °C, 45 min). [b] Equivalents of Cu(I) salt per equivalent of RLi (R = α-aminoalkyl ligand). [c] Yields based upon isolated products purified by column chromatography. Yields in brackets refer to yields obtained from the diphenyl phosphate generated in situ. [d] Insoluble CuCN was employed. [e] Yields determined by NMR.

Although these reaction conditions gave modest yields of substitution products (Table 1, entry 9), the chemical yields were often capricious with varying amounts of starting carbamate recovered from experiment to experiment. Reliable and reproducible yields of α-(*N*-carbamoyl) allenes could be obtained via an S_N2'-substitution process when the cuprate reagents were prepared from THF-soluble CuCN·2LiCl. The thermal stability of the α-lithio carbamates and the temperature at which the cuprate reagent is formed play major roles in the efficiency of α-(*N*-carbamoyl)alkylcuprate chemistry.[28] Utilization of soluble forms of Cu(I) salts allows formation of the cuprate reagent to occur rapidly at −78 °C where the α-lithio carbamates are thermally stable. When solid CuCN was employed, a warming−cooling protocol (e.g., warming to −50 to −40 °C, stirring for 0.5−1.0 h, and then cooling to −78 °C before addition of the electrophile) was used to ensure complete cuprate formation, and variations in time and temperature from experiment to experiment gave considerable variation in the chemical yields of coupled products.

Optimization efforts probed several parameters including cuprate composition (e.g., RCuCNLi and R_2CuLi·LiX), copper(I) salt (e.g., CuX, X = CN, Cl), leaving group (e.g., bromide, mesylate, tosylate, phosphate, acetate), and α-(*N*-carbamoyl)alkyl ligands [e.g., acyclic (Table 1) and cyclic (Table 2) carbamoyl ligands]. A number of general patterns emerged. Good yields of allenes were obtained from cuprates prepared from 1 equiv of *N*-lithiomethyl-*N*-methyl carbamate (i.e., **1A-Li**) and either CuCl·2LiCl

(28) (a) Dieter, R. K.; Topping, C. M.; Nice, L. E. *J. Org. Chem.* **2001**, *66*, 2302−2311. (b) For a review, see: Dieter, R. K. Heteroatomcuprates and α-Heteroatomalkylcuprates in Organic Synthesis. In *Modern Organocopper Chemistry*; Krause, N., Ed.; John Wiley & Sons: New York, 2002; pp 79−144.

TABLE 2. Reaction of Propargylic Acetates, Halides, Sulfonates, and Phosphates with Cyclic α-(*N*-Carbamoyl)alkylcuprates

entry	carbamate[a]	n	propargyl substrate	X	R	E⁺ No.	CuCN equiv[b]	product	product No.	% yield[c] (dr)
1		1		Br	H	**6a**	0.5		**3Ba**	59
2		1		Br	H	**6a**	1.0		**3Ba**	60
3		2		Br	H	**6a**	1.0		**3Ca**	44[d]
4	**1B** n = 1	1		OMs	H	**2a**	1.0		**3Ba**	58
5	**1C** n = 2	1		OTs	H	**7a**	0.5		**3Ba**	83
6		1		OAc	H	**8a**	1.0		**3Ba**	trace
7		1		OMs	^{n}Bu	**2b**	0.5		**3Bb**	70
8		1		OMs	^{n}Bu	**2b**	1.0		**3Bb**	65
9		2		OMs	^{n}Bu	**2b**	1.0		**3Cb**	50
10		2		OMs	^{n}Bu	**2c**	1.0		**3Cc**	53
11		1		OMs	^{n}Bu	**2c**	0.5		**3Bc**	78
12		1		OMs	^{n}Bu	**2c**	1.0		**3Bc**	68 (41:59)
13		1		OMs	Me_3Si	**2d**	1.0		**3Bd**	63[e]
14		1		OMs	TBDMSO(CH_2)-	**2e**	1.0		**3Be**	41
15		2		OMs	TBDMSO(CH_2)-	**2e**	1.0		**3Ce**	34
16		1		OMs	Ph	**2f**	0.5		**3Bf**	54 (66:34)
17		1		OMs	Ph	**2f**	1.0		**3Bf**	92 (39:61)
18		2		OMs	Ph	**2f**	1.0		**3Cf**	44
19		1		-	^{n}Bu	**2g**	1.0		**3Bg**	52 (55:45)
20		1		-	Ph	**2h**	1.0		**3Bh**	42 (59:41)
21		1		-	Ph(CH_2)$_3$-	**2i**	1.0		**3Bi**	65 (55:45)
22		1		-	Ph(CH_2)$_3$-	**2i**	0.5		**3Bi**	10
23		1		-	$PhCO_2(CH_2)_2$-	**2j**	1.0		**3Bj**	51 (56:44)
24		1		-	TBDMSO(CH_2)$_2$-	**2k**	1.0		**3Bk**	81
25		1		-	TBDMSO(CH_2)$_2$-	**2k**	0.5		**3Bk**	10
26		1		Cl	Ph(CH_2)$_3$-	**9n**	1.0		**3Bn**	53 (56:44)
27		1		$(PhO)_2PO$	Ph(CH_2)$_3$-	**10n**	1.0		**3Bn**	47 (55:45)
28				$(PhO)_2PO$	^{n}Bu	**10l**	1.0		**3Bl**	64[f] (59:41)
29		1			^{t}Bu	**2o**			**3Bo**	73
30		1		$(PhO)_2PO$		**13c**	1.0		**17**	55 [82][f]

[a] Cuprates were prepared from the carbamates by sequential deprotonation (*s*-BuLi, TMEDA, or sparteine, THF, −78 °C) and addition of CuCN·2LiCl (−55 °C, 45 min). [b] Equivalents of Cu(I) salt per equivalent of RLi (R = α-aminoalkyl ligand). [c] Yields based upon isolated products purified by column chromatography. [d] A mixture of regioisomers. [e] Ratio of S_N2:S_N2' (55:45). [f] In-situ generation and use of the phosphate was employed.

or CuCN·2LiCl. The latter reagent gave comparable or slightly better results (Table 1, entries 1 vs 2−3 and 6 vs 5). Although the reaction of 1 equiv of RLi with CuCl implies formation of an organocopper(I) reagent (i.e., RCu + LiCl) based on stoichiometry, the effectiveness of the reaction suggests formation of a cuprate reagent (e.g., RCuClLi). Because CuCl is significantly more air and moisture sensitive than CuCN, the latter reagent was employed throughout the study. Both of these cuprate reagents (i.e., RCuXLi, X = CN, Cl) contain only one α-(*N*-carbamoyl)alkyl ligand and are more efficient than the reagent prepared from 2 equiv of RLi and 1 equiv of CuCN·2LiCl even though similar chemical yields are sometimes obtained (Table 1, entry 12 vs 13, Table 2, entry 1 vs 2). More commonly, however, the dialkylcuprate reagent R_2CuLi gave yields that were about 10−30% lower than the RCuCNLi reagent (Table 1 entries 4 vs 5, 7 vs 8, 21 vs 22) when the carbamoylalkyl ligand was acyclic. Although this was also true for phosphate **10l** and the cuprates derived from *N*,*N*-dimethyl carbamate **1A** when the reactions were performed on the isolated phosphate, reaction of in-situ-generated phosphate **10l** gave a significantly better yield of allenyl carbamate **3Al** (entry 20). This proved to be a general phenomenon (Table 1, entries 16, 20, 22, and 23 vs 24; Table 2, entry 30) reflecting the instability of the isolated propargyl phosphates. Mixed results were obtained when the carbamoylalkyl ligand was cyclic. Comparable yields were obtained when the RCuCNLi and R_2CuLi·LiX reagents derived from *N*-Boc pyrrolidine (**1B**) reacted

with propargyl substrate **6a** (Table 2, entries 1 vs 2), and higher yields were obtained with R_2CuLi when substrate **2c** was employed (entries 11 vs 12). Significantly lower yields were obtained with the lithium bis-pyrrolidinyl cuprate when propargyl substrates **2f**, **2i**, or **2k** (Table 2, entries 16 vs 17, 22 vs 21, and 25 vs 24) were employed. Although the origin of this effect is unclear, the R_2CuLi reagents become less effective for the pyrrolidinyl cuprates as the proparagyl substrate becomes sterically encumbered (e.g., **2i, k**) or electronically modified (e.g., **2f**).

The nature of the leaving group also played a significant role in the effectiveness of these substitution reactions. Propargyl bromides and mesylates gave comparable yields (Table 1, entries 2−3 vs 5, Table 2, entries 2 vs 4), while the acetate leaving group gave very poor yields in all instances (Table 1, entries 14−15, Table 2, entry 6). With the ineffective acetate leaving group, significantly lower yields were obtained with R_2CuLi than with RCuCNLi (Table 1, entries 14−15). In one experiment, the tosylate **7a** gave a better yield with the bis-pyrrolidinyl cuprate than bromide **6a** or the mesylate **2a** with the pyrrolidinylcyanocuprate reagent (Table 2, entries 5 vs 1, 4). Reaction of mesylate **2c**, tosylate **7c**, chloride **9c**, and phosphate **10c** with the alkylcyanocuprate (i.e., RCuCNLi) derived from the *N*,*N*-dimethyl carbamate **1A** gave comparable yields (76%, 67%, 81%, 69%, respectively) of carbamoyl allene **3Ac**, suggesting that all four leaving groups display comparable efficacy in this substitution reaction.

The variation in chemical yield from experiment to experiment for the same reaction is difficult to understand. In most instances, the propargyl substrates were not purified and were used as crude materials. Considering the possibility that the yields of the cuprate substitution reactions reflected impurities in the crude mesylates, a series of control experiments were performed on mesylate **2i**, which was stable to column chromatography. Reaction of crude **2i**, column purified **2i**, and crude **2i** washed several times with $NaHCO_3$ with the RCuCNLi reagent derived from *N*-Boc pyrrolidine **1B** gave **3Bi** in yields of 61%, 67%, and 67%, respectively. In a number of instances, the starting mesylate and *N*-Boc carbamate were present in the crude product mixtures (30−35% yields) as a 1:1 ratio as determined by ^1H NMR spectroscopy. In some experiments, participation of the *sec*-butyl ligand was observed, indicating the presence of excess *sec*-BuLi in the initial deprotonation procedure. As noted before, utilization of in-situ-generated phosphates always gave higher yields of carbamoyl allenes than when isolated phosphates were used, and in one instance the yield obtained with the isolated mesylate (40%) was nearly doubled by using the in-situ-generated phosphate (Table 1, entry 16). Collectively, these results suggest that better yields will generally be obtained by utilization of in-situ-generated propargyl phosphates.

Reactions between stereogenic cuprates derived from *N*-Boc-pyrrolidine **1B** (Table 2, entries 11−14, 16−17, 19−29), *N*-Boc-piperidine **1C** (Table 2, entries 10, 15, 18), or *N*-ethyl-*N*-benzyl carbamate **1D** (Table 1, entries 25−26) and propargyl substrates [**2c**−**k**,**o**, **9n**, and **10l**,**n**], **2c,e,f**, and **2c,f**, respectively, gave mixtures of diastereomers ranging between 50:50 and 60:40 mixtures. Because racemic stereogenic cuprate reagents and racemic propargyl substrates were employed in these reactions, poor diastereomeric ratios were anticipated. Efforts are currently underway to effect enantio- and diastereocontrol using enantioenriched stereogenic cuprates and propargyl substrates where synthetically useful diastereomeric ratios are more likely to be achieved.[29]

The cuprate reagents generated from *N*,*N*-dimethyl carbamate **1A** and *N*-Boc-pyrrolidine **1B** gave the carbamoyl allenes regiospecifically for all propargyl substrates except **2d** where the **1B**-derived cuprate gave a nearly 1:1 mixture of regioisomers resulting from α-(S_N2) and γ-(S_N2') substitution (Table 2, entry 13). The cuprate reagent prepared from *N*-Boc-protected piperidine (**1C**) also gave a mixture of regioisomers resulting from attack at both the α- and the γ-positions of the starting propargyl bromide (**6a**) (Table 2, entry 3). The piperidinylcuprates did give clean S_N2'-substitution with propargyl substrates **2b**,**c** and **2e**,**f**, although diminished chemical yields were obtained (Table 2, entries 9, 10, 15, and 18). Because the cuprate derived from **1A** reacted with propargyl mesylate **2d** with clean S_N2'-regioselectivity, formation of propargylamines (S_N2-substitution) reflects steric hindrance in the cuprate reagent or the propargyl substrate. The overwhelming tendency in the propargyl systems is for substitution with rearrangement (S_N2') in contrast to the allylic systems where mixtures are often encountered.[29]

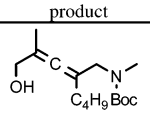
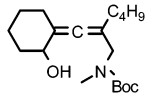
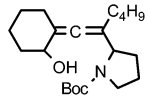
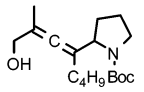
In the initial studies, tertiary mesylate **13a** as well as the corresponding chloride **13b** (Scheme 3) failed to undergo any substitution reaction with the cuprate reagents prepared from either **1A** or **1B**, reflecting the difficulty of preparing the mesylate and perhaps the reactivity of the chloride. Generation of the phosphate **13c** in situ and immediate use gave reasonably good yields of the carbamoyl allenes **16** and **17**, respectively, upon reaction with cuprates derived from **1A**,**B** (Table 1, entry 24; Table 2, entry 30). Similarly, the mesylates **2l**−**n** could not be prepared and isolated, and the isolated phosphates **10l**−**n** or chloride **9n** reacted with the **1A**,**B**-derived cuprates to give α-carbamoyl allenes in moderate yields (Table 1, entries 20−22; Table 2, entries 26−28). The in-situ-generated phosphates thus provide a solution to tertiary propargyl phosphates and those phosphates flanked by two unsaturated moieties and hence chemically unstable to solvolysis.

Propargyl epoxides **14** and **15** also participated in the substitution reaction but with widely varying yields (Table 3). Initial experiments employed 5 equiv of TMSCl (entries 1, 3, 5, and 8), although later experiments suggested that this was unnecessary (entries 4 and 6). While the use of Lewis acids[30] such as $Sc(OTf)_3$ appeared to increase the yields of substitution products (entries 2, 7, 9, and 11), good yields were obtained in the reaction of **14** with both the R_2CuLi and the RCuCNLi reagents derived from **1A** (entries 4 and 6) in the absence of Lewis Acids. Reexamination of **14** with bis-pyrrolidinylcuprate indicated that good yields of carbamoyl allene **20** could be obtained without the use of TMSCl or Lewis acids (entry 10). These allenyl alcohols were acid sensitive but could be purified on neutral alumina.

(29) Dieter, R. K.; Gore, V. K.; Chen, N. *Org. Lett*. **2004**, *6*, 763−766.

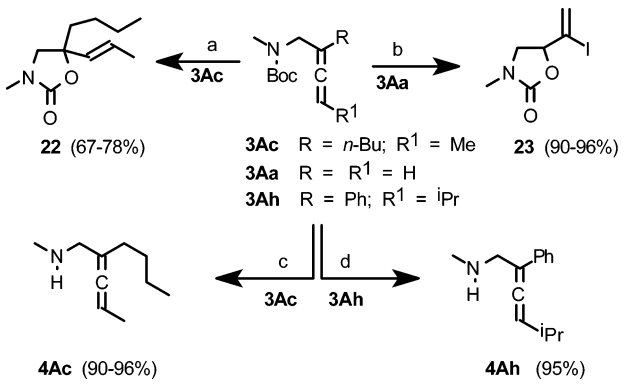
(30) Lipshutz, B. H.; Sclafani, J. A.; Takanami, T. *J. Am. Chem. Soc.* **1998**, *120*, 4021−4022.

TABLE 3. Reaction of Propargylic Epoxides with α-(*N*-Carbamoyl)alkylcuprate Reagents

entry	*N*-Boc[a]	alkynyl epoxide	CuCN equiv[b]	product	Prod. No.	% yield[c] (dr)
1	**1A**	**15**	1.0		**18**	44[e]
2	**1A**	**15**	1.0		**18**	77[f]
3	**1A**	**14**	0.5		**19**	83[e]
4	**1A**	**14**	0.5		**19**	90-94
5	**1A**	**14**	1.0		**19**	72[e]
6	**1A**	**14**	1.0		**19**	60
7	**1A**	**14**	1.0		**19**	94[f]
8	**1B**	**14**	1.0		**20**	31[e]
9	**1B**	**14**	1.0		**20**	46[f]
10	**1B**	**14**	0.5		**20**	78
11	**1B**	**15**	1.0		**21**	69[f] (1:1)

[a] Cuprates were prepared from the carbamates by sequential deprotonation (*s*-BuLi, TMEDA, or sparteine, THF, −78 °C) and addition of CuCN·2LiCl (−55 °C, 45 min). [b] Equivalents of CuCN salt per equivalent of RLi [R = α-(*N*-carbamoyl)alkyl ligand]. [c] Yields based upon isolated products purified by column chromatography. [e] TMSCl (5 equiv) was employed. [f] $Sc(OTf)_3$ (5 mol %) was employed.

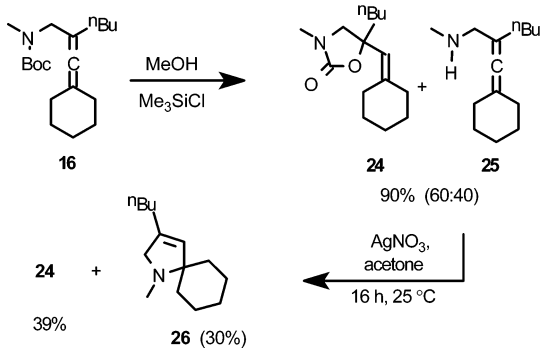
SCHEME 4[a]



[a] (a) PhOH, TMSCl, CH_2Cl_2; (b) I_2 (3.0 equiv), CH_2Cl_2, 0 °C; (c) Me_3SiOTf, CH_2Cl_2, −30 to 25 °C; (d) MeOH, TMSCl, 25 °C.

Considerable difficulty was encountered in initial efforts to effect *N*-Boc deprotection of the α-(*N*-carbamoyl) allenes. Treatment of these allenyl carbamates with PhOH/TMSCl[31] promoted a 5-*exo-trig* cyclization of the *tert*-butoxycarbonyl moiety onto the allene to afford an oxazolidinone (Scheme 4, **22**). A similar reaction occurred with I_2, affording an oxazolidinone containing a vinyl iodide moiety (i.e., **23**). Cyclization and addition of I_2 across the terminal double bond of **3Aa** (40−72%) occurred when I_2/KI/$NaHCO_3$/H_2O/CH_2Cl_2 was employed.[32] The reagents $^tBuMe_2SiOTf$[33a] and $Ce(NH_4)_2(NO_3)_6$[33b] failed to effect *N*-Boc deprotection, while catechol boron bromide[33c] and $AlCl_3$[33d] gave a complex mixture of products. Treatment of the *N*-Boc-protected amino allenes with trimethylsilyltriflate [CH_2Cl_2, −30 to 25 °C] gave the free amino allenes in good to excellent yields (Table 4, entries 1−3, 5−7, 10−17, 20, and 21, 62−99%).[34] Methanolic HCl generated by addition of TMSCl to methanol proved to be far more convenient and economical, affording the amino allenes in nearly quantitative yields (Scheme 4, Table 4, entries 4−9, 15−20, and 22, 83−95%).[35] The tetrasubstituted allene **16** gave oxazolidinones **24** as the major product arising from protonation of the allene and neighboring group participation of the carbamate carbonyl (Scheme 5).

SCHEME 5



Reaction of the amino allenes with a catalytic amount of $AgNO_3$ in acetone (25 °C, in the dark) gave 3-pyrrolines in good to excellent yields. The reaction readily formed both simple (Table 4, entries 1−12) and annulated (entries 13−24) pyrrolines. The procedure is very reliable and appears capable of tolerating a wide range of substitution patterns (e.g., 2,3-disubstitution in **5Dc** and **5Df**, entries 10−11). As expected, utilization of racemic propargyl mesylates and racemic α-(*N*-carbamoyl)alkylcuprates afforded mixtures of diastereomers with little or no diastereoselectivity. The formation of spiro-fused pyrrolines (entries 23−24) proved problematic involving difficulty in the *N*-Boc deprotection step. The minor free amino allene from **16** could be cyclized to the spiro pyrroline **26** (Scheme 5).

Although precedented, the 5-*endo-trig*-cyclizations of O-[17] and N-heteroatoms[16,18c,19] onto allenes is dependent upon the metal catalyst and reaction conditions. $AgNO_3$ is particularly effective for 5-*endo-trig*-cyclizations of α-hydroxy allenes[17] and α-amino or protected amino allenes.[19,20] Similar palladium-promoted cyclizations[16,20,7b] show greater variations that often depend on the solvent employed and the functional group containing the heteroatom participating in the cyclization. This appears to reflect the ability of palladium catalysts to form π-allyl complexes from allenes as well as ligand effects (i.e., heteroatom functionality and solvent effects)[7b] not present in $AgNO_3$ catalysis. The scope and limitations of these 5-*endo-trig*-cyclizations is not fully established.

Free amino allene **4Ah** was employed in an effort to effect ruthenium-catalyzed carbonylation and cyclization to afford pyrrolin-2-one **30** (eq 6).[36] Treatment of **4Ah** with $Ru_3(CO)_{12}$ at 100 °C and bubbling in carbon mon-

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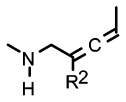
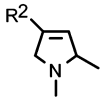
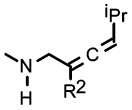
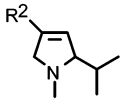
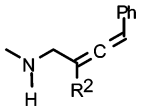
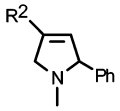
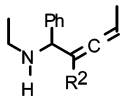
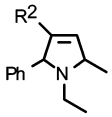
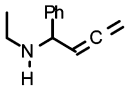
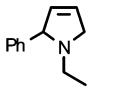
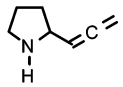
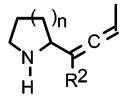
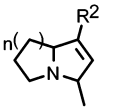
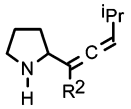
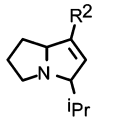
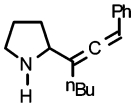
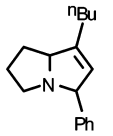
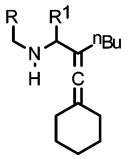
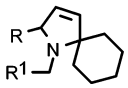
(32) Wang, Y.-F.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465−6466.

(33) (a) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870−876. (b) Hwu, J. R.; Jain, M. L.; Tsay, S.-C.; Hakimelahi, G. H. *Tetrahedron Lett.* **1996**, *37*, 2035−2038. (c) Boeckman, R. K., Jr.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411−1414. (d) Bose, D. S.; Lakshminarayana, V. *Synthesis* **1999**, 66−68.

(34) Hamada, Y.; Kato, S.; Shioiri, T. *Tetrahedron Lett.* **1985**, *26*, 3223−3226.

(35) Bechor, Y.; Falb, E.; Fischer, B.; Wexler, B. A.; Nudelman, A. *Synth. Commun.* **1998**, *28*, 471−474.

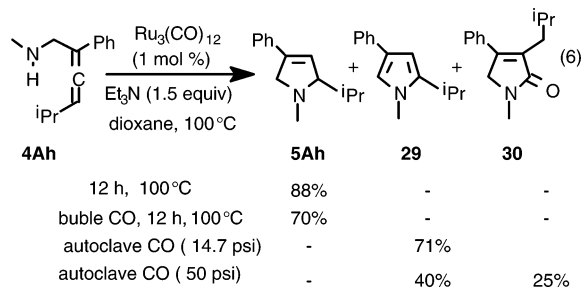
TABLE 4. $AgNO_3$ or $Ru_3(CO)_{12}$ Promoted Cyclization of α-Amino Allenes (from *N*-Boc Deprotection) to Δ^3-Pyrrolines

entry	*N*-Boc (**3**)[a]	amino allene (**4**)	R^2 or R,R^1	n	Prod. No.[b]	%[c] yield	pyrroline (**5**)	Prod. No.	%[d] yield	dr[e]
1	**3Ac**		^{n}Bu		**4Ac**	92		**5Ac**	82 (67)	
2	**3Ad**		Me_3Si		**4Ad**	62		**5Ad**	71	
3	**3Ae**		TBDMSOCH$_2$		**4Ae**	75		**5Ae**	77	
4	**3Ag**		nBu		**4Ag**	(83)		**5Ag**	57	
5	**3Ah**		Ph		**4Ah**	89-96 (95)		**5Ah**	63-70	
6	**3Ai**		Ph(CH$_2$)$_3$-		**4Ai**	84-88 (95)		**5Ai**	67	
7	**3Aj**		PhCO$_2$(CH$_2$)$_2$-		**4Aj**	86 (95)		**5Aj**	74	
8	**3Al**		^{n}Bu		**4Al**	(98)		**5Al**	72	
9	**3Am**		Ph		**4Am**	(95)		**5Am**	65	
10	**3Dc**		^{n}Bu		**4Dc**	86		**5Dc**	70	45:55
11	**3Df**		Ph		**4Df**	92		**5Df**	88 (56)	36:64
12	**3Da**				**4Da**	99		**5Da**	74	
13	**3Ba**				**4Ba**	83		**5Ba**	50	
14	**3Bc**		^{n}Bu	1	**4Bc**	83		**5Bc**	90 (78)	41:59
15	**3Cc**		^{n}Bu	2	**4Cc**	60 (95)		**5Cc**	67 (55)	50:50
16	**3Bf**		Ph	1	**4Bf**	80 (95)		**5Bf**	67 (86)	39:61
17	**3Cf**		Ph	2	**4Cf**	70 (95)		**5Cf**	63	48:52
18	**3Bg**		^{n}Bu		**4Bg**	(95)		**5Bg**	64	55:45
19	**3Bh**		Ph		**4Bh**	(95)		**5Bh**	69	59:41
20	**3Bi**		Ph(CH$_2$)$_3$-		**4Bi**	87 (95)		**5Bi**	60	55:45
21	**3Bj**		PhCO$_2$(CH$_2$)$_2$		**4Bj**	98		**5Bj**	47	56:44
22	**3Bl**				**4Bl**	(95)		**5Bl**	69	50:50
23	**16**		H		**25**	36		**26**	30	
24	**17**		-(CH$_2$)$_2$-		**27**	trace		**28**	trace	

[a] α-Carbamoyl allene derived from cuprate substitution reaction. [b] Free α-amino allenes **4** were obtained by *N*-Boc deprotection of **3** with TMSOTf [CH_2Cl_2, −30 to 25 °C, 2 h] or with MeOH/TMSCl (yields in parentheses). [c] Yields are based upon crude products homogeneous by ^{1}H and ^{13}C NMR measurements. [d] Yields based upon isolated products purified by flash column chromatography. Yields are for the $AgNO_3$-mediated cyclization, and those in parentheses are for the $Ru_3(CO)_{12}$ catalyzed cyclization reaction. [e] Diastereomeric ratios determined from ^{1}H NMR integration values and/or from ^{13}C NMR peak heights.

oxide gave a good yield of pyrroline **5Ah**. Simple treatment of **4Ah** with the ruthenium catalyst gave an excellent yield of pyrroline **5Ah**, and modest to good yields of pyrrolines could be obtained from the α-amino allenes **4Ac**, **4Df**, **4Bc**, **4Cc**, and **4Bf** (Table 4, entries 1, 11, 14−16). In general, the $AgNO_3$ method gave better yields of pyrrolines than the ruthenium-catalyzed protocol with the exception of amino allene **4Bf**. Utilization of an autoclave with an approximately 1 psi atmosphere of CO afforded pyrrole **29** again with no incorporation of CO. Increasing the CO pressure to approximately 50 psi afforded a mixture of pyrrole **29** and pyrrolin-2-one **30** in a 57:43 ratio in 70% yield. The similar carbonylation reactions of Takahashi were carried out at a CO pressure of 150 psi, and these results suggest that the ruthenium-catalyzed reaction conditions can be adjusted to afford either pyrroline, pyrrole, or pyrolinone derivatives from α-amino allenes.

(36) (a) Yoneda, E.; Kaneko, T.; Zhang, S. W.; Onitsuka, K.; Takahashi, S. *Org. Lett.* **2000**, *2*, 441−443. (b) Yoneda, E.; Zhang, S. W.; Onitsuka, K.; Takahashi, S. *Tetrahedron Lett.* **2001**, *42*, 5459−5461.



Summary

In summary, α-(*N*-carbamoyl)alkylcuprates undergo a regioselective S_N2'-substitution reaction with propargyl mesylates and phosphates, and S_N2-substitution products only arise when there is steric hindrance in the cuprate reagent or the propargyl substrate. The α-[(*N*-carbamoyl)-alkyl]cyanocuprates (RCuCNLi) are generally more effective than the lithium bis-α-(*N*-carbamoyl)alkylcuprates (R_2CuLi), although the latter reagents occasionally provide better results with sterically hindered substrates. Formation of the proparyl phosphate in situ affords a useful protocol for preparation of tertiary and allylic or benzylic propargyl phosphates, which are often unstable to isolation and purification, and this is likely to be a general procedure that will give higher yields even for those cases where the mesylate can be isolated. The resulting carbamoyl allenes can be easily deprotected to the free α-amino allenes in all cases except the tetrasubstituted allenes where formation of oxazolidinones occurs via participation of the carbamate moiety. Cyclization to pyrrolines is achieved in good to excellent yields with $AgNO_3$, and a wide array of substituted pyrrolines is available via this three-step procedure. The ready availability of enantioenriched propargyl alcohols should afford a convenient route to enantioenriched pyrrolines, and this methodology is currently under investigation. Preliminary results with ruthenium catalysts suggest that reaction conditions may be adjusted to afford synthetic routes to pyrrolines, pyrroles, or pyrrolinones from α-amino allenes.

Experimental Section

Carbamic Acid, [2,3-Butadienyl]methyl, 1,1-Dimethylethyl Ester (3Aa). To the solution of *N*-*tert*-butoxycarbonyl *N*,*N*-dimethylamine (0.290 g, 2.0 mmol) in THF (4 mL) was added TMEDA (0.330 mL, 2.2 mmol) at −78 °C under argon. *sec*-BuLi (1 M, 2.2 mL, 2.2 mmol) was added dropwise by syringe, and the reaction mixture was allowed to stir for 1 h at −78 °C. A solution of THF-soluble CuCN·2LiCl complex [prepared by dissolving CuCN (0.180 g, 2.0 mmol) and LiCl (0.168 g, 4.0 mmol); LiCl was flamed dried under vacuum prior to use and purged with argon] in THF (2 mL) at room temperature was added slowly via syringe to the 2-lithio-*N*-Boc *N*,*N*-dimethylamine at −78 °C to form the RCuCNLi reagent. The mixture was allowed to stir for 45 min at −78 °C to generate the cuprate as a homogeneous solution. A solution of propargyl bromide (0.238 g, 2.0 mmol) dissolved in THF (1 mL) was added, and the reaction mixture was allowed to warm to room temperature over 3 h. The reaction mixture was quenched with saturated NH_4Cl (aq). The mixture was diluted with Et_2O, filtered by vacuum through a thin layer of Celite, the organic phase was separated, and the aqueous phase was extracted three times with Et_2O (5 mL). The combined organic phases were washed one time with brine and dried over $MgSO_4$. Evaporation of the solvent in vacuo afforded the crude products. Purification was accomplished using flash column chromatography eluting with 5% EtOAc−95% petroleum ether (v/v) to give pure pruduct **3Aa** as a colorless oil (0.352 g, 96%): IR (neat) 2982 (s), 2933 (s), 2254 (w), 1956 (s), 1697 (s), 1486 (s), 1387 (s), 1154 (s), 876 (s), 847 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 9H), 2.80 (s, 3H), 3.78 (s, 2H), 4.72−4.80 (m, 2H), 4.97−5.09 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.4, 33.8, 47.5, 76.6, 79.4, 86.8, 155.6, 208.8. Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.57; H, 9.29; N, 7.65. Found: C, 65.54; H, 9.40; N, 7.57.

2-[(1-Propenylidene)pentyl]-1-pyrrolidinecarboxylic Acid, 1,1-Dimethylethyl Ester (3Bc). To *N*-*tert*-butoxycarbonylpyrrolidine (0.342 g, 2.0 mmol) in THF (4 mL) cooled to −78 °C was added TMEDA (0.33 mL, 2.2 mmol). *sec*-BuLi (1 M, 2.2 mL, 2.2 mmol) was added by syringe, and the reaction mixture was allowed to stir for 1 h at −78 °C. A solution of THF-soluble CuCN·2LiCl complex [prepared by dissolving CuCN (0.090 g, 1.0 mmol) and LiCl (0.084 g, 2.0 mmol); LiCl was flamed dried under vacuum prior to use and purged with argon] in THF (2 mL) at room temperature was added slowly via syringe to the 2-lithio-*N*-*tert*-butoxycarbonylpyrrolidine at −78 °C to form the R_2CuLi·LiCN reagent. The mixture was allowed to stir for 45 min at −78 °C to generate the cuprate as a homogeneous solution. A solution of the propargyl mesylate **2c** (0.204 g, 1.0 mmol) [prepared from alcohol **11c** (1.260 g, 10.0 mmol) in dry CH_2Cl_2 (20 mL) added with Et_3N (1.52 g, 15.0 mmol) and methanesulfonyl chloride (1.38 g, 12.0 mmol) at −40 °C. The reaction mixture was stirred under nitrogen from −40 °C to room temperature over 2 h, quenched with saturated $NaHCO_3$ (aq), and extracted by CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under vacuum to afford crude mesylate **2c** (1.99 g, 98%) which was used without further purification] dissolved in THF (1 mL) was added, and the reaction mixture was allowed to warm to room temperature over 3 h. The reaction was quenched with saturated NH_4Cl (aq). The mixture was diluted with Et_2O, filtered by vacuum through Celite, the organic phase was separated, and the aqueous phase was extracted three times with Et_2O (10 mL). The combined organic phases were washed one time with brine and dried over $MgSO_4$. Evaporation of the solvent in vacuo afforded the crude product. Purification was accomplished using flash column chromatography eluting with 5% EtOAc−95% petroleum ether (v/v) to give pure **3Bc** (0.218 g, 78.0%) as a colorless oil: IR (neat) 2979 (s), 2877 (shoulder), 1966 (w), 1710 (s), 1470 (s), 1387 (s), 1260 (s), 1174 (s), 1115 (s), 928 (m), 885 (s), 783 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, J = 6.70−6.87 Hz, 3H), 1.20−1.50 (m, 4H), 1.41 (s, 9H) (1.40), 1.57 (d, J = 6.85 Hz, 3H), 1.68−2.00 (m, 6H), 3.17−3.41 (m, 2H), 3.96−4.24 (m, 1H), 5.00−5.21 (m, 1H) (rotamer and/or diastereomer); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 14.6, 22.4, 23.2, 28.5, 29.2, 29.8, 31.1, 45.8, 58.8 (59.3), 78.7, 88.8 (88.6), 106.3, 154.3, 200.1 (rotamer and/or diastereomer); mass spectrum *m*/*z* (relative intensity) EI 223 (18, $M^+ - C_4H_8$), 222 (5, $M^+ - C_4H_9$), 194 (10), 170 (7, $M^+ - C_8H_{13}$), 114 (100), 70 (81, $C_4H_8N^+$), 57 (69, $C_4H_9^+$). Anal. Calcd for $C_{17}H_{29}NO_2$: C, 73.07; H, 10.46; N, 5.01. Found: C, 73.30; H, 10.57; N, 5.15.

2-(1-Phenyl-1,2-butadienyl)pyrrolidine (4Bf). To a solution of *N*-Boc-protected amino allene **3Bf** (0.301 g, 1.0 mmol) in MeOH (5.0 mL) was added TMSCl (0.540 g, 5.0 mmol) via syringe at 25 °C. Stirring was continued at room temperature for 12 h. The reaction mixture was then quenched with saturated $NaHCO_3$ (aq) and diluted with CH_2Cl_2. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extractions were dried over $MgSO_4$, concentrated under vacuum to afford crude product **4Bf** (0.190 g, 95%), which was pure by both ^1H and ^{13}C NMR analysis: IR (neat) 3058 (m), 3024 (m), 2962 (s), 2968 (s), 1949 (m), 1587 (m), 1450 (s), 1287 (s), 1259 (s), 732 (s), 639 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.52−2.01 (m, 6H), 2.73−3.02 (m, 3H), 4.05 (s, 1H), 5.11−5.21 (m, 1H), 5.46−

5.63 (m, 1H), 7.12−7.49 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4 (14.6), 25.2 (25.3), 31.7 (31.9), 46.4 (46.5), 57.1 (57.3), 91.8 (92.0), 109.3 (109.5), 126.6 (126.7), 126.8 (126.9), 128.5, 136.2 (136.3), 202.2 (202.4) (diasteromers, 39/61); mass spectrum *m/z* (relative intensity), EI 200 (7, $M^+ + 1$), 199 (41, M^+), 184 (100), 170 (44), 156 (28), 128 (17), 115 (16), 77 (10), 51 (7).

Alternatively, to a solution of *N*-Boc-protected amino allene **3Bf** (0.939 g, 3.14 mmol) in CH_2Cl_2 (10 mL) was added TMSOTf (0.74 mL, 4.07 mmol) via syringe at −40 °C. The reaction mixture was slowly warmed to room temperature over 3 h. The reaction mixture was washed with saturated K_2CO_3 (aq). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extractions were dried over $MgSO_4$, concentrated under vacuum to afford crude product **4Bf** (0.570 g, 91%).

1-Methyl-3-isopropyl-4-phenyl-2,5-dihydro-1H-pyrrole (5Ah). Crude amino allene **4Ah** (0.135 g, 0.67 mmol) was dissolved in technical grade acetone (from drum, without further purification), followed by addition of a catalytic amount of $AgNO_3$ (0.023 g, 0.14 mmol). The reaction mixture was stirred at room temperature under nitrogen in the dark for 12 h (flask was wrapped with aluminum foil). The reaction mixture was then diluted with Et_2O, filtered through a thin layer of Celite, and concentrated under vacuum to afford crude product **5Ah** which was purified by flash chromatography (silica gel, 100% diethyl ether as eluent) to give a colorless oil (0.094 g, 70%): IR 2960 (s), 2868 (s), 2774 (s), 1496 (s), 1467 (s), 1452 (s), 1387 (s), 1357 (m), 912 (s), 740 (s); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (d, J = 6.7 Hz, 3H), 1.03 (d, J = 6.9 Hz, 3H), 1.72−1.88 (m, 1H), 2.54 (s, 3H), 3.31−3.42 (m, 1H), 3.57−3.65 (m, 1H), 4.21−4.32 (m, 1H), 6.08 (d, J = 1.5 Hz, 1H), 7.24−7.44 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.0, 19.9, 31.9, 43.0, 63.4, 79.6, 123.6, 125.4, 127.4, 128.4, 134.4, 138.9; mass spectrum *m/z* (relative intensity) EI 201 (2, M^+), 200 (6, $M^+ - 1$), 199 (32, $M^+ - 2$), 184 (97), 158 (100), 143 (19), 128 (11), 115 (17), 91 (99), 77 (98), 51 (7). Anal. Calcd for $C_{14}H_{19}N$: C, 83.58; H, 9.45. Found: C, 83.31; H, 9.65.

Carbamic Acid, [2-[(Cyclohexylidene)methylene]hexyl]-methyl-, 1,1-Dimethylethyl Ester (16). To *N-tert*-butoxycarbonyl-*N*,*N*-dimethylamine (0.145 g, 1.0 mmol) in THF (2 mL) cooled to −78 °C was added TMEDA (0.16 mL, 1.2 mmol). *sec*-BuLi (1.0 mmol) was added by syringe, and the mixture was allowed to stir for 1 h at −78 °C. A THF-soluble CuCN·2LiCl complex [prepared by dissolving CuCN (0.0895 g, 1 mmol) and LiCl (0.0840 g, 2 mmol); LiCl was flamed dried under vacuum prior to use and purged with argon] in THF (2 mL) at room temperature was added via syringe to the 2-lithio-*N*-Boc-pyrrolidine at −78 °C. The mixture was allowed to stir at −78 °C for 45 min to generate a clear homogeneous solution of the RCuCNLi reagent. A crude sample of propargyl phosphate **13c** was added dropwise [prepared in situ from alcohol **12** (0.180 g, 1 mmol) in 3 mL of THF at −78 °C by addition of LDA (prepared from diisopropylamine 0.202 g, 2.0 mmol) and *n*-BuLi (2 M, 0.75 mL, 1.5 mmol) in THF at −40 °C for 1 h) or alternatively *n*-BuLi (2 M, 0.6 mL, 1.2 mmol) followed by the addition of diphenyl chlorophosphate (0.403 g, 1.5 mmol) and stirring for 1 h at −40 °C, and then at 0 °C for another hour] whereupon the reaction mixture was allowed to warm to room temperature over a 3 h period. The reaction was quenched with saturated NH_4Cl (aq). The mixture was diluted with Et_2O, filtered by vacuum through Celite, the organic phase was separated, and the aqueous phase was extracted three times with 10 mL of Et_2O. The combined organic phases were washed one time with brine and dried over $MgSO_4$. Evaporation of the solvent in vacuo afforded product. Purification was accomplished using flash column chromatography eluting with 5% EtOAc−95% petroleum ether (v/v) to give **16** (0.221 g, 72%): IR (neat) 2923 (s), 2852 (m), 1700 (s), 1481 (w), 1448 (m), 1383 (s), 1361 (m), 1235 (m), 1181 (m), 1137 (m), 880 (w), 766 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.3 Hz, 3H), 1.44 (s, 9H), 1.25−1.75 (m, 13H), 1.84 (t, J = 7.2 Hz, 1H), 2.06 (2.07) (s, 2H), 2.79 (s, 3H), 3.71 (br s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 22.2, 26.2, 27.7, 28.4, 29.7, 29.8, 31.9, 33.5, 51.5 (51.0), 79.0, 98.1, 104.6, 155.7, 195.2; mass spectrum *m/z* (relative intensity) EI 307 (M^+, 0.05), 251 (30), 234 (8), 206 (6), 178 (9), 163 (13), 134 (35), 88 (22), 57 (100).

2-[1-[(2-Hydroxycyclohexylidene)methylene]pentyl]-1-pyrrolidinecarboxylic Acid, 1,1-Dimethylethyl Ester (20). To *N-tert*-butoxycarbonylpyrrolidine (0.171 g, 1.0 mmol) in THF (2 mL) cooled to −78 °C was added (−)-sparteine (0.280 g, 1.2 mmol). *sec*-BuLi (1 M, 1.1 mmol) was added by syringe, and the mixture was allowed to stir for 1 h at −78 °C. A light-green solution of THF-soluble CuCN·2LiCl complex [prepared by dissolving CuCN (0.090 g, 1 mmol) and LiCl (0.084 g, 2 mmol); LiCl was flamed dried under vacuum prior to use and purged with argon] in THF (2 mL) at room temperature was added via syringe to the 2-lithio-*N*-Boc-pyrrolidine (clear to pale yellow) at −78 °C. The mixture was stirred at −78 °C for 0.5 to 1 h to generate the RCuCNLi cuprate as a clear to light-yellow homogeneous solution. Next, 0.049 g, 0.10 mmol of Sc(OTf)$_3$ was added to the resultant cuprate, and the solution was stirred at −50 °C for 10 min. A solution of 1-hexynyl-7-oxabicyclo [4.1.0] heptane (0.178 g, 1.0 mmol) dissolved in ether (1 mL) was added, and the reaction mixture was stirred at −50 °C for 1 h. The reaction was quenched with saturated NH_4Cl (aq). The mixture was further diluted with Et_2O and filtered by vacuum through Celite. The organic phase was separated, and the aqueous phase was extracted three times with Et_2O. The crude product was obtained, and purification by column chromatography eluting with 10% EtOAc−90% petroleum ether (v/v) solvent mixture gave pure **20** (0.161 g, 46 % yield): IR (neat) 3437 (broad), 2939 (s), 2867 (shoulder), 1966 (w), 1685 (s), 1411 (s), 1267 (s), 1186 (s), 1114 (s), 1043 (s), 1018 (s), 921 (m), 849 (s), 737 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, J = 7.1 Hz, 3H), 1.09−1.55 (m, 8H), 1.38 (s, 9H), 1.57−1.98 (m, 9H), 2.00−2.14 (m, 1H), 2.15−2.32 (m, 1H), 3.10−3.35 (m, 2H), 3.71−3.85 (m, 1H) (3.85−3.96), 4.07 (br d, J = 4.07 Hz, 1H) (rotamers and/or diastereomer); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9 (13.8), 22.3 (22.1), 22.9 (23.7), 24.5, 27.1 (26.9), 28.3, 29.3 (29.5), 29.8 (2C) (29.9), 30.3 (30.9), 35.5, 46.3 (45.8), 59.1 (59.5), 69.0 (68.6), 79.2 (79.9), 109.3, 112.2 (112.0), 154.9 (154.0), 189.7 (rotamer and/or diastereomer); mass spectrum *m/z* (relative intensity) EI 293 (1, $M^+ - C_4H_8$), 275 (10), 258 (2), 218 (30), 188 (4), 162 (9), 114 (86), 91 (12), 70 (100), 57 (62, $C_4H_9^+$).

5-Butyl-5-[(*E*)-1-propenyl)-3-methyl-2-oxazolidinone (22). A solution of 1 M TMSCl (6.23 mL, 49.1 mmol) in CH_2Cl_2 and 4 M phenol (13.9 g, 148 mmol) in CH_2Cl_2 was stirred under a nitrogen atmosphere at room temperature for 20 min. This solution was added by syringe to *N*-Boc allene **3Ac** (0.84 g, 3.32 mmol) in CH_2Cl_2 at room temperature and stirred for 12 h. The reaction mixture was washed three times with 10 mL of 10% NaOH, and then the organic layer was dried over $MgSO_4$. The solvent was evaporated in vacuo and afforded **22**. Purification was accomplished using column chromatography eluting with 10% EtOAc−90% petroleum ether (v/v) mixture of solvent to give **22** (0.496 g, 76%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.79 (t, J = 6.9 Hz, 3H), 1.08−1.40 (m, 4H), 1.51−1.76 (m, 2H), 1.62 (d, J = 6.5 Hz, 3H), 2.76 (2.78) (s, 3H), 3.31 [center of AB quartet, J_{AB} = 8.4, $\Delta\upsilon$ = 42 Hz, δ_A = 3.24, δ_B = 3.38, 2H], 5.36 (d, J = 13 Hz, 1H), 5.66 (dq, J = 13.0 Hz, J = 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7 (14.3), 17.4, 22.5, 25.1, 30.7 (30.6), 39.2 (40.2), 56.8 (58.0), 80.0 (80.9), 125.5 (126.9), 131.4 (131.9), 157.7 (157.5).

3-Isobutyl-1,5-dihydro-1-methyl-4-phenyl-(2H)-pyrrol-2-one (30). Amino allene **4Ah** (0.065 g, 0.32 mmol) was dissolved in 1,4-dioxane (10 mL) in an autoclave (100 mL), followed by Et_3N (0.07 mL, 0.48 mmol) and $Ru_3(CO)_{12}$ (0.002 g). The autoclave was sealed, evacuated under vacuum, and flushed with CO three times (directly from CO tank regulator, 50 PSI maximum). The autoclave was heated with a heating tape to 100 °C overnight. The reaction mixture was cooled to room temperature and transferred to a flask. The solvent was removed under vacuum to afford the crude product, which was

purified by flash chromatography (silica gel, ether/petroleum ether, 1/1, v/v) to afford pyrrole **29** 0.025 g (40%) and lactam **30** 0.019 g (25%). Lactam **30**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.79 (d, J = 6.9 Hz, 6H), 1.92−2.04 (m, 1H), 2.35 (d, J = 7.3 Hz, 2H), 3.04 (s, 3H), 4.08 (s, 2H), 7.27−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.7, 22.8, 27.5, 29.3, 33.5, 54.7, 127.3, 127.4, 128.7, 133.8, 134.2, 146.8, 172.4; mass spectrum *m/z* (relative intensity) EI 230 (12, $M^+ + 1$), 229 (73, M^+), 228 (54), 214 (27), 187 (100), 186 (71), 172 (47), 158 (13), 144 (12), 128 (24), 115 (18), 91 (8), 77 (10).

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Supporting Information Available: General experimental information, materials, and data reduction for **3A**(**b**−**j**, **l**, **m**), **3B**(**a**, **b**, **d**−**l**, **n**, **o**), **3C**(**a**−**c**, **e**, **f**), **3D**(**a**, **c**, **f**), **4A**(**c**−**e**, **g**−**j**, **l**, **m**), **4B**(**a**, **c**, **g**−**j**, **l**), **4C**(**c**, **f**), **4D**(**a**, **c**, **f**), **5A**(**c**−**e**, **g**, **i**, **j**, **l**, **m**), **5B**(**a**, **c**, **f**−**j**, **l**), **5C**(**c**, **f**), **5D**(**a**, **c**, **f**), **17**−**19**, **21**, **23**−**26**, and ^{13}C NMR spectra for **3A**(**d**, **g**−**j**, **l**, **m**), **3B**(**b**, **g**−**l**, **n**, **o**), **3C**(**a**, **c**, **f**), **3D**(**a**, **c**, **f**), **4A**(**c**, **e**, **g**−**j**, **l**, **m**), **4B**(**a**, **g**−**i**, **l**), **4C**(**c**, **f**), **4D**(**a**, **c**, **f**), **5A**(**c**−**e**, **g**), **5B**(**a**, **f**−**j**), **5C**(**c**, **f**), **5D**(**a**, **c**, **f**), **16**, **17**, **19**, **20**, **22**, **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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