

Synthesis of 3-Pyrrolines, Annulated 3-Pyrrolines, and Pyrroles from α -Amino Allenes

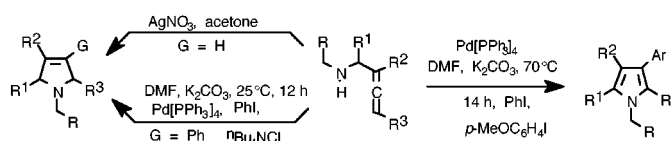
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ABSTRACT



α -Amino allenes, readily prepared from reaction of α -(*N*-carbamoyl)alkylcuprates with propargyl substrates followed by *N*-Boc deprotection, are converted in high yields to pyrrolines with AgNO_3 . Palladium-catalyzed cyclization of amino allenes affords either the pyrroline or the pyrrole depending on reaction conditions and provides for introduction of an aryl substituent at the C-3 position of the pyrroline or pyrrole. Enantioenriched pyrrolines are readily prepared from scalemic propargyl alcohols.

Pyrroles¹ and pyrrolines² are important classes of heterocyclic compounds, and many synthetic routes are available for their preparation.³ Many procedures, however, are limited in terms of substituents and substitution patterns. With increasing frequency, the transition-metal-promoted cyclization of a heteroatom onto an allene moiety provides a powerful strategy for heterocyclic synthesis.⁴ Furan formation via silver

ion-catalyzed cyclization of α -hydroxy allenes occurs in a highly regio- and stereoselective manner.⁵ 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 functionalities, many of the cyclizations proceeded in an exocyclic fashion to afford 2-vinyl-substituted ring systems.⁶ Nevertheless, several recent reports describe silver nitrate-promoted endo cyclization processes involving either a benzylamine functionality,^{7a} sulfonamides,^{7b} or acyclic amino allenes.^{7c} Similarly, the vast majority of palladium-promoted cyclizations of nitrogen functionalities onto adjacent double bonds involve nitrogen centers containing electron-withdrawing

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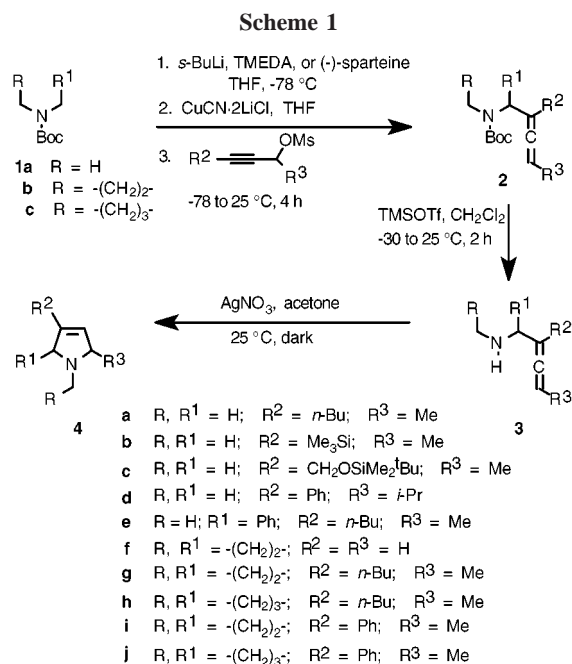
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substituents,^{7b,8} although examples of amine participation have been reported.⁴ This is significant since strongly basic amines can function as ligands for the palladium catalyst and potentially interfere with the cyclization reaction. Although some 5-*endo-trig* cyclizations have been reported,^{7,8} most of these procedures also involve *exo* cyclizations,⁹ raising questions about the generality of the *endo* cyclization process particularly for annulated 3-pyrrolines and pyrroles. With these questions in mind, we have explored the use of α -amino allenes, available via reaction of α -(*N*-carbamoyl)-alkylcuprates with propargyl substrates,¹⁰ in these cyclization reactions.

Treatment of the *N*-Boc-protected amino allenes with trimethylsilyltriflate (CH_2Cl_2 , from -30 to 25°C) gave the free amino allenes (Scheme 1) in good to excellent yields



(Table 1, 62–99%).¹⁰ 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 1, entries 1–5) and annulated 3-pyrrolines (entries 6–10). The procedure is very reliable and appears to be capable of tolerating a wide range of substitution patterns (e.g., 2,3-disubstitution in **4e**, entry 5). As expected, utilization of racemic propargyl mesylates and racemic α -(*N*-carbamoyl)alkylcuprates afforded mixtures of diastereomers with little or no diastereoselectivity.

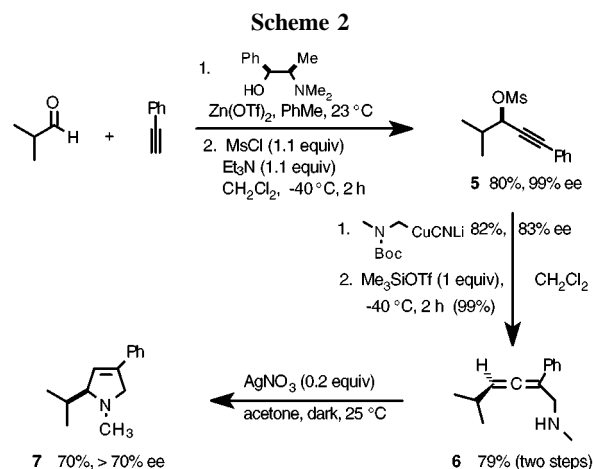
The C-2 substitution pattern in pyrrolines **4a–d** and **4g–j** and the C-5 pattern in **4e** derive from the terminal position of the allene providing opportunities for asymmetric induc-

Table 1. AgNO_3 -Promoted Cyclization of α -Amino Allenes to Pyrrolines

entry	allene (3) ^a	(n)	% ^b yield	pyrroline (4a–j) ^c	% ^b yield	dr ^d
1	3a		92		82	
2	3b		62		71	
3	3c		75		60	
4	3d		99		70	
5	3e		86		75	50:50
6	3f		83		50	
7	3g	1	83		90	41:59
8	3h	2	60		67	50:50
9	3i	1	80		67	39:61
10	3j	2	70		63	48:52

^a Obtained from **2** (TMSOTf, CH_2Cl_2 , from -30 to 25°C , 2 h). ^b Yields based upon isolated products purified by chromatography. ^c Obtained from **3** (AgNO_3 , acetone, 25°C). ^d Diastereomeric ratio determined from ^1H NMR integration values and/or ^{13}C NMR peak heights.

tion during the cuprate-mediated allylic substitution reaction. The requisite scalemic propargyl alcohols are readily available from the zinc triflate-catalyzed 1,2-addition of terminal alkynes to aldehydes.¹¹ Reaction of phenyl acetylene with isobutyryl aldehyde afforded the propargyl alcohol, in good yield (Scheme 2) and with excellent enantioselectivity (ee,



99%), which could be mesylated in quantitative yield. Reaction of **5** with the cyanocuprate derived from **1a** afforded

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the *N*-Boc amino allene in 80% yield and 83% ee (91.5:8.5 enantiomeric ratio (er)), which gave **6** after Boc deprotection with trimethylsilyl triflate. Cyclization with AgNO₃ gave pyrroline **7** in good yield and with good enantioselectivity (ee ≥ 70%). The er (85:15) of **7** was measured by chiral stationary-phase HPLC on a CHIRALCEL OD column (cellulose tris(3,5-dimethylphenylcarbamate) on silica gel) and was difficult to determine precisely because of extensive tailing of the peaks with the major isomer eluting first. The reaction is assumed to proceed with *anti* selectivity, and on this basis, the (*S*)-configuration is assigned to C-2.¹² The *syn*-selective S_N2' substitution on propargyl substrates appears to be largely limited to cuprates derived from RMgCl (i.e., the halogen effect) reacting with propargyl ethers.¹³ Consequently, 2,4-disubstituted 3-pyrrolines of high enantiomeric purity are readily available by a five-step sequence in a roughly 50% overall yield, although the generality of the synthesis remains to be examined.

This cyclization protocol, however, does not allow for the introduction of substituents at the C-3 position. To overcome this limitation, palladium(II)-promoted cyclizations were examined. The catalytic cycle involving oxidative addition, palladium(II)-promoted nucleophilic cyclization, and reductive elimination has been achieved in a variety of allenes containing weakly basic nitrogen nucleophiles with electron-withdrawing substituents on the nitrogen atom.^{4,7b,8} Although examples of amine participation have been reported,^{4,8a} failures of the reaction have been attributed to Pd(II) deactivation via nitrogen chelation.^{8a}

Initial treatment of allene **2a** with Pd[PPh₃]₄ in the presence of triethylamine gave the pyrroline in a low yield of 31% (Table 2, entry 1). Increasing the amount of triethylamine resulted in diminished yield of pyrroline **8** and formation of the pyrrole **9**, confirming the concern of amine ligands interfering with the palladium-promoted catalytic cycle (entry 1 vs entries 2–3). Efforts to facilitate ligand exchange in the catalytic cycle by addition of 10 mol % CuCN¹⁴ resulted only in reduced yields of cyclization products (entry 3). The effect of solvent and base was examined in an effort to improve the yields of these tandem cyclization–coupling reactions. Employing potassium carbonate as a base, DMF as a solvent,^{8a} and tetrabutylammonium chloride as an additive resulted in a modest yield of pyrroline **8** (entry 4). Phase-transfer catalysts may facilitate oxidative addition, carbopalladation of the allene, and intramolecular nucleophilic substitution while not changing the regioselectivity of the transformation.¹⁵ Modification of this procedure using tetrabutylammonium bromide or tetrabutylammonium chloride with soluble CuN·2LiCl resulted in diminished yields of **8** (entries 5–6). Efforts to increase the yields by utilizing

Table 2. Palladium-Catalyzed [Pd(PPh₃)₄] Cyclization of Amino Allenes to Arylated Pyrrolines and Pyrroles

entry	base	equiv	additive ^a	solvent	<i>T</i> (°C)/ <i>t</i> (h)	% yield	
						8	9
1	Et ₃ N	1.5		THF	25/14	31	
2	Et ₃ N	2.0		THF	70/20	10	10
3	Et ₃ N	2.0	A	THF	25/14	5	
4	K ₂ CO ₃	4.0	B	DMF	25/20	50	
5	K ₂ CO ₃	4.0	C	DMF	25/20	40	
6	K ₂ CO ₃	4.0	D	DMF	25/20	37	
7	K ₂ CO ₃	4.0		DMF	70/14		71
8	K ₂ CO ₃	4.0	B	DMF	80/20		57

^a A = CuCN (10 mol %). B = *n*-Bu₄NCl (1.0). C = *n*-Bu₄NBr (1.0). D = *n*-Bu₄NCl (1.0), CuCN·2LiCl (10 mol %).

softer ligands (e.g., SbPh₃ and AsPh₃) did not succeed, and greater yields of cyclization products were not obtained when active Pd(0) obtained by potassium metal reduction of PdCl₂ was used.¹⁶

When the reaction was conducted at elevated temperatures in DMF, pyrrole derivative **9** was formed in good yields. Presumably, formation of pyrroles involves initial formation of the 3-pyrrolines followed by palladium-promoted dehydrogenation. Treatment of **8** under the reaction conditions (PhI, DMF, Pd(PPh₃)₄, K₂CO₃, 70 °C, 12 h) gave recovered **8** (20%) and **9** (60%). Treatment of **8** with Pd(OAc)₂/K₂CO₃/DMF (70–80 °C, 12 h) in the absence of PhI also gave **8** (26%) and **9** (36%). These control experiments implicate Pd(II) species in the conversion of **8** to **9** observed at higher temperatures. Neither procedure, however, could be extended to amino allene **3i**. Cyclization of **3i** and subsequent arylation gave either the tetrahydropyrrolizine (K₂CO₃/*n*-Bu₄NCl/PhI/Pd(PPh₃)₄/DMF/25 °C, 5%) or the dihydropyrrolizine (K₂CO₃/*n*-Bu₄NCl/PhI/Pd(PPh₃)₄/DMF/80 °C, 18%) in low yields.¹⁷

The palladium-catalyzed cyclization of amino allenes to pyrroles, employing the optimal conditions cited in Table 2, displays some generality as evidenced by the formation of **10** and **11** in modest yields (Table 3). Good yields of pyrrolines appear to require the absence of electron-donating substituents on the aromatic ring (Table 3, **12** vs **13**).

In summary, α-amino allenes readily available by coupling of α-(*N*-carbamoyl)alkylcuprates with propargyl mesylates

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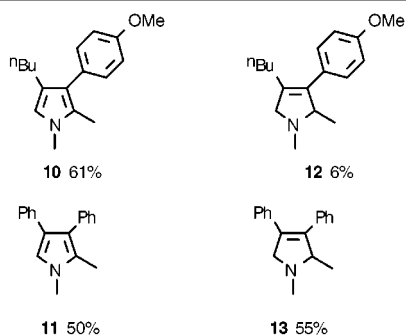
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(17) Products formed from **3i** were 5-methyl-6,7-diphenyl-2,3,5,7a-tetrahydro-1*H*-pyrrolizine and 5-methyl-6,7-diphenyl-2,3-dihydro-1*H*-pyrrolizine, respectively.

Table 3. Palladium-Catalyzed [Pd(PPh₃)₄] Cyclization of Amino Allenes to Arylated Pyrrolines and Pyrroles Employing Conditions Shown in Table 2



followed by carbamate deprotection can be cyclized to either 3-pyrrolines or pyrroles. Treatment of the α -amino allenes with AgNO₃ effects cyclization to 1,2,4-tri-substituted 3-pyrrolines, while palladium-promoted tandem cyclization and coupling with aryl iodides in DMF at 25 °C can afford 1,2,3,4-tetra-substituted 3-pyrrolines (e.g., **8**). The latter reaction appears to be limited to aryl iodides that undergo facile oxidative addition to Pd(0), given the low yields observed for **12**. Additional substitution on the carbamate moiety can, in principle, afford 1,2,3,5-tetra-substituted and 1,2,3,4,5-penta-substituted 3-pyrrolines for the AgNO₃ cyclizations and the palladium-induced cyclization and coupling processes, respectively. Utilization of higher reaction tem-

peratures in the palladium-catalyzed reactions provides good yields of the corresponding pyrroles providing for the introduction of aryl groups at the C-3 position. This protocol complements a synthetic route to polysubstituted pyrroles involving the conjugate addition of α -(*N*-carbamoyl)alkylcuprates to α,β -alkynyl ketones followed by Boc deprotection and cyclization.¹⁸ Finally, reaction of α -(*N*-carbamoyl)alkylcuprates with scalemic propargyl mesylates followed by *N*-Boc deprotection provides an alternative route to the reaction of scalemic propargyl aziridines with cuprate reagents to produce scalemic α -amino allenes.^{12b} The scalemic amino allenes can be converted into scalemic 3-pyrrolines with configurational integrity through the *N*-Boc deprotection and AgNO₃ sequence.

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Supporting Information Available: ¹H and ¹³C NMR spectra for compounds **2d**, **4j**, **8**, and **7** and data reduction and experimental procedures for **2d**, **5** (and the precursor alcohol), and **6–9**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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