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Efficient Synthesis of Allylic Amines from α-Aminoalkyl Cuprates and Enol Triflates

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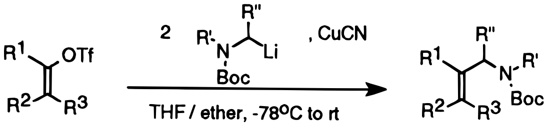
Allylic amines[1] are an important class of compounds in organic synthesis as evidenced by the continuing development of numerous methods for their preparation.[2−12] A characteristic feature of these methods is the narrow range of applicability for generating a wide array of substitution patterns in both cyclic and acyclic amines. It appears that a simple, regioselective synthetic route to allylic amines of diverse substitution patterns is unavailable. We now report that α-aminoalkyl cuprates prepared from CuCN and 2 equiv of *tert*-butoxycarbonyl-protected α-amino organolithium reagents undergo substitution reactions with enol triflates to afford a direct and efficient synthesis of allylic amines.

Organocopper reagents are a powerful tool in the arsenal of synthetic organic chemists, and innovative developments continue to emerge.[13] The reaction of enol triflates with organocuprates[14a,b] has recently been extended to allylcuprate[14c] reagents. Recently, we reported[15] the development of α-aminoalkyl cuprates as useful reagents for conjugate addition reactions and now report that these reagents undergo substitution reactions with enol triflates to afford allylic amines in good to excellent yields (eq 1). The enol triflates used in this study were readily prepared by established procedures.[16]



(1)

Initially, the *tert*-butyl carbamate derivative of *N*,*N*-dimethylamine was deprotonated with *sec*-butyllithium (Et_2O, −78 °C, 0.5 M in carbamate)[17] in the presence of sparteine or TMEDA and added to 0.5 equiv of CuCN suspended in THF. The solution was warmed to −55 °C (30 min) to ensure cuprate formation and then cooled to −78 °C. The cuprate reagent underwent a substitution reaction (−78 °C to room temperature) with 1-cyclohexen-1-yl trifluoromethanesulfonate to afford the allylic amine in 57% (sparteine) and 77% (TMEDA) yield (Table 1, entries 1 and 2). Coaddition of chlorotrimethylsilane and the enol triflate resulted in a slightly higher yield (Table 1, entry 3) in contrast to the conjugate addition reactions.[15]

Preparation of the organolithium reagent by direct deprotonation or by transmetalation via the organostannane appears to make little difference (Table 1, entries 5 and 6). Deprotonation of the *tert*-butyl carbamate of pyrrolidine requires use of sparteine since the presence of TMEDA has a deleterious effect upon either the cuprate formation, stability, or reactivity (Table 1, entries 11 and 17).[15b] Reaction of the mixed dialkyl cuprates [RLi, MeLi, CuCN, entry 7 (Table 1) and RCuMeLi, entry 8 (Table 1)] with the enol triflate of cyclohexanone affords the substitution product. Reaction of a mixed dialkyl cuprate prepared from CuCN with the enol triflate derived from 4-phenylcyclohexanone (Table 1, entry 13) reveals that the diminished yield (Table 1, entries 2 *vs* 7 and 12 *vs* 13) is due in large part to competitive transfer of the methyl ligand. This suggests that α-aminoalkyl ligands have reactivities roughly comparable to the methyl ligand and lower than other alkyl ligands. In our hands preparation of the phosphido[18] mixed cuprate from CuI gave significantly higher yields than that obtained by preparation from $CuBr{\cdot}Me_2S$ (Table 1, entries 9 and 10). Although $CuBr{\cdot}Me_2S$ is often superior to CuI for cuprate preparations,[18,19a] the observation is consistent with higher product yields sometimes observed with cuprates prepared from CuI than from CuBr.[19]

This methodology provides an opportunity to control olefin regiochemistry in the product allylic amine as illustrated for the regioisomeric enol triflates generated from 2-methylcyclohexanone (Table 1, entries 14 and 15). The more highly alkyl-substituted enol triflate was obtained as a 90:10 mixture contaminated with the less substituted regioisomer and this same ratio was retained in the resultant allylic amines (Table 1, entry 15).

The enol triflate derived from 2-cyclohexenone gave excellent yields with α-aminoalkyl cuprates derived from *N*,*N*-dimethylamine and pyrrolidine (Table 1, entries 16 and 17) while the triflate derived from camphor (Table 1, entry 18) gave low yields of substitution product. These yields in conjunction with those obtained with the regioisomeric enol triflates of 2-methylcyclohexanone

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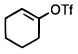
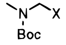
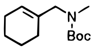
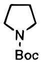
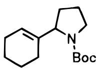
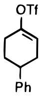
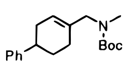
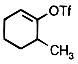
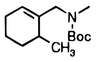
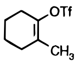
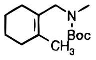
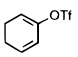
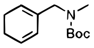
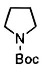
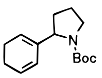
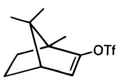
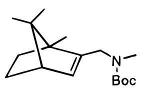
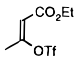
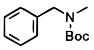
Table 1. Substitution Reactions of Vinyl Triflates with α-Aminoalkyl Cuprates

Entry	Triflate	N-Boc amine[a,b]	Cuprate[c,d]	Additives[e]	Products[f]	% Yield[g]
						
1		X = H	2 RLi/CuCN	sparteine		57
2				TMEDA		77
3				TMEDA / TMSCl		82
4			R_2CuLi, LiI	TMEDA		21
5			RCu-C≡C-C_4H_9	TMEDA		17
6		X = $SnBu_3$	RCu-C≡C-C_4H_9	-		16
7		X = H	RLi, MeLi, CuCN	TMEDA		56
8			RCuMeLi·LiI	TMEDA		40
9			($RCuPPh_2$)Li,[h] Me_2S, LiBr	TMEDA		10
10			$RCuPPh_2Li$·LiI[i]	TMEDA		43
11			2 RLi / CuCN	sparteine/TMSCl		77
12			2 RLi / CuCN	TMEDA / TMSCl		72
13			RLi, MeLi, CuCN	TMEDA		56 (32)[j]
14			2 RLi / CuCN	TMEDA / TMSCl		55
15				TMEDA / TMSCl		39 (90:10)[k]
16				TMEDA / TMSCl		88
17				sparteine/TMSCl		89
18				TMEDA / TMSCl		32
19				TMEDA / TMSCl	—	0
20	PhOTf			TMEDA / TMSCl		0
21	PhI			TMEDA		10

[a] Boc = *tert*-butoxycarbonyl. [b] α-Aminocarbanion obtained by deprotonation with *sec*-BuLi or via transmetallation of the α-aminostannane with *n*-BuLi. [c] 1.15 equiv of reagent employed unless noted. [d] R = α-aminoalkyl ligand. [e] (-)-Sparteine or TMEDA was added to assist deprotonation. TMSCl was added concurrently with the enol triflate when noted. [f] Products were characterized by IR, PMR, CMR, and combustion analysis. [g] Isolated yield based upon material purified by column chromatography. [h] Prepared from CuBr·Me_2S. [i] Prepared from CuI. [j] Yield of 1-methyl-4-phenylcyclohexene. [k] A 90:10 mixture of regioisomeric 2- and 6-methylcyclohexene derivatives.

suggest that the reaction is moderately sensitive to steric hindrance in the triflate.

These α-aminoalkyl cuprates did not undergo substitution reactions with the enol triflate derived from ethyl acetoacetate or with aryl triflates (Table 1, entries 19 and 20). Iodobenzene did undergo reaction with the cuprate reagent prepared from *N*,*N*-dimethylamine to afford the benzylamine in 10% yield (Table 1, entry 21).

In summary, the reaction of α-aminoalkyl cuprates with enol triflates affords an efficient synthesis of allylic amines. Although cuprates containing nontransferable ligands gave low yields of allylic amines and only a single group is transferred from the 2 RLi/CuCN reagent, the unused ligand can be recovered. Regiospecific generation of enol triflates provides a regiocontrolled route to allylic amines which may be problematic in Pd-promoted reactions.[2] In addition, the Pd/CuCN promoted coupling of α-aminoalkyl lithium reagents with aryl iodides[20a] is not readily extended to vinyl iodides or bromides[20b] (yield 30%). Consequently, the α-aminoalkyl cuprate/vinyl triflate and (α-aminoalkyl)lithium/aryl iodide couplings provide complementary solutions to the coupling of α-metalated amines with sp^2-carbon centers. Although sensitive to steric factors in the enol triflate and restricted to amines with functional groups compatible with carbanion formation, the method is extremely versatile with regard to substitution patterns in both the substrate and α-aminoalkyl cuprate reagent and should provide a versatile synthetic route to a wide range of cyclic and acyclic allylic amines.

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Supporting Information Available: Spectra and a procedure (18 pages).

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(20) Dieter, R. K.; Li, S. *Tetrahedron Lett.* **1995**, *36*, 3613; (b) unpublished results.