(α-Aminoalkyl)cuprates Prepared from Soluble Copper(I) Salts: Conjugate Additions to α,β-Unsaturated Carboxylic Acid Derivatives

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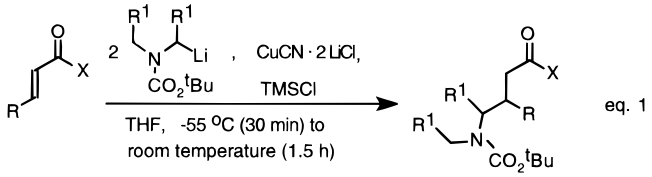
The development of (α-aminoalkyl)cuprate chemistry has been hampered by the limited reactivity of these reagents. While they undergo conjugate addition to α,β-enones,[1] the reaction could not be extended to α,β-enoates consistent with cuprate−enoate reactivity profiles. Although numerous homo and mixed organocuprates readily transfer alkyl ligands to the β-carbon atom of α,β-enones, the conjugate addition reaction is often sluggish with the less reactive enoate substrates. Cuprates prepared from CuCN (2 RLi + CuCN),[2] cuprous thiophenoxides,[3] and copper(I) (trimethylsilyl)acetylide[4] have provided partial solutions to this problem. The reactivity of the latter reagent was enhanced by solvent composition (4:1 ether: THF) and by the addition of chlorotrimethylsilane.[4] Gilman reagents also effect high-yield conjugate addition reactions with mono β-alkyl-substituted enoates, enamides, and enecarbamates in ether in the presence of TMSCl.[5] Alkylcopper compounds also participate with enoates in conjugate addition reactions in synthetically useful yields in the presence of additives such as $BF_3 \cdot Et_2O$ and chloro- or iodotrimethylsilane.[6]

The choice of copper(I) salt often plays a significant role in the chemistry of the resultant organocopper and cuprate reagents, and CuCN and $CuBr \cdot SMe_2$ have been promoted as the best Cu(I) precursors.[7] Organocopper reagents prepared from CuCN and either 1 or 2 equiv of an alkyllithium reagent often display superior attributes with regard to chemical yields, suggesting an important role of the cyanide anion. The structure of the latter reagent has been the subject of considerable interest centering around the location of the cyanide ion.[8] Although THF-soluble CuCN·2LiCl has been extensively used by Knochel in the Cu-promoted reactions of organozinc reagents,[9] this source of Cu(I) has not been widely used in the generation of cuprates from alkyllithium or Grignard reagents.[10] We have found that the combined use of LiCl-solubilized CuCN and TMSCl synergistically improve chemical yields in the conjugate addition reactions of (α-aminoalkyl)cuprates to a variety of carboxylic acid derivatives (eq 1).



eq. 1

X = -OR, -SR, -NCO(CH$_2$)$_3$- R^1 = H, or R^1, R^1 = -CH$_2$CH$_2$-

In initial studies, (α-aminoalkyl)cuprates prepared from *tert*-butoxycarbonyl (Boc)-protected pyrrolidine (**1**) or *N*,*N*-dimethylamine (**2**) and CuCN in either Et_2O or THF failed to undergo conjugate addition to either methyl acrylate or methyl crotonate. Cuprates prepared from the Boc carbamate of *N*-methyl-*N*-[(tri-*n*-butylstannyl)methyl]amine via transmetallation ((i) *n*-BuLi, −78 °C, THF, absence of sparteine; (ii) CuCN) also failed to react with methyl acrylate.[11] Low yields of conjugate adducts could be obtained with the alkylcopper reagent prepared from CuI in Et_2O (9%) or CH_2Cl_2 (28%).[11] Subsequent experimentation revealed that preparation of the cuprate reagent from **1** or **2** [i. *sec*-BuLi, (−)-sparteine, THF, −78 °C, 1 h; (ii) CuCN·2LiCl, THF, −78 to −55 °C, 45 min] and LiCl-solubilized CuCN generated efficacious reagents that underwent conjugate addition to methyl acrylate [THF, TMSCl, −55 °C, 0.5 h to room temperature (1.5 h)] in the presence of TMSCl in high yields (Table 1, entries 1 and 2). Utilization of ethyl crotonate resulted in significantly reduced yields of conjugate adducts accompanied by recovered carbamates (Table 1, entries 3 and 8). Deprotonation of **1**, aided by either TMEDA or (−)-sparteine, gave similar results for the subsequent cuprate conjugate additions to ethyl crotonate (52% vs 56−77% yields, respectively), and the use of CuCN·2LiI (53%) or excess LiCl (i.e., CuCN·4LiCl) had little effect (58% vs 56−77%, Table 1, entry 8).[1a] Cuprates prepared from **2** failed to react with ethyl tiglate or with methyl cyclohexene-1-carboxylate, while cuprates prepared from **1** gave low yields with the former (Table 1, entry 17) and no conjugate adduct with the latter (Table 1, entry 19).

In an effort to circumvent the deleterious effects of α-alkyl substitution, the corresponding thiol ester functionality was examined with the expectation that the lower LUMO energies of these substrates might enhance their reactivity with cuprate reagents.[12] Anticipating competitive acylation[13] and conjugate addition pathways, both the *n*-butyl and *tert*-butyl thiol esters were examined. Surprisingly, both derivatives gave good to excellent yields of conjugate adducts with no acylation products being observed (Table 1, entries 4, 6, 10, and 12). The thiol esters offered little advantage in the reactions with the acyclic α-alkyl-substituted substrates (Table 1, entry 18) but facilitated the reaction with the 1-cyclohexene derivative (Table 1, entry 20). In an effort to probe the greater reactivity of the thiol esters, a series of organocopper reagents were examined. The cyano-

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[12] AM1 calculations obtained from the MacSpartan program (Wavefunction, Inc., 18401 Von Karman Ave, #370, Irvine, CA 92715) gave the following relative ordering of LUMO energies: thiol esters < esters < imides. The calculated magnitude of the LUMO energies displayed no clear correlation with the observed chemical yields.

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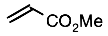
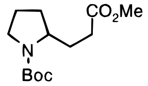
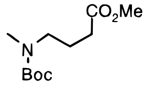
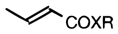
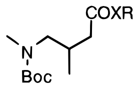
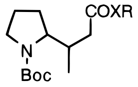
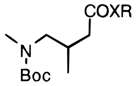
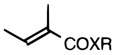
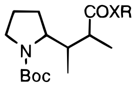
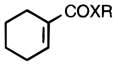
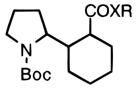
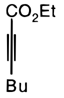
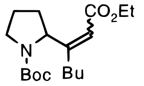
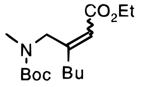
Table 1. Conjugate Addition of (α-Aminoalkyl)cuprates with α,β-Alkenyl and Alkynyl Carboxylic Acid Derivatives

entry	amine	substrate	copper reagent[a]	product[b]	% yield[c]
1	**1**		A		94
2	**2**		A		83
					
3	**2**	X = O; R = Et	A		39[d]
4		X = S; R = *n*-Bu	A		78
5			B		72
6		X = S; R = *t*-Bu	A		62
7			B		53-57
8	**1**	X = O; R = Et	A		56-77
9			B		32
10		X = S; R = *n*-Bu	A		94
11			B		83
12		X = S; R = *t*-Bu	A		100
13			B		88
14			C		53
15		X = N; R^1=-CO(CH_2)$_3$-	A		91
16	**2**		A		46
					
17	**1**	X = O; R = Et	A		30[d]
18		X = S; R = *t*-Bu	A		37[d]
					
19		X = O; R = Et	A		0
20		X = S; R =^{n}Bu	A		20[d]
21	**1**		B		91-95
22			A		68[d]
23	**2**		B		88

[a] A = 2RLi + CuCN·2LiCl. B = RLi + CuCN·2LiCl. C = RLi + CuCl·2LiCl. [b] Reaction of the organocopper reagent with the unsaturated substrate and TMSCl (5.0 equivs) in THF at −55 °C (30 min) and then at rt (1.5 h) gave the conjuate addition products. [c] Yields are based upon isolated purified products unless otherwise noted. [d] Yield determined by NMR using tetrachloroethane as internal standard.

cuprate reagents, RCuCNLi, gave good to excellent yields of conjugate addition products with the thiol esters (Table 1, entries 5, 7, 11, and 13) and poor yields with esters (Table 1, entry 9). Utilization of an alkylcopper reagent prepared from **1** and CuCl·2LiCl gave a modest yield of product (Table 1, entry 14). These results suggest the possibility that the cuprate and copper reagents are coordinating to the thiol esters and in this manner facilitating the conjugate addition reactions.

A cuprate reagent prepared from 2 equiv of **1** and CuCN·2LiCl gave a modest yield of conjugate adduct (Table 1, entry 22) with an α,β-ynoate, while nearly quantitative yields could be achieved with RCuCNLi reagents prepared from **1** or **2** under similar conditions (Table 1, entries 21 and 23). The product enoate obtained from **1** was isolated as a 65:35 mixture of *Z*:*E* geometrical isomers, which was confirmed by amine deprotection to quantitatively afford a lactam and (*E*)-ethyl 3-(2-pyrrolidinyl)-2-heptenoate in a 65:35 ratio, respectively.

The cuprate reagents prepared from **1** or **2** and CuCN·2LiCl also underwent conjugate addition to an imide in excellent to modest yields (Table 1, entries 15 and 16 respectively). These yields are intriguing since the imides have particularly high LUMO energies in comparison to the esters or thiol esters.[12] These results are suggestive of the crucial role that lithium cation coordination to the unsaturated carbonyl moiety plays in these conjugate addition reactions.

The success of these conjugate addition reactions requires the activating influence of TMSCl and the utilization of LiCl-solubilized CuCN for the preparation of the cuprate reagents. The presence of the LiCl dramatically raises the yields of these reactions from zero to 39−77% for the ester substrates in THF and is consistent with added LiCl acting as a Lewis acid via coordination with the carbonyl oxygen atom. This is in marked contrast to the report that cuprate reactivity is greater in conjugate addition reactions in the absence of LiX.[14] The failure of the conjugate addition reactions of (α-aminoalkyl)cuprates to proceed with esters in the absence of added LiCl finds analogy in the poor reactivity of *ortho*-substituted β-aryl enoates containing three oxygen atoms in the side chain with lithium dialkylcuprates.[15] In cuprates prepared from CuCN alone, it appears that the dipole-stabilizing carbamate functionality ties up the lithium ions, making them unavailable for coordination to the enoate carbonyl, which is necessary for the conjugate addition reaction to proceed. Conjugate addition of cuprates prepared from **1** to ethyl crotonate are not promoted by BF_3·Et_2O (2.0 equivs)/TMSCl (5 equivs) while addition of BF_3·Et_2O (2.0 equiv) to the CuCN·2LiCl/TMSCl (5 equivs) system has little effect (52% vs 56−77% yields, Table 1, entry 8).

In summary, reaction conditions have been developed for the conjugate addition of relatively unreactive heteroatom-functionalized cuprate reagents with the less reactive carboxylic acid derivatives. The conjugate addition reaction of (α-aminoalkyl)cuprates to α,β-unsaturated carboxylic acid derivatives is a feasible transformation if the reagents are prepared from LiCl-solubilized CuCN and TMSCl is used as an additive. Yields can be improved by utilization of thiol esters. The method currently fails with cyclic substrates and is limited to derivatives lacking an α-alkyl substituent. *These results suggest that LiCl-solubilized CuCN may be a particularly useful source of Cu(I) for the preparation of heteroatom-functionalized cuprate reagents where intramolecular lithium ion complexation reduces the reactivity of the cuprate reagent.*

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Supporting Information Available: ^{1}H and ^{13}C spectra and a procedure (29 pages).

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