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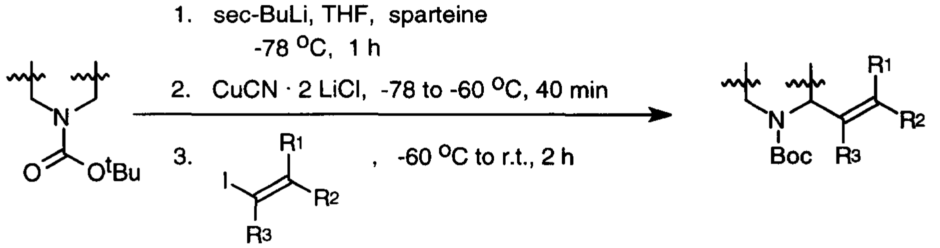
Stereospecific Coupling of α-Aminoalkylcuprates with Vinyl Iodides

R. Karl Dieter* and Ram R. Sharma

Howard L. Hunter Laboratory, Clemson University, Clemson, South Carolina 29634-1905

Abstract: Allylic amines can be prepared stereospecifically via a coupling reaction of vinyl iodides and α-aminoalkylcuprates prepared from the corresponding lithium reagents and LiCl solubilized CuCN. The reaction works well for both *E* and *Z* dialkyl substituted vinyl iodides. 1-Iodoalkynes can also be coupled in modest yields to afford propargyl amines. © 1997 Elsevier Science Ltd.

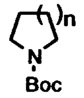
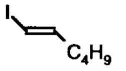
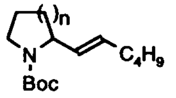
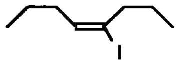
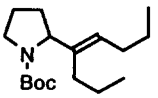
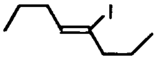
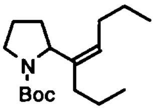
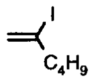
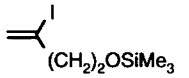
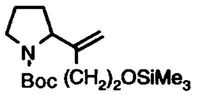
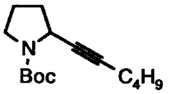
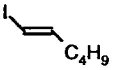
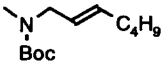
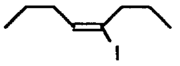
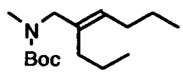
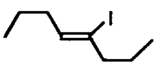
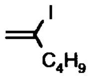
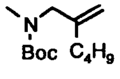
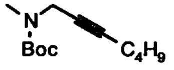
The extensive development of α–aminoalkyl carbanions by Meyers and Beak has focused largely on organolithium reagents and their reactions with a variety of electrophiles.[1] Recently, we have extended the range of α-aminoalkyl metal reagents with the development of the corresponding cuprate and/or copper reagents.[2] These reagents display reduced reactivity relative to simple dialkylcuprate reagents hindering the general expansion of the methodology to the wide range of reactions characteristic of cuprate reagents. In particular, the α-aminoalkycuprates underwent substitution reactions with cyclic vinyl triflates[2c] to afford a simple synthesis of allylic amines but failed to undergo reaction with aryl triflates and reacted with aryl iodides and vinyl iodides in very low yields. These coupling reactions are particularly useful for the preparation of pyrrolidine and piperidine derivatives for which few synthetic procedures exist.[3] Efforts to employ simple acyclic vinyl triflates were not successful due to their diminished stability and the difficulty of preparing them stereoselectively.[4] We now report that α-aminoalkylcuprates can be induced to couple with vinyl iodides if the cuprate reagent is prepared from LiCl solubilized CuCN in THF providing a simple stereospecific synthesis of acyclic allylic amines (eq. 1).



eq. 1

The principle advantage of using vinyl halides in coupling reactions with organometallic reagents is that they can easily be prepared with complete control of double bond geometry. The vinyl iodides used in the present study were prepared via DIBAL or catechol borane reduction of alkynes or by the regioselective addition of hydrogen iodide to a terminal alkyne.[5]

Table. Coupling of α-aminoalkylcuprates prepared from CuCN·2LiCl with vinyl iodides.

entry	carbamate[a]	n	vinyl or alkynyl halide	reagent[b]	allylic amine	% yield[c]
1		1		A		80-88
2		1		B		77-83
3		1		C		69-73
4		2[d]		A		35
5		1		A		95
6		1		A		86
7		1		A		58-86
8		1		A		90
9		1	I—≡—C_4H_9	A		48
10		-		A		90
11		-		A		60-87
12		-		A		79
13		-		A		92
14		-	I—≡—C_4H_9	A		50

[a] The carbamate was deprotonated with sec-BuLi in THF. Sparteine was used to facilitate deprotonation. [b] A = 2 RLi + CuCN·2LiCl. B = RLi + CuCl·2LiCl. C = RLi + CuCN·2LiCl. The cuprate reagent was prepared between -78 °C to -60 °C (40-50 min) followed by addition of the vinyl iodide at -60 °C and warming to room temperature (2 h). [c] Yields are based upon purified isolated products unless otherwise noted. [d] TMEDA was used to facilitate deprotonation in Et_2O.

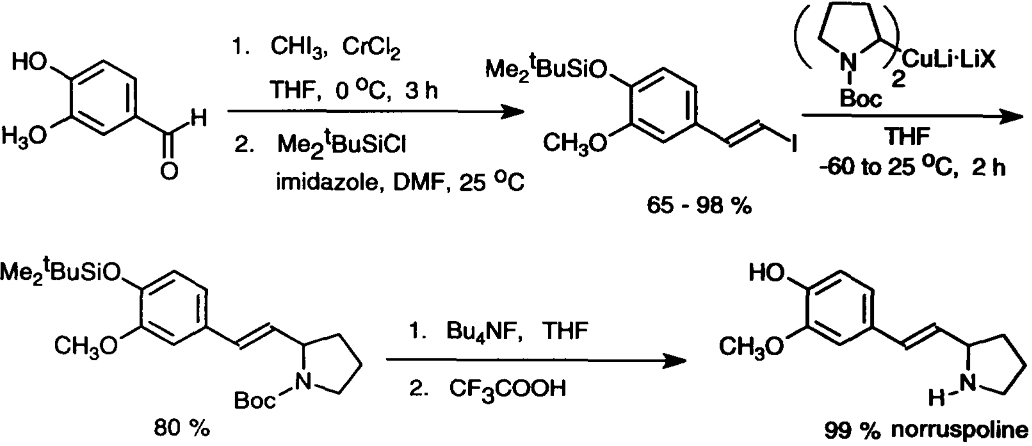
α-Aminoalkylcuprates were initially prepared from the *tert*-butyl carbamates of pyrrolidine (**1**) and *N,N*-dimethylamine (**2**) via deprotonation [*sec*-BuLi, THF, sparteine, -78 °C, 1 h] and subsequent addition to CuCN suspended in THF at -55 to -50 °C. Addition of vinyl iodides to the cuprates at -55 to -50 °C followed by warming to room temperature gave only trace amounts of coupling product as evidenced by gc-ms analysis. Subsequently, it was discovered that cuprate reagents prepared from THF soluble CuCN·2LiCl reacted with vinyl iodides to afford the allylic amines in good to excellent yields (Table). The cuprates were prepared from CuCN·2LiCl between -78 °C and -60 °C over a period of 40-50 minutes. Addition of the vinyl iodides at -60 °C followed by warming to room temperature and stirring for 2 hours afforded clean products in good to excellent yields for both terminal (entries 1, 10) and internal alkenes (entries 5-8, 11-13). Reaction of the cuprate reagent prepared from either carbamate **1** or **2** gave higher yields of coupling product with *E*-4-iodo-4-octene than with the *Z* -diastereomer suggestive of some sensitivity of the reaction to steric factors (entries 5 & 11 vs 6 & 12). The reaction can also tolerate additional functionality in the vinyl iodide as illustrated by the successful coupling of the homo allylic silyl ether (entry 8). The cuprate reagent prepared from *N*-Boc piperidine gave only modest yields of coupled product (entry 4).

Since the cuprate reagents inefficiently use only one of the two α-aminoalkyl ligands, an α-aminoalkylcopper(I) reagent and a cuprate reagent containing a non-transferable ligand were examined. Preparation of an alkylcopper(I) reagent from CuCl·2LiCl gave coupling product in yields comparable to that obtained with the cuprate reagent (entry 2) and slightly higher than that obtained with the cyano cuprate reagent (entry 3).

The coupling reaction could be extended to 1-iodoalkynes[6] which coupled with α-aminoalkylcuprates prepared from carbamates **1** and **2** in modest yields (entries 9, 14).

This method for the direct vinylation of α-aminoalkylcuprates provides for a stereospecific synthesis of the alkaloid norruspoline isolated from ***Ruspolia hypercrateriformis***; a member of the plant family *Acanthaceae*.[7] Treatment of Vanillin with the $CHI_3/CrCl_2$ system[8] resulted in homologation of the aldehyde with stereoselective formation of the the *E* vinyl iodide (*E*:*Z* = 9:1) in 65-98% yield (Scheme I). The lower yields were obtained on the larger scale reactions. Reaction of the vinyl iodide with the α-aminoalkylcuprate

Scheme I



prepared from *N*-Boc pyrrolidine and LiCl solubilized CuCN afforded the allylic amine stereospecifically in 80% yield. Sequential removal of the *tert*-butyldimethylsilyl and *N*-Boc protecting groups afforded (±)-norruspolind in 99% yield.

In summary, α-aminoalkylcuprates undergo a high yield stereospecific coupling reaction with vinyl iodides when prepared in THF from LiCl solubilized CuCN. This dramatic effect of CuCN·2LiCl in promoting the coupling reaction with vinyl iodides provides a powerful method for the stereospecific synthesis of allylic amines from acyclic stereodefined vinyl iodides that are easily prepared. Although the direct arylation of α-lithioamines can be effected with CuCN catalyzed palladium coupling,[10] the palladium promoted vinylation proceeds in very low yields and the α-aminoalkylcuprate coupling provides a superior alternative.

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