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Reaction of α-(*N*-Carbamoyl)alkylcuprates with Enantioenriched Propargyl Electrophiles: Synthesis of Enantioenriched 3-Pyrrolines

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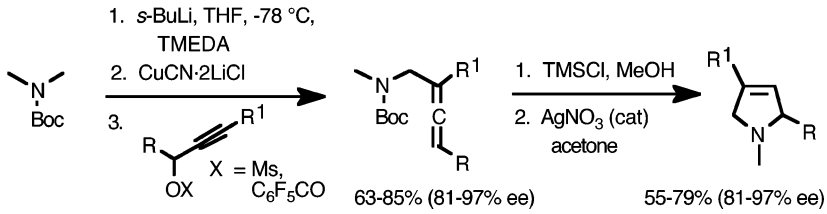

Enantioenriched propargyl mesylates or perfluorobenzoates react with α-(*N*-carbamoyl)alkylcuprates to afford scalemic α-(*N*-carbamoyl) allenes which undergo *N*-Boc deprotection and $AgNO_3$-promoted cyclization to afford *N*-alkyl-3-pyrrolines. The synthetic sequence proceeds under optimal conditions with no loss of enantiopurity relative to the starting propargyl alcohols prepared by asymmetric addition of terminal alkynes to aldehydes.

Introduction

Δ^3-Pyrrolines are a synthetically useful[1,2] and biologically[3] interesting class of *N*-containing compounds. They serve as inhibitors of monoamine oxidase (MAO)[3a−d] which plays an important role in psychopharmacology.[4] A variety of synthetic routes to racemic 3-pyrrolines have been reported,[5] and some of these approaches are amenable to the synthesis of enantioenriched (i.e., scalemic) products. Asymmetric syntheses have included reaction of α-(*N*-carbamoyl)alkyl[6a] and α-iminoalkylcuprates[6b] with scalemic propargyl substrates, alkylidene carbene 1,5-CH insertion reactions,[7] addition of 1-lithio-1-methoxy allene to SAMP or RAMP hydrazones[8a−c] or chiral imines,[8d] cyclization of (*Z*)-amino allylic mesylates,[9] reaction of scalemic α-amino ketones with vinyl phosphonium salts,[10] and asymmetric arylation[11] of 2-pyrrolines. More recently, the base[12a] and $AuCl_3$-catalyzed[5c] cyclization of α-allenylsulfonamides has been reported.

Although proof of concept for the α-(*N*-carbamoyl)alkylcuprate route was demonstrated with a single example,[6a] the enantioselectivity appeared to degrade at some point along the synthetic sequence. We now report an efficient enantioselective synthesis of 3-pyrrolines wherein the enantiomeric purity of the

(1) Garcia, A. L. L.; Carpes, M. J. S.; de Oca, A. C. B. M.; dos Santos, M. A. G.; Santana, C. C.; Correia, C. R. D. *J. Org. Chem.* **2005**, *70*, 1050−1053.

(2) For use of pyrrolines in aza sugar synthesis, see: (a) Chang, D.; Heringa, M. F.; Witholt, B.; Li, Z. *J. Org. Chem.* **2003**, *68*, 8599−8606. (b) Huwe, C. M.; Blechert, S. *Tetrahedron Lett.* **1995**, *36*, 1621−1624.

(3) For pyrrolines as monoamine oxidase inhibitors, see: (a) Lee, Y.; Ling, K.-Q.; Lu, X.; Silverman, R. B.; Shepard, E. M.; Dooly, D. M.; Sayre, L. M. *J. Am. Chem. Soc.* **2002**, *124*, 12135−12143. (b) Williams, C. H.; Lawson, J. *Neurobiology* **1999**, *7*, 225−233. (c) Williams, C. H.; Lawson, J. *Biochem. J.* **1998**, *336*, 63−67. (d) Lee, Y.; Huang, H.; Sayre, L. M. *J. Am. Chem. Soc.* **1996**, *118*, 7241−7242. As NMDA receptor agonists see: (e) Rondeau, D.; Gill, P.; Chan, M.; Curry, K.; Lubell, W. D. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 771−773. As k-agonists see: (f) 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: (g) Anderson, W. K.; Milowsky, A. S. *J. Med. Chem.* **1987**, *30*, 2144−2147.

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(6) (a) Dieter, R. K.; Yu, H. *Org. Lett.* **2001**, *3*, 3855−3858. (b) Horváth, A.; Benner, J.; Bäckvall, J.-E. *Eur. J. Org. Chem.* **2004**, 3240−3243.

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(10) Burley, I.; Hewson, A. T. *Tetrahedron Lett.* **1994**, *35*, 7099−7102.

(11) Ozawa, F.; Hayashi, T. *J. Organomet. Chem.* **1992**, *428*, 267−277.

(12) Ohno, H.; Kadoh, Y.; Fujii, N.; Tanaka, T. *Org. Lett.* **2006**, *8*, 947−950.

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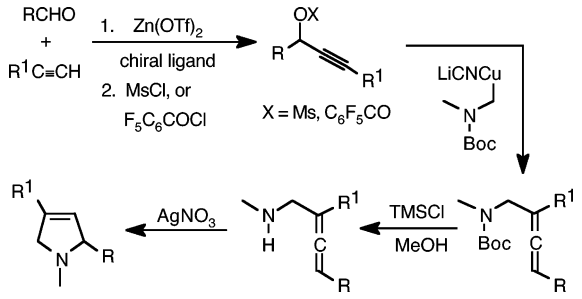
SCHEME 1

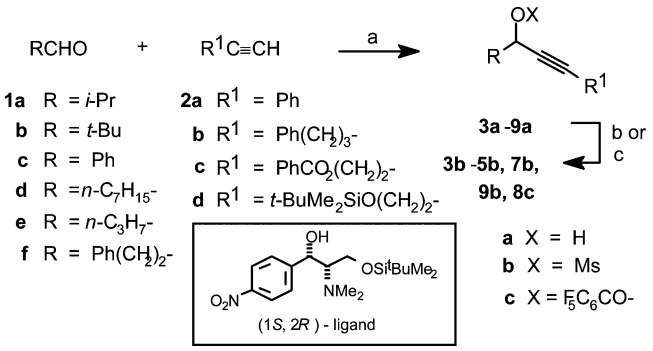


3-pyrroline reflects the enantiomeric ratio of the starting propargyl alcohol. The synthetic sequence involves asymmetric 1,2-addition of metalated 1-alkynes to aldehydes,[13,14] mesylate or perfluorobenzoate[15] formation, cuprate S_N2' substitution on propargyl substrates,[16] *N*-Boc deprotection, and $AgNO_3$-promoted cyclization (Scheme 1).[5a] The near quantitative yields in mesylate formation and *N*-Boc deprotection provide for an efficient process. Although the α-(*N*-carbamoyl)alkylcuprates provide for variation in substitution pattern, the focus of this study was on controlling the enantioselectivity throughout the synthetic sequence.

Results and Discussion

Although scalemic propargyl alcohols can be prepared by asymmetric reduction of α,*β*-ynones,[17] we utilized Jiang's[14] modification of Carreira's[13] strategy for the asymmetric addition of 1-alkynylzinc reagents to aldehydes in the presence of chiral amino alcohols (Scheme 2, Table 1.). Heating (70 °C, 48 h) a mixture of aldehyde (1.0 equiv), 1-alkyne (3.0 equiv), and catalytic amounts of reagents [$Zn(OTf)_2$, Et_3N, (1*S*,2*R*), or (1*R*,2*S*)-3-(*tert*-butyldimethylsilyloxy)-2-*N*,*N*-(dimethylamino)-1-(*p*-nitrophenyl)propan-1-ol][14c] under solvent-free conditions gave good yields of propargyl alcohols with excellent enantiomeric excesses with α-branched aldehydes (Table 1, entries 1−9 and 14). The reaction tolerated alkynyl alcohols protected as esters or silyl ethers (entries 3, 4 and 7, 8). Utilization of butanal or 3-phenylpropanal afforded only traces of product (entries 12, 13 and 17, 18) under solvent-free conditions. The *diminished yields with* straight chain aldehydes[13c,d] *or n*-alkyl-substituted glyoxylates[14a] have been attributed to enolization followed by aldol condensation reactions. Utilization of toluene as solvent,

SCHEME 2[a]



[a] Conditions: (a) RCHO (1.0 equiv), $Zn(OTf)_2$ (0.22 equiv), (1*S*,2*R*) or (1*R*,2*S*)-3-(*tert*-butyldimethylsilyloxy)-2-*N*,*N*-(dimethylamino)-1-(*p*-nitrophenyl)propan-1-ol (0.22 equiv), alkyne (3.0 equiv), Et_3N (0.3 equiv), 25 °C, 2 h, 70 °C, 48 h; (b) $MeSO_2Cl$, Et_3N, CH_2Cl_2, −40 °C, 2 h (93−95%); (c) F_5C_6COCl (1.2 equiv), CH_2Cl_2, pyridine (1.5 equiv), DMAP (0.05 equiv), 0 to 25 °C, 2 h (82%).

coupled with slow addition of the aldehyde,[13c] gave modest yields with octanal (entries 11 and 16), although the procedure could not be extended to shorter chain aldehydes, such as butanal or 3-phenylpropanal. For straight chain aldehydes, stoichiometric amounts of the chiral ligand (+)-*N*-methylephedrine could be employed since it gave the same enantiomeric excess as (1*S*,2*R*)-3-(*tert*-butyldimethylsilyloxy)-2-*N*,*N*-(dimethylamino)-1-(*p*-nitrophenyl)propan-1-ol (entry 11). Similarly, benzaldehyde gave only trace amounts of propargyl alcohols under solvent-free conditions, and modest yields could be achieved using toluene as solvent and stoichiometric amounts of chiral ligand (entries 10 and 15). In all instances where modest to excellent chemical yields could be achieved, excellent enantioselectivity (81−99% ee) was observed. Although our chemical yields and enantioselectivities were comparable to those reported by Jiang[14] and Carreira,[13c,d] it should be noted that difficulties have been reported in the literature, and these appear to revolve around the source and particle size of the $Zn(OTf)_2$ and its dryness.[13e,f]

The monoconjugated propargyl sulfonate esters were readily prepared ($MeSO_2Cl$, Et_3N, CH_2Cl_2, −40 °C) in excellent yields (93−95%) at low temperatures and were isolated and used without purification. When the alcohol was both benzylic and propargylic, attempts to prepare the mesylate were unsuccessful, resulting in formation of the corresponding chloride.[18] These propargyl benzyl alcohols could be readily converted into the perfluorobenzoates which were stable to chromatography.[15]

Carbamate deprotonation (*s*-BuLi, THF, TMEDA, −78 °C, 1 h),[19] cuprate formation, and reaction with the propargyl mesylates proceeded as previously described for the racemic analogues.[5a] Good chemical yields and enantiomeric excesses were obtained (Table 2). Although formation of metallic copper is known to isomerize scalemic allenes,[20] the enantiomeric excesses of the α-*N*-carbamoyl allenes were identical to the values measured for the starting propargyl alcohols (i.e., Table 1 entries reproduced in Table 2 vs Table 2 product entries, respectively). Although the use of tri-*n*-butylphoshine to suppress allene isomerization[20] can be quite dramatic,[20b] its use in

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(14) (a) Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451−3453. (b) Jiang, B.; Chen, Z.; Xiong, W. *Chem. Commun.* **2002**, 1524−1525. (c) The chiral ligand (1*S*,2*R*)-3-(*tert*-butyldimethylsilyloxy)-2-*N*,*N*-(dimethylamino)-1-(*p*-nitrophenyl)propan-1-ol], derived from the (1*S*,2*S*) alcohol, is incorrectly labeled as the (1*S*,2*S*) silyl ether isomer in these papers.

(15) Harrington-Frost, N.; Leuser, H. M.; Calaza, I.; Kneisel, F. F.; Knochel, P. *Org. Lett.* **2003**, *5*, 2111−2114.

(16) (a) Ohno, H.; Nagaoka, Y.; Tomioka, K. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Chapter 4, pp 141−181. (b) Jansen, A.; Krause, N. *Inorg. Chim. Acta* **2006**, *359*, 1761−1766 and references therein.

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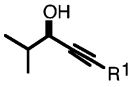
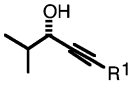
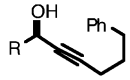
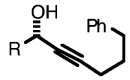
(18) The downfield absorptions for the carbinol methine proton [δ 6.76 (t, J = 2.1 Hz, 1H)] and carbinol carbon [δ = 64.9] were shifted upfield, δ 4.03 and δ 46.2, respectively, as expected for the less electronegative chlorine substituent.

(19) Beak, P.; Lee, W. K. *J. Org. Chem.* **1990**, *55*, 2578−2580.

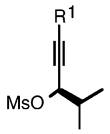
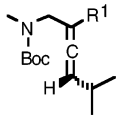
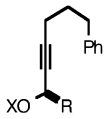
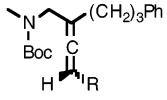
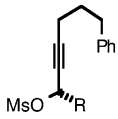
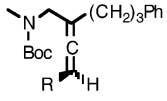
(20) (a) Alexakis, A. *Pure Appl. Chem.* **1992**, *64*, 387−392. (b) Krause, N.; Purpura, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4355−4356.

TABLE 1. Asymmetric Addition of Terminal Alkynes to Aldehydes

entry	RCHO	alkyne	ligand[a]	product[b]	R^1 or R	cpd no.	% yield[c]	% ee[d]
1	**1a**	**2a**	(1*S*, 2*R*)		Ph-	**3a*R***	81	81[e]
2	**1a**	**2b**	(1*S*, 2*R*)		$Ph(CH_2)_3$-	**4a*R***	85	93
3	**1a**	**2c**	(1*S*, 2*R*)		$PhCO_2(CH_2)_2$-	**5a*R***	87	99
4	**1a**	**2d**	(1*S*, 2*R*)		*t*-$BuMe_2SiO(CH_2)_2$-	**6a*R***	85	90
5	**1a**	**2a**	(1*R*, 2*S*)		Ph-	**3a*S***	83	86-78
6	**1a**	**2b**	(1*R*, 2*S*)		$Ph(CH_2)_3$-	**4a*S***	84	80
7	**1a**	**2c**	(1*R*, 2*S*)		$PhCO_2(CH_2)_2$-	**5a*S***	83	99
8	**1a**	**2d**	(1*R*, 2*S*)		*t*-$BuMe_2SiO(CH_2)_2$-	**6a*S***	87	90
9	**1b**	**2b**	(1*S*, 2*R*)		*t*-Bu-	**7a*R***	91	93
10	**1c**	**2b**	(1*S*, 2*R*)		Ph-	**8a*R***	53[e]	90
11	**1d**	**2b**	(+)-NME		n-C_7H_{15}-	**9a*R***	48[f]	90
12	**1e**	**2b**	(1*S*, 2*R*)		n-C_3H_7-	**10a*R***	trace	-
13	**1f**	**2b**	(1*S*, 2*R*)		$Ph(CH_2)_2$-	**11a*R***	10	-
14	**1b**	**2b**	(1*R*, 2*S*)		*t*-Bu-	**7a*S***	91	93
15	**1c**	**2b**	(1*R*, 2*S*)		Ph-	**8a*S***	59[e]	93
16	**1d**	**2b**	(1*R*, 2*S*)		n-C_7H_{15}-	**9a*S***	55[g]	97
17	**1e**	**2b**	(1*R*, 2*S*)		n-C_3H_7-	**10a*S***	trace	-
18	**1f**	**2b**	(1*R*, 2*S*)		$Ph(CH_2)_2$-	**11a*S***	10	

[a] (1*S*,2*R*) or (1*R*,2*S*)-3-(*tert*-butyldimethylsilyloxy)-2-*N*,*N*-(dimethylamino)-1-(*p*-nitrophenyl)propan-1-ol. [b] Catalytic procedure was used unless otherwise noted. (i) $Zn(OTf)_2$ (0.22 equiv), chiral ligand (0.22 equiv), alkyne (3.0 equiv), Et_3N (0.3 equiv), 25 °C, 2 h; (ii) aldehyde (1.0 equiv), 70 °C, 48 h. [c] Yields are based upon isolated products purified by column chromatography. [d] Enantiomeric ratios were determined by chiral stationary phase HPLC on a CHIRALCEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel] on the benzoate derivatives of chiral alcohols **3**−**9**. [e] PhMe was used as solvent with a stoichiometric amount of chiral ligand. [f] A stoichiometric amount of (+)-*N*-methylephedrine (NME) was employed. [g] Stoichiometric amount of the (1*R*,2*S*) ligand was employed.

TABLE 2. Reactions of the Cuprate (RCuCNLi) Reagent Derived from *N*-Boc-*N*,*N*-Dimethylamine with Scalemic Propargyl Electrophiles

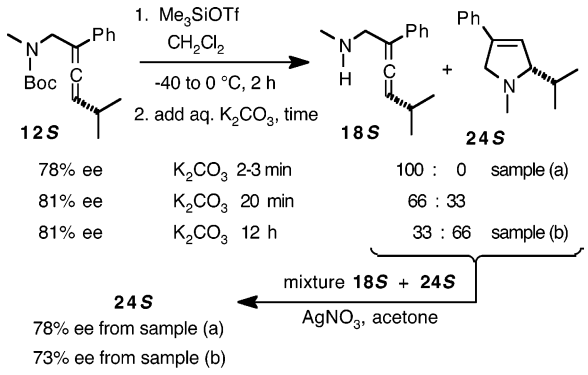
entry	propargyl substrate[a]	R^1 or R	% ee[b]	cpd no.	% yield[c]	product[d]	cpd no.	% yield[e]	% ee[f]
1		Ph	81	**3b*R***	95		**12*S***	81	81
2		Ph	81	**3b*R***	93		**12*S***	63	78[g]
3		$Ph(CH_2)_3$-	93	**4b*R***	95		**13*S***	78	93
4		$PhCO_2(CH_2)_2$-	99	**5b*R***			**14*S***	74	99
5		*t* –Bu	93	**7bR**	95		**15*S***	85	93
6		Ph	90	**8cR**	82[h]		**16*S***	77	90
7		n-C_7H_{15}	90	**9bR**	95		**17*S***	79	90
	b X = Ms **c** X = F_5C_6CO								
8		*t* –Bu	93	**7bS**	95		**15*R***	85	93
9		n-C_7H_{15}	97	**9bS**	95		**17*R***	80	97

[a] Prepared from the alcohols with methanesulfonyl chloride or pentafluorobenzoyl chloride. [b] Enantiomeric ratios were determined by chiral stationary phase HPLC on a CHIRALCEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel] on the benzoate esters of the enantiomerically enriched propargyl alcohols and are assumed to be the same for the mesylate or perfluorobenzoate esters. [c] Yield of crude propargyl mesylate which was used without purification. [d] *N*-Boc deprotonation [*s*-BuLi, THF, TMEDA, −78 °C, 1 h], cuprate formation [−78 °C, 45 min] followed by reaction with scalemic propargyl substrate [−78 to 25 °C, 12 h]. [e] Average yields of 2−3 reactions based upon isolated material purified by column chromatography. [f] Enantiomeric ratios were determined by chiral stationary phase HPLC on a CHIRALCEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel]. [g] *n*-Bu_3P (1.0 equiv) was added to the cuprate solution prior to addition of the propargyl mesylate **3b*R*** (81% ee). [h] The perfluorobenzoate propargyl ester was employed.

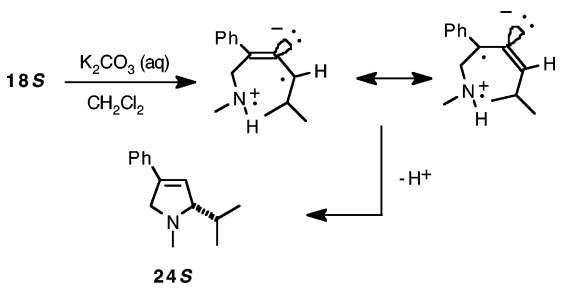
the present cuprate substitution reaction was examined and did not give higher enantiomeric purities in the product α-*N*-carbamoyl allenes (entry 2).

N-Boc deprotection of α-(*N*-carbamoyl)alkylcuprates was initially achieved with trimethylsilyltriflate [TMSOTf (1.1 equiv), CH_2Cl_2, −40 to 0 °C] followed by neutralization with K_2CO_3 (Scheme 3). Variation among several experiments revealed that the free amine **18*S*** underwent cyclization to pyrroline **24*S*** in the CH_2Cl_2/K_2CO_3 biphasic medium with loss of enantiomeric purity as a function of time (Scheme 3). When aqueous K_2CO_3 was added to the reaction mixture and stirred for 2−3 min followed by separation of the layers, only **18*S*** was isolated. If the CH_2Cl_2/K_2CO_3 biphasic medium containing **18*S*** was allowed to stir for longer periods of time, increasing amounts of **24*S*** were present in the product mixture reaching a 33:66 ratio of **18*S***:**24*S*** after 12 h. Treatment of sample (a) containing only **18*S*** with $AgNO_3$ gave pyrroline **24*S*** of the same enantiomeric purity as the starting *N*-Boc allene **12*S***. In contrast,

SCHEME 3



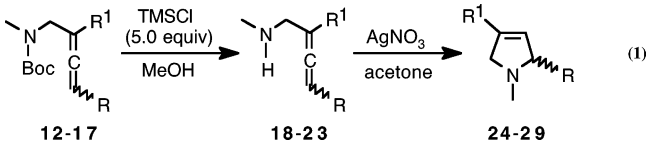
SCHEME 4



treatment of sample (b) containing a 33:66 mixture of **18*S***:**24*S*** with $AgNO_3$ gave **24*S*** with diminished enantiomeric purity relative to that measured for the starting *N*-Boc allene **12*S***.

Precedent for this base-induced cyclization is found in the reported cyclization of *ortho*-allenyl phenoxides[21] and α-allenyl alkoxides,[22] sulfonamide anions,[8d,12] and hydrazides.[8a−c] In contrast to the formal 5-*endo-trig* intramolecular cyclizations, oxime[23] and thiolate[24] anions (as well as the *ortho*-substituted phenoxide) add to the central carbon atom of allene. The latter reactions occur in the presence of allene−propyne isomerization events and may well involve nucleophilic addition to propyne. It has been suggested that nucleophilic additions to allene do not occur.[24] Mechanistic studies of α-allenyl alkoxide[22d] and hydrazide[8b] cyclizations implicate a SET pathway generating a heteroatom radical and an allyl radical anion that collapse to the heterocyclic product. Although many of these cyclizations are conducted between 50 and 180 °C,[8d,12,22a,d] several α-allenyl hydrazide anions[8a,b] with favorable substitution patterns undergo cyclization at −25 °C. The K_2CO_3-promoted cyclization of α-allenyl sulfonamides was conducted between 80 and 180 °C[12] and was reported to be stereospecific, affording single diastereomers. This is in contrast to the low temperatures, small loss of stereospecificity, and participation of a neutral aliphatic amine observed in our experiments. SET from the aliphatic amine to the allene moiety in **18*S*** would afford a zwitterionic diradical intermediate (Scheme 4) that under the basic aqueous conditions could undergo the necessary proton transfer events and cyclization. Minimum motion after SET and slow geometrical isomerization[22d] of the allyl radical are necessary for maintaining stereochemical integrity. Although the effect of allene and N-atom substituents on substrate reactivity and stereochemical outcome was not examined, it is expected that these would play significant roles.

Treatment of the *N*-Boc carbamates with MeOH/TMSCl effected cleavage of the *N*-Boc protecting group without concomitant cyclization to 3-pyrrolines and without isomerization of the scalemic allenes. Under this deprotection protocol, nearly quantitative yields of the free α-amino allenes could be obtained (eq 1, Table 3), although when the solution was allowed to stir for longer than 48 h, some amino allene decomposition occurred.



(1)

Treatment of the free α-amino allenes with a catalytic amount of $AgNO_3$ afforded the 3-pyrrolines in good chemical yields and with excellent enantiomeric purities that reflected the enantiomeric purities of the starting propargyl alcohols (eq 1, Table 3). The assignment of absolute configuration is predicated upon the observed high degree of enantioselectivity, the assumption of *anti*-S_N2' stereochemistry in the cuprate-mediated propargyl substitution reaction,[16] and the orthogonal arrangement of substituents at the end of an allene moiety. Approach of silver nitrate occurs on the π-face opposite that of the aminomethyl substituent leading to the 3-pyrroline derivatives with the predicted absolute stereochemistry. This predicted stereoselectivity for α-heteroatom allene cyclizations has been assumed[6,25] and found to agree with product stereochemistry determined by X-ray analysis[26] and by synthesis of both stereoisomers[12a] in the diastereoselective reactions. The stereoselective cyclization of α-heteroatom allenes has been mediated by acids,[25b] Cu(II) salts,[26] $AgNO_3$,[6a,25a] $AuCl_3$,[5c,25b] *N*-bromosuccinimide,[6b] and bases[12a] for both oxygen[25,26] and nitrogen[6,12] heteroatoms and in all cases gave the predicted stereochemistry (i.e., *anti*-addition of proton or transition metal ion and heteroatom to the allene double bond).[27]

Although the base-promoted cyclization of α-allenyl alcohols[22d] and α-allenyl hydrazines[8a,b] sometimes affords vinyl epoxides and azetidines, respectively, 3-pyrrolines are obtained exclusively with $AgNO_3$, $AuCl_3$, or NBS. The absence of aziridines suggests that the 3-pyrrolines are kinetically favored, although it is unclear whether the rate-determining step involves silver ion complexation or heteroatom cyclization.[28]

The resulting *N*-methyl-3-pyrrolines are relatively stable to silica gel chromatography and storage. Although the present study focused only on the integrity of the chirality transfer

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(27) For reviews, see: (a) Ma, S. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Chapter 10, Vol. 2, pp 595−699. (b) Tius, M. A. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Chapter 13, Vol. 2, pp 817−845. (c) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127−2198. (d) Hatem, J. *Targets Heterocycl. Syst.* **2002**, *6*, 399−417. (e) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701−712.
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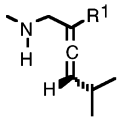
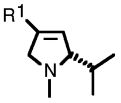
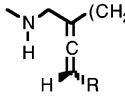
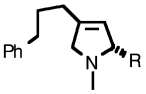
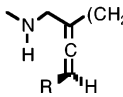
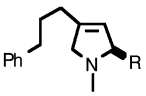
TABLE 3. Preparation and Conversion of Scalemic α-Amino Allenes to 3-Pyrrolines (eq 1)

entry	allene[a]	R^1 or R	cpd no.	% yield[b]	% ee[c]	cyclization product	cpd no.	% yield[d]	% ee[e]
1		Ph	**18*S***	95	81		**24*S***	55	81
2		$Ph(CH_2)_3$-	**19*S***	95	93		**25*S***	61	93
3		$PhCO_2(CH_2)_2$-	**20*S***	95	99		**26*S***	57	99
4		*t*–Bu	**21*S***	95	93		**27*R***	61	93
5		Ph	**22*S***	97	90		**28*R***	79	90
6		*n*-C_7H_{15}-	**23*S***	95	90		**29*S***	66	90
7		*t*–Bu	**21*R***	95	93		**27*S***	61	93
8		*n*-C_7H_{15}-	**23R**	95	97		**29*R***	68	97

[a] *N*-Boc deprotection [MeOH, TMSCl (5.0 equiv), 25 °C, 12 h]. [b] Yields based upon crude weight of amino allenes, which were used without further purification. [c] Enantiomeric ratios were determined by chiral stationary phase HPLC on a CHIRALCEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel] on the *N*-Boc-protected allenes. The enantiomeric ratios were assumed to be the same for the deprotected amines, which was confirmed by determinations on the pyrroline products. [d] Average yield of 2−3 reactions based upon isolated products purified by column chromatography. [e] Enantiomeric ratios were determined by chiral stationary phase HPLC on a CHIRALCEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel].

operations, the procedure should be amenable to the synthesis of a wide range of *N*-alkyl- or *N*-aryl 3-pyrrolines.

Summary

In summary, a rapid synthesis of enantioenriched 3-substituted pyrrolines is available by reaction of α-(*N*-carbamoyl)alkylcuprates with scalemic propargyl mesylates or perfluorobenzoates. The perfluorobenzoates are used when the carbinol center is in conjugation with two unsaturated functional groups (e.g., aryl or propargyl) since the corresponding mesylates are easily converted to the chlorides when methanesulfonyl chloride is used for mesylate preparation. The synthetic sequence can be carried out to afford 3-pyrrolines that have the same enantiopurity as that of the starting propargyl alcohols. The procedure should be amenable to the synthesis of a wide variety of *N*-alkyl- or *N*-aryl-substituted 3-pyrrolines.

Experimental Section

General Procedure B: Propargylic Mesylate Preparation. Under argon, a solution of propargylic alcohol (5.0 mmol) in CH_2Cl_2 (20 mL) was treated with redistilled Et_3N (0.76 g, 7.5 mmol) and methanesulfonyl chloride (0.69 g, 6.0 mmol) at −40 °C. The stirring was continued under argon for 1 h at −40 °C, and the reaction mixture was then warmed to room temperature, quenched with saturated $NaHCO_3$ (aq), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under vacuum to afford neat crude product, which was clean by both ^1H and ^{13}C NMR analysis. The mesylate was used for the next reaction without purification.

General Procedure G: Reaction of RCuCNLi with Propargyl Mesylates. To *N*-Boc-*N*,*N*-dimethylamine (1.0 mmol) in THF (2.0 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, 1.0 mmol) and LiCl (0.0840 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 via syringe to the 2-lithio-*N*-Boc amine at −78 °C. The mixture was allowed to stir at −78 °C for 45 min to generate a clear homogeneous solution. A solution of the propargyl substrate (1.0 mmol) dissolved in THF (1.0 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 and filtered by vacuum through Celite; the organic phase separated, and the aqueous phase was extracted three times with Et_2O. The combined organic phases were washed one time with saturated brine and dried over $MgSO_4$. Evaporation of the solvent in vacuo afforded the products. Purification was accomplished using flash column chromatography eluting with 5% EtOAc/95% petroleum ether (v/v) to give pure adduct.

Carbamic acid, Methyl[2-(3-phenyl-5,5-dimethyl-2,3-hexadienyl], 1,1-Dimethylethyl ester (15*S*). Employing General Procedure G with *N*-Boc-*N*,*N*-dimethylamine (0.145 g, 1.0 mmol) and **7b*R*** (0.308 g, 1.0 mmol) afforded **15*S*** (0.256 g, 85%) as a colorless oil after purification by flash column chromatography (silica gel, ether/petroleum ether, 1:5, v/v): IR (neat) 2954 (vs), 2921 (vs), 2855 (s), 1956, 1693 (vs), 1448 (vs), 1382 (vs), 1354 (vs), 1241, 1161 (vs), 879, 737, 690 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (s, 9H), 1.48 (s, 9 H), 1.80 (quint, J = 7.1 Hz, 2H), 1.94−1.99 (m, 2H), 2.68 (t, J = 7.1 Hz, 2H), 2.85 (s, 3H), 3.73 (dd, J = 15.1, 2.6 Hz, 1H), 3.87−3.99 (m, 1H), 5.27 (t, J = 2.6 Hz, 1H), 7.16−7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.7, 28.5, 29.3 (29.4), 30.3, 32.2, 33.7 (34.1), 35.6, (50.9) 51.63, (79.1) 79.3, 102.8 (103.0), 105.6 (105.7), 125.7, 128.3, 128.4, 142.3, 155.6, (197.8) 198.2; mass spectrum *m*/*z* (relative intensity) EI 301 (55), 284 (10), 244 (8), 197 (10), 170 (11), 122 (20), 88 (35), 57 (100).

The enantiomeric purity of **15*S*** was determined by chiral HPLC analysis on a CHIRACEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel] to be 93% ee (hexane/^{i}PrOH, 99.8:0.2 (v/v), flow rate = 0.5 mL/min, detection at λ = 210 nm. The (*S*)-enantiomer eluted first with a retention time of 30.6 min followed by the (*R*)-isomer (minor) at 32.8 min.

General Procedure H: Deprotection of *N*-Boc Carbamates with Chlorotrimethylsilane (TMSCl) in Methanol. To a solution of *N*-Boc-protected amino allene (1.0 mmol) in MeOH (5.0 mL) was added TMSCl (0.540 g, 5.0 mmol) via syringe at 25 °C. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was 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 $MgSO_4$ and concentrated under vacuum to afford crude product, which was pure (>95%) by both ^1H and ^{13}C NMR analysis.

N*-Methyl-2-(3-phenylpropyl)-5,5-dimethyl-2,3-hexadienyl-1-amine (21*S*).** General Procedure H was employed on **15*S (0.357 g, 1.0 mmol) to afford **21*S*** (0.244 g, 95%) which was pure by both ^1H and ^{13}C NMR analysis: IR (neat) 3322 (br s), 2957 (vs), 2358, 2335, 1960, 1450, 1357, 739, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (s, 9H), 1.82 (quint, J = 7.4 Hz, 2H), 2.02−2.06 (m, 2H), 2.20−2.80 (br s, 4H), 2.70 (t, J = 7.2 Hz, 2H), 2.90−3.50 (br s, 2H), 5.31 (s, 1H), 7.17−7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.8,

29.4, 30.3, 32.0, 32.2, 35.7, 53.9, 105.1, 105.8, 125.7, 128.3, 128.4, 142.4, 197.4; mass spectrum *m*/*z* (relative intensity) 257 (6, M^+), 242 (10), 201 (21), 91 (100), 77 (49), 57 (48).

General Procedure I: $AgNO_3$-Catalyzed Cyclization of Amino Allenes. Crude amino allene (e.g., **18**−**23**) (0.67 mmol), prepared by General Procedure I or J, was dissolved in acetone (from drum, without further purification), followed by the 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 (flask was wrapped with aluminum foil). The reaction was monitored by TLC until starting material was consumed (R_f = 0.2−0.5 on silica gel, 100% ether as eluent). Then the reaction mixture was diluted with diethyl ether, filtered through a thin layer of Celite, and concentrated under vacuum to afford crude product, which was purified by flash column chromatography (silica gel, 100% diethyl ether as eluent) to give colorless oils.

1-Methyl-2-(1,1-dimethylethyl)-4-(3-phenylpropyl)-3-pyrroline (27*R*). General Procedure I was employed on **21*S*** (0.172 g, 0.6 mmol) to afford **27*R*** (94 mg, 61%) after purification by flash column chromatography (silica gel, ether/petroleum ether, 1/1 (v/v)): $[\alpha]^{22}_D$ = +40.4 (*c* 0.0025, $CHCl_3$); IR (neat) 2942 (vs), 2852, 2831, 2774, 1444, 1387 (vs), 1350, 861, 745, 693 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (s, 9H), 1.80 (quint, J = 6.8 Hz, 2H), 2.13 (t, J = 7.4 Hz, 2H), 2.51 (s, 3H), 2.65 (t, J = 7.4 Hz, 2H), 3.11 (br s, 2H), 3.86−3.90 (m, 1H), 5.33−5.34 (m, 1H), 7.19−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 26.5, 28.3, 29.6, 35.6, 35.9, 47.1, 66.7, 77.2, 84.6, 121.6, 125.8, 128.4, 140.5, 142.3; mass spectrum *m*/*z* (relative intensity) 257 (1, M^+), 255 (3), 200 (100), 151 (12), 91 (51). High-resolution mass spectrum *m*/*z* 257.2143 (M^+) (calcd for $C_{18}H_{27}N$ 257.2143).

The enantiomeric purity of **27*R*** was determined by chiral HPLC analysis on a CHIRACEL OD column [cellulose tris(3,5-dimethylphenylcarbamate) on silica gel] to be 93% ee (hexane/^{i}PrOH/diethylamine, 99:0.5:0.5 (v/v), flow rate = 1.0 mL/min, detection at λ = 210 nm). The (*R*)-enantiomer eluted first with a retention time of 22.8 min followed by the (*S*)-isomer at 27.7 min. The enantiomer, **27*S***, gave a specific rotation $[\alpha]^{22}_D$ = −47.3 (*c* 0.002, $CHCl_3$).

Acknowledgment. This work was generously supported by the National Science Foundation (CHE-0132539). Support of the NSF Chemical Instrumentation Program for purchase of a JEOL 500 MHz NMR instrument is gratefully acknowledged (CHE-9700278).

Supporting Information Available: General experimental information, materials, data reduction for **3a*R***−**9a*R***, **3b*R***−**5b*R***, **7b*R***, **8c*R***, **9b*R***, **12*S***−**14*S***, **18*S***, **19*S***−**23*S***, **24*S***, **25*S***−**26*S***, **28*R***, **29*S***, isomerization studies for **18*S***, and ^1H and ^{13}C NMR spectra for **13*S***−**17*S*** and **19*S***−**23*S***. This material is available free of charge via the Internet at http://pubs.acs.org.

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