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Diethylzinc-Mediated Metalloamination-Alkylation of *N,N*-Dimethylhydrazinoalkenes. Catalysis of C-Zn Alkylation Using Simple Cu(I) Salts

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Abstract

Metalloamination-alkylation of representative *N,N*-dimethyl-hydrazinoalkenes has been shown to be effectively catalyzed by CuBr·SMe₂, CuCN, and CuI. The current method obviates the use of stoichiometric CuCN(LiCl)₂ as a promoter for the electrophilic functionalization event.

Graphical Abstract

Keywords

metalloamination–cyclization; Cu(I) catalysis; allylation

Saturated N-heterocycles have come to be recognized as privileged scaffolds for drug discovery and development as a consequence of their decreased lipophilicities, improved solubility, bioavailability, and pharmacokinetics.^{1a,b} This class of heterocycles, many of which contain chiral centers, presents synthetic challenges that are often not well addressed by traditional synthetic methods.^{1c} We have previously advanced a powerful new method for achieving N- C/C-C bond construction by way of simultaneous N-C/C-Zn metalloamination.^{2a,b} Several laboratories have documented synthetically viable methods for achieving sequential N-C → C-M → C-C bond formation, with the seminal discoveries of the Bower,^{3a,b} Chemler,^{3c,d} Knowles^{3e-g} and Wolfe^{3h-k} laboratories being major advancements.⁴ From a synthetic standpoint, it is significant that virtually all current procedures are limited in the

This manuscript is dedicated to Professor Albert Padwa on the occasion of his 80th birthday.

Supporting Information

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final C-C bond-forming step due to the fleeting nature of their requisite organometallic or free-radical intermediates. By way of contrast, our work involves the intermediacy of organozinc reagents, which are comparatively robust and can be synthetically differentiated via numerous C-Zn functionalization procedures. In addition, many of the catalytic metalloamination methods for forming five-membered rings (as well as the very few that give six-membered rings) greatly benefit from conformational biasing effects favoring annulation. In contrast, our Zn(II)-mediated annulation procedure is not reliant on conformational constraints. We have previously reported that *stoichiometric* CuCN(LiCl)₂⁵ is an effective reagent for promoting allylations of the C-Zn bond present in nitrogenous heterocycles of the type **2**.^{2a,b} In this communication we show that CuBr-SMe₂, CuCN, and CuI are effective catalysts for allylation at carbon.

The influence of aromatic solvents on the efficiency of metalloamination was initially investigated by a direct comparison of toluene to its more polar counterpart benzonitrile (BTF).⁶ Whereas the use of each of these solvents resulted in excellent conversion (>95%) of the *N,N*-dimethylhydrazinoalkene **1a** to the corresponding cyclic organozinc **2a** at 90 °C, reactions conducted in BTF proceeded more rapidly, requiring six hours compared to 24 hours when PhMe was employed. From the standpoint of economics, the use of chlorobenzene led to metalloamination in the intermediate range of 12 hours. In addition, the 'π-excessive' aromatic thiophene was found to offer no obvious advantages as a solvent over chlorobenzene or PhMe (Scheme 1).

The efficacy of selected Cu(I) salts (and complexes) as allylation catalysts was then studied. From the standpoint of experimental simplicity, it is noteworthy that the 'conventional' Cu(I) sources CuBr-SMe₂, CuCN, and CuI proved to be excellent catalysts for the conversion of **2a** to **3a**.

In a representative experimental procedure, exposure of **1a** (0.10 mmol) to Et₂Zn (1.0 equiv as a 2.0 M solution in BTF) in BTF (0.4 mL) at 90 °C for six hours generated **2a** (95%, as a 20:1 *cis/trans* diastereomeric mixture).⁷ Subsequently, tetrahydrothiophene (THT, 0.1 mL), CuBr-SMe₂ (1.02 mg, 5 mol%), and allyl bromide (4 equiv) were added in succession. Allylation was monitored by ¹H NMR at 23 °C for 12 hours, whereupon complete conversion into **3a** was achieved. Upon workup (*vide infra*) the pyrrolidine **3a** (95%, dr 20:1) was furnished as a clear liquid (which could also be conveniently isolated as the trifluoroacetate salt). Although methallyl chloride had previously been found highly satisfactory as a trapping agent when *stoichiometric* CuCN(LiCl)₂^{2a} was used as a promoter, this complex proved much less effective when used as a catalyst (5 mol%) with the less reactive methallyl chloride. In sharp contrast, the use of CuCN(LiBr)₂ admixed with LiBr (1 equiv) led to rapid and highly efficient methallylation (possibly due to an internal Finkelstein activation process). Additionally, the use of THT as a Cu(I) stabilizer was determined unnecessary. The simple addition of LiBr (1 equiv) also provided solutions of mixed Cu/Zn intermediates that were endowed with substantial lifetimes. Alternative Cu(I) complexes [i.e., CuBr-P(*n*-Bu)₃, CuBr-P(2-furyl)₃, CuCl-(PPh₃)₂] and CuSPh were subsequently tested and found to be inferior as catalysts, as was AuCl-PPh₃. The results of this study are summarized in Table 1. In addition, Mo(CO)₆ and Mo(CO)₄ bipy⁸ were not competent as catalysts for the present transformation.

The synthetic scope of metalloamination-allylation was explored by subjecting additional *N,N*-dimethylhydrazino- alkenes (e.g., **1a-d**) to an experimental protocol closely related to that described for the conversion of **1a** into **3a**. The details of this study are summarized in Table 2. The results presented in Table 2 are noteworthy in that the isolated yields are excellent in almost all cases. Significantly, the presence of Thorpe-Ingold conformational acceleration that is of crucial importance in many hydroamination- cyclizations is not a prerequisite for successful metalloami- nation-cyclization. In addition, these reactions were readily scalable (e.g., 1 mmol). Two examples are presented in entries 1 and 4, in which simple 5- and 6-membered rings are formed efficiently *and with faster rates* than observed for **1b** (entry 2). In addition, excellent levels of diastereoselec- tivity are achievable. Specific cases include the metalloamination-allylation of **1a** to provide pyrrolidines **3a** (*cis/trans* 20:1) and **1c** to give pyrrolidine **3c** (*cis/trans* = 1:15).^{2a} As revealed by Table 2, entry 4, facile metalloamination-allyla- tion is also extendible to the formation of piperidines from a *N,N*-dimethylhydrazinoalkene that lacks conformational biasing favoring ring closure (**1d** → **3d**).

It is also significant that alternative halides readily participate in the C-functionalization process. Thus, the use of propargyl bromide provided allene **3a_{allene}** and methyl 2-(bromomethyl)acrylate furnished enoate **3a_{methacrylate}** in respectable yields (Table 3, entries 3 and 4).

In conclusion, we have shown that the readily available Cu(I) derivatives CuBr-SMe₂, CuCN, and CuI are highly effective catalysts for the allylation of zinc-bearing azacycles generated by Et₂Zn-driven metalloamination-cyclization of representative *N,N*-dimethylhydrazinoalkenes.⁹ Metalloamination-cyclization proceeded more rapidly in benzonitrile (BTF) and chlorobenzene than toluene, but all three solvents proved very well suited for overall cyclization-allylation. In addition, alternative attractive modes of electrophilic functionalization of the intermediate C-Zn bond have been revealed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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- (9). General Procedure for CuBr-SMe₂-Catalyzed Metalloamination-Allylation An oven-dried J. Young tube under an argon atmosphere was charged with Et₂Zn (50 µL, 2.0 M in BTF, 0.1 mmol, 1.0 equiv), BTF (0.4 mL), and the requisite *N,N*-dimethylhydrazinoalkene (0.1 mmol, 1.0 equiv). The tube was then placed into an oil bath (of indicated temperature) and metalloamination-cyclization was monitored using BTF as an internal standard (as evidenced by the disappearance of the alkene signals with concurrent emergence of new C-Zn methylene peaks). The temperature of the reactant mixture was subsequently returned to 23 °C for the addition of THT (0.1 mL) followed by the addition of the Cu(I) catalyst (5 mol%). Allyl bromide (4.0 equiv) was then added and its consumption, with simultaneous recession of the intermediate C-Zn methylene resonance, was monitored by No-D proton NMR. Upon completion of allylation, the reactant mixture was dispersed in Et₂O (2 mL) and washed with 1:1 sat. NH₄Cl (aq)/sat. aq NH₄OH (3 × 3 mL). The aqueous layers were then extracted with Et₂O (3 mL), and the combined organic layers were dried successively with brine (5 mL) and MgSO₄, and then filtered through a plug of silica. To the ethereal solution was added TFA (8.5 µL, 0.11 mmol, 1.1 equiv), and the mixture was concentrated *in vacuo*. The resulting salt was triturated with pentane (3 × 1 mL), and the volatiles were removed to provide the cyclization-allylation product (>95%) as a clear viscous oil (which could also be isolated as the mono-TFA salt).

Scheme 1.
Metalloamination-allylation of *N,N*-dimethyl-hydrazinoalkenes

Table 1

Catalyst Evaluation Using Allyl Bromide as the Electrophile

Entry	Catalyst	<i>t</i> _{final}	Yield ^a
1	CuBr.DMS ^c	12 h	95%
2	CuBr.DMS ^{b,d}	3 h	95%
3	CuCN.2LiBr ^{b,d}	8 h	95%
4	CuI ^c	15 h	95%
5	CuBr.P(2-furyl) ₃ ^c	12 h	74%
6	CuBr.P(<i>n</i> -Bu) ₃ ^c	12 h	70%
7	CuCl.2PPh ₃ ^c	22 h	67%
8	PhSCu ^{b,c}	10 h	65%
9	AuCl.PPh ₃ ^c	22 h	25%

^a Monitored by No-D ¹H NMR⁷ using disappearance of C-Zn methylene peak to determine completion.

^b BTF was removed and allylation was performed in THF.

^c Reaction conducted with 1.1 equiv of THT.

^d One equiv of LiBr was added.

Table 2
Metalloamination-Allylation of *N,N*-Dimethylhydrazinoalkenes Utilizing Allyl Bromide as the Electrophile

Entry	Hydrazine	^a t _{cyclize}	^{e,f} t _{allylation}	^d dr	Product ^b	Yield ^{d,c}
1		6 h (90 °C)	12 h (23 °C)	20:1		95%
2		18 h (90 °C)	24 h (23 °C)	-		95%
3		24 h (23 °C)	22 h (23 °C)	15:1		90%
4		1 h (60 °C)	8 h (23 °C)	-		95%

Entry	Hydrazine	^a t _{cyclize}	^{e,f} t _{allylation}	^d dr	Product ^b	Yield ^{d,c}
5		24 h (23 °C)	12 h (23 °C)	6:1		80%
6		–	–	–		–

^aMonitored by No-D ¹H NMR using BTF as the internal standard.⁷

^bProducts were isolated as TFA salts.

^cA small quantity of the TFA salt of the starting *N,N*-dimethylhydrazinoalkene (**1**) was admixed with the product.

^dDiastereomeric ratios were derived from proton NMR.^{3e}

^eMonitored by the disappearance of C-Zn methylene peak to determine completion.⁷

^fThe allylation was catalyzed by CuCN(LiBr)₂ and conducted in THF.

Table 3

Catalytic CuCN.2LiBr (5 mol%) Mediated Allylation of 1-Methyl- *N,N*-Dimethyl-4-pentene in THF with Representative Halides

Entry	Halides	Time	Temp	Product ^b	Yield ^{a,c}
1		12 h	23 °C	 3a	95%
2		10h	23 °C	 3a-Me	95%
3		5 h	23 °C	 3a_{allene}	60%
4		4 h	23 °C	 3a_{methacrylate}	65%

^aMonitored by No-D ¹H NMR using disappearance of C-Zn methylene peak to determine completion.⁷

^bProducts were isolated as TFA salts subsequent to allylation in THF.

^cA small quantity of the TFA salt of the starting *N,N*-dimethylhydrazinoalkene **1** was admixed with the product.