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Synthesis of Amino Allenes via Reaction of α-Aminoalkylcuprates with Propargyl Substrates

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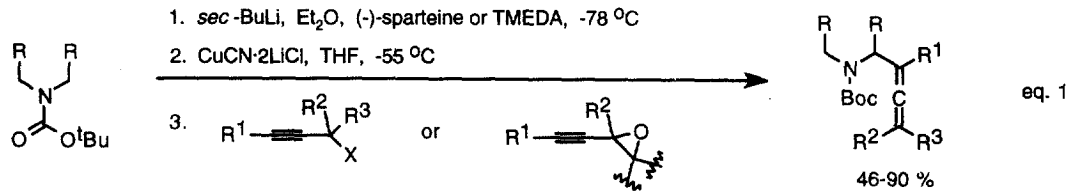
Abstract: α-Aminoalkylcuprates prepared from carbamates via sequential deprotonation and treatment with CuCN·2LiCl react with propargyl bromides, mesylates, tosylates, acetates, and epoxides to afford amino allenes via a S_N2' substitution process. Propargyl bromides and sulfonates give good yields of amino allenes while the acetates afford low yields. Substrates undergo regiospecific S_N2' substitution and the use $Sc(OTf)_3$ affords improved yields of amino allenes from propargyl epoxides. The Boc protected α-amino allenes can be cyclized to oxazolidones or deprotected to afford the free amines.

The reaction of allylic substrates with nucleophiles often poses problems of regiochemical control affording, in many cases, mixtures of isomeric products arising from attack at the α and γ-positions.[1,2] In an effort to extend α-aminoalkylcuprate chemistry,[3] we found that these reagents reacted with allylic sulfides of benzothiolzole-2-thiol to give excellent S_N2 regioselectivity while other leaving groups afforded a range of selectivities dependent upon solvent, cuprate reagent, and reaction conditions.[4] Envisaging greater regiocontrol and potential synthetic utility, we undertook an examination of propargyl substrates. Although initial efforts were unsuccessful, we now report that α-aminoalkylcuprates prepared from carbamates and CuCN·2LiCl react with propargyl substrates in an S_N2' fashion with complete regiospecificity (eq. 1).



eq. 1

A series of propargyl halides, tosylates,[5] mesylates,[6a,b] and acetates[7] were prepared from the corresponding propargyl alcohols while the propargyl epoxides were prepared by epoxidation[8a] of conjugated enynes or from chlorohydrins.[8b] The preparation of mesylates from alcohols containing unsaturated functionalities (e.g., double bond, triple bond, aromatic ring) on both sides of the carbinol carbon proved difficult as the resultant sulfonates underwent rearrangements and facile nucleophilic substitution reactions.

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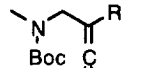
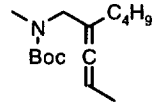
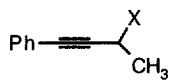
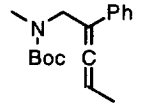
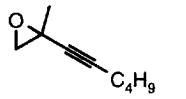
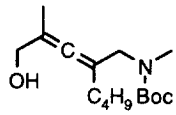
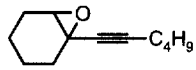
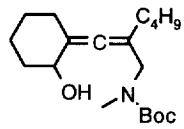
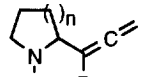
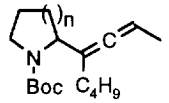
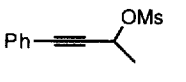
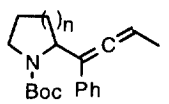
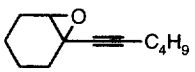
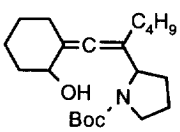
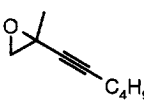
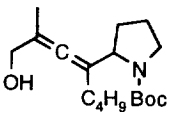
Table. Reaction of propargylic substrates with α-aminoalkylcuprates and α-aminoalkylcopper reagents.

entry	carbamate[a]	n	propargyl substrate	X	R	CuX·2LiCl	equiv[b]	product	% yield[c]
1				Br	H	CuCl	1.0		59
2				Br	H	CuCN	1.0		76
3				OMs	Bu	CuCN	0.5		67
4	**1**			OMs	Bu	CuCN	1.0		57-78
5				OMs	Bu	CuCl	1.0		63
6				-	-	CuCN	0.5		47
7				-	-	CuCN	1.0		75-90
8				-	-	CuCN[d]	1.0		56
9				OMs	-	CuCN	0.5		65
10				OMs	-	CuCN	1.0		68
11				OAc	-	CuCN	1.0		39
12				OAc	-	CuCN	0.5		11[e]
13				-	-	CuCN	1.0		44[f]
14				-	-	CuCN	1.0		77[g]
15				-	-	CuCN	0.5		83[f]
16				-	-	CuCN	1.0		72[f]
17				-	-	CuCN	1.0		94[g]
18		1		Br	H	CuCN	0.5		59
19		2		Br	H	CuCN	1.0		44[h]
20		1		OMs	H	CuCN	1.0		58
21		1		OTs	H	CuCN	0.5		83
22		1		OAc	H	CuCN	1.0		trace
23	**2** n = 1	1		OMs	Bu	CuCN	0.5		70
24	**3** n = 2	1		OMs	Bu	CuCN	1.0		65
25		2		OMs	Bu	CuCN	1.0		50
26		1		OMs	-	CuCN	0.5		78
27		1		OMs	-	CuCN	1.0		68
28		1		-	-	CuCN	0.5		54 (2:1)[i]
29		1		-	-	CuCN	1.0		92
30		1		-	-	CuCN	1.0		31[f,i]
31		1		-	-	CuCN	1.0		46[i,g]
32		1		-	-	CuCN	1.0		69[g] (1:1)[i]

[a] Cuprates were prepared from the carbamates by sequential deprotonation (*s*-BuLi, sparteine, Et_2O, -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] Insoluble CuCN was employed. [e] Yields determined by NMR. [f] TMSCl (5 equiv) was employed. [g] $Sc(OTf)_3$ (5 mol %) was employed. [h] A mixture of regioisomers. [i] Mixture of diastereomers.

In initial studies, *tert*-butoxycarbonyl protected amines were deprotonated via Beak's methodology[9] [*sec*-BuLi, Et_2O, sparteine or TMEDA, -78 °C (-20 °C for piperidine)] and treated with CuCN to afford the cuprate reagents. Under these conditions, substitution products were often formed in capricious amounts, although modest yields could be obtained (Table, entry 8). Generally, the starting carbamate was recovered. Eventually it was discovered that cupate reagents prepared from CuCN·2LiCl afforded modest to good yields of allenes resulting from a S_N2' substitution process. Several parameters were examined. Cuprate reagents prepared from either CuCl·2LiCl or CuCN·2LiCl and one equivalent of RLi gave good yields of allenes with the latter reagent giving slightly better results (Table entries 1 vs. 2 and 4 vs. 5). Both of these cuprate reagents (i.e., RCuXLi, X = CN, Cl) contain only one α-aminoalkyl ligand and are more efficient than the reagent prepared from 2 RLi and CuCN·2LiCl even though similar chemical yields are obtained with each reagent (entries 3 & 4, 6 & 7, 9 & 10, 15 & 16, 20 & 21, 23 & 24 and 26 & 27). The effectiveness of the reagent prepared from CuCl and one equivalent of RLi is more suggestive of a cuprate reagent than the organocopper(I) reagent (i.e., RCu) suggested by stoichiometry. Propargyl bromides and sulfonates afford similar yields (entries 2 & 4, 18 & 21, and 19 & 25). This is significant since the sulfonates are generally easier to prepare from propargyl tertiary alcohols than the corresponding bromides. In all instances examined, propargyl acetates gave very low yields (entries 11-12, 22).

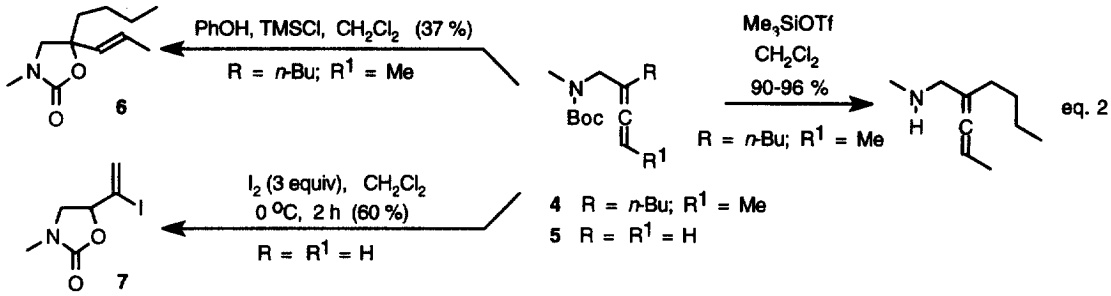
Propargyl epoxides also participated in the substitution reaction but with widely varing yields in the presence of five equivalents of TMSCl. The cuprate reagent derived from Boc-protected *N,N*-dimethylamine (**1**) gave good yields with the cyclohexene oxide derivative (entries 15-16) but rather modest yields with an acyclic analogue (entry 13). The more sterically encumbered cuprate reagent derived from Boc-protected pyrrolidine gave modest yields with the cyclohxene oxide propargyl derivative (entry 30). These allenyl allylic alcohols were acid sensitive but could be purified on neutral alumina. The yields of amino allenes could be significantly increased by the use of $Sc(OTf)_3$, as opposed to TMSCl, as a mild Lewis acid compatible with the cuprate reagents [entries 14, 17, 31, 32 vs 13, 16, 30 respectively].[10]

The cuprate reagents generated from **1** and **2** gave the amino allenes regiospecifically while the cuprate reagent prepared from Boc-protected piperidine (**3**) gave a mixture of regioisomers resulting from attack at both the α and γ-positions of the starting propargyl bromide (entry 19). Utilization of the propargyl mesylate of 2-heptyn-1-ol resulted in regiospecific S_N2' substitution (entry 25).

The mesylate of 1-(1-hexynyl)cyclohexanol as well as the corresponding chloride failed to undergo any substitution reaction with the cuprate reagents prepared from either **1** or **2**. This result is attributed to steric crowding about the alkyne functionality hindering complex formation between alkyne and the cuprate reagents. This is consistent with the diminished yields observed in the reaction of **2** with the cyclohexene oxide (entries 30-31) compared to the reaction of the cyclohexene oxide with **1** (entries 15-17).

Removal of the Boc-protecting group proved particulary difficult in these allenyl amines. Attempted cleavage with PhOH/TMSCl[11] afforded an oxazolidone arising via a 5-*exo-trig* cyclization of the Boc-carbonyl oxygen atom onto the allenyl system (eq. 2, **6**). An oxazolidone was also prepared with iodine under reaction conditions employed for carbamate cyclizations onto olefins (eq. 2, **7**), although cyclization with I_2/KI/$NaHCO_3$/H_2O/CH_2Cl_2 also afforded di-iodo compounds arising from addition across the terminal carbon-carbon double bond of **5** (40-72%).[12] Other reagents either failed to effect deprotection (e.g., $^tBuMe_2SiOTf$,[13a] $Ce(NH_4)_2(NO_3)_6$[13b]) or afforded a complex mixture of products (catechol boron bromide,[13c] $AlCl_3$[13d]). Boc-deprotection could be achieved with Me_3SiOTf in excellent yields.[14]

In summary, α-aminoalkylcuprate reagents undergo clean S_N2' substitution reactions with propargyl bromides, mesylates, and epoxides to afford α-amino allenes. Propargyl acetates are not sufficiently reactive and



give low yields of allenes. The Boc-protecting group can be removed with Me_3SiOTf while intramolecular cyclization to an oxazolidone can be effected under iodolactonization conditions or by acid catalysis. The ready availability of scalemic propargyl alcohols provides, in principle, a facile route to scalemic amino alcohols from the oxazolidones. Deprotection to the free amine and subsequent cyclization provides potential synthetic routes to scalemic pyrrolines.

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