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Published on Web 09/02/2004

CuBr-Catalyzed Efficient Alkynylation of sp^3 C−H Bonds Adjacent to a Nitrogen Atom

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Received July 1, 2004; E-mail: cj.li@mcgill.ca

Transition metal-catalyzed C−H bond activation and subsequent C−C bond formations have attracted much interest in recent years.[1] Although many excellent results have been achieved, catalytic functionlization of sp^3 C−H bonds is still a challenge.[2] Various transition metals such as Rh, Ru, Ir, Pd, Au, and Pt have been used to activate sp^3 C−H bonds.[3]

Direct oxidative functionalization of tertiary amines is of importance both enzymatically and synthetically.[4] Propargylic amines are of great pharmaceutical interest and are synthetic intermediates for the synthesis of various nitrogen compounds as well as carbohydrates.[5] There are three main methods to construct propargylic amines (Scheme 1): *Path A* stands for stoichiometric nucleophilic reactions.[6] *Path B* is the transition metal-catalyzed reactions of alkynes and imines generated from aldehydes and amines. There are many excellent examples of these two methods. Recently, we[7] and others[8] have described the direct addition of a terminal alkyne to aldehyde and imines to afford propargyl alcohols and propargylamines. With Cu(I)-pybox as a chiral catalyst, a highly enantioselective imine addition in either water or toluene was developed.[9] We also developed the coupling of alkynes with *N*-acylimines and *N*-acyliminium ions by a CuBr catalyst and the gold or silver-catalyzed coupling reaction of alkyne, aldehyde, and amine in water.[10] Although these are effective methods, they need a leaving group or imines formed from aldehyde and amine. Therefore, the direct construction of propargylic amines by the catalytic coupling of sp^3 C−H adjacent to nitrogen with a terminal alkyne is an attractive method (*Path C*).[11] Herein we report an effective CuBr-catalyzed oxidative cross-coupling of amine with alkyne via a direct sp^3 C−H bond alkynylation.

To begin our study, various copper salts were examined as catalysts for the alkynylation of *N*,*N*-dimethylaniline (Table 1). CuBr and CuCl proved to be the best catalysts. CuI and $Cu(I)_2Se$ showed lower catalytic activities. No reaction was observed in the absence of copper catalyst. To improve the yields, various ratios of *N*,*N*-dimethylaniline and alkynes as well as *tert*-butyl hydroperoxide were examined. The best yield was obtained when the *N*,*N*-dimethylaniline/alkynes/*tert*-butyl hydroperoxide ratio wass 2:1:1. From the NMR spectrum of crude reaction mixture, nearly 1 equiv of *N*,*N*-dimethylaniline remained after the reaction was finished. When the amount of *N*,*N*-dimethylaniline was reduced, however, the yields also decreased. The yields were markedly decreased when the amount of *tert*-butyl hydroperoxide was reduced to 0.5 equiv and 0.25 equiv. The reaction did not proceed without *tert*-butyl hydroperoxide.

Subsequently, various alkynes were reacted with amines. Representative examples are shown in Table 2. The reaction of *N*,*N*-dimethylaniline (2 equiv) with phenylacetylene in the presence of a CuBr catalyst (5 mol %) and *tert*-butyl hydroperoxide (1.0−1.2 equiv) at 100 °C for 3 h gave *N*-methyl-*N*-(3-phenylprop-2-ynyl)-benzenamine in 74% isolated yield (entry 1). For aromatic alkynes, the reaction often provided good yields of the desired products.

Scheme 1. Various Methods for Forming Propargylamines

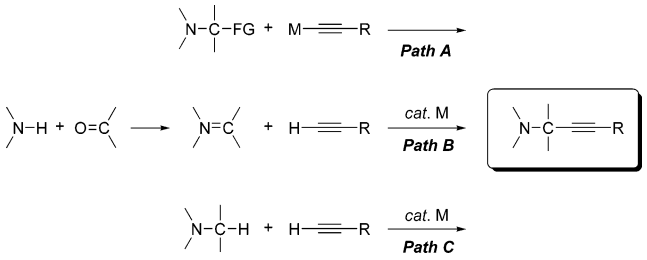
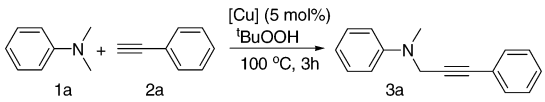


Table 1. Selection of Copper Catalyst[a]



entry	catalyst	NMR yield[b]
1	CuBr	77
2	CuB_2	72
3	CuCl	75
4	$CuCl_2$	73
5	CuI	56
6	$Cu(I)_2Se$	61
7	CuOTf	25
8	$Cu(OTf)_2$	8
9	no	0

[a] 4.0 mmol aniline, 2.0 mmol phenylacetylene, 0.1 mmol copper salt, and 0.8 mL ^{t}BuOOH (5−6 M in decane). [b] Reported yields were based on alkynes and determined by NMR using an internal standard.

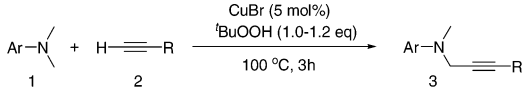
For aliphatic alkynes, the corresponding product was formed in lower yields (entry 10). The reactions also tolerated functional groups such as alcohol and ester (entries 7−9).

When benzyldimethylamine was reacted with phenylacetylene under the standard conditions, alkynylation of the methyl group was the main product (Scheme 2). The minor product could not be isolated. This result, where the alkynylation takes place preferentially at the alkyl rather than the benzyl position, is similar to anodic methoxylation of the amine.[12]

Cyclic amines such as tetrahydroisoquinoline can be selectively converted into the corresponding α-alkynylation compound in 74% isolated yield (Scheme 3). Interestingly, 1-phenyl-piperidine reacted with phenylacetylene in the presence of a catalytic amount of CuBr and 1 equiv of *tert*-butyl hydroperoxide to give the desired direct alkynylation product in 12% yield together with a *tert*-butyloxide alkynylation compound (12%) (Scheme 4). The ^{1}H NMR spectrum of the *tert*-butyloxide alkynylation product showed the expected AB system, $J_{H^1-H^2}$ 2.4 Hz. Chemdraw 3D models indicate that in the *trans*-H^1, H^2 case, the dihedral angle between H^1 and H^2 is approximately 74°, while the cis-isomer is 53° (after minimizing the molecular energy). Compared with similar compounds,[13] our product is most likely the trans-isomer.

10.1021/ja0460763 CCC: $27.50

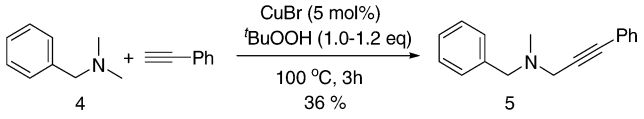
Table 2. Copper-Catalyzed Alkynylation of Amines[a]



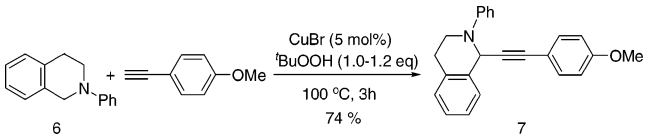
entry	Ar	R	product	yield[b]
1	Ph	Ph	3a	74
2	Ph	4-MeOPh	3b	82
3	Ph	4-MePh	3c	74
4	Ph	4-BrPh	3d	74
5	Ph	4-PhPh	3e	60
6	Ph	2-Py	3f	36
7	Ph	$HOCH_2$	3g	40
8	Ph	$EtCOOCH_2$	3h	58
9	Ph	CH_3OCO	3i	25
10	Ph	Bu	3j	12
11	4-MePh	Ph	3k	73
12	2-MePh	Ph	3l	53
13	4-BrPh	Ph	3m	69

[a] 4.0 mmol amine, 2.0 mmol alkyne, 0.1 mmol copper bromide, and 0.4 mL ^{t}BuOOH (5−6 M in decane). [b] Isolated yields were based on alkynes.

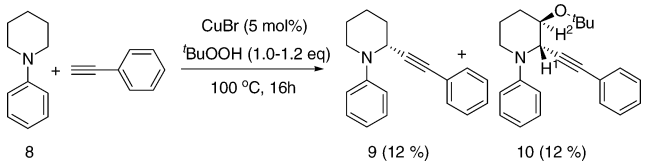
Scheme 2. Reaction of *N,N*-Dimethylbenzylamine



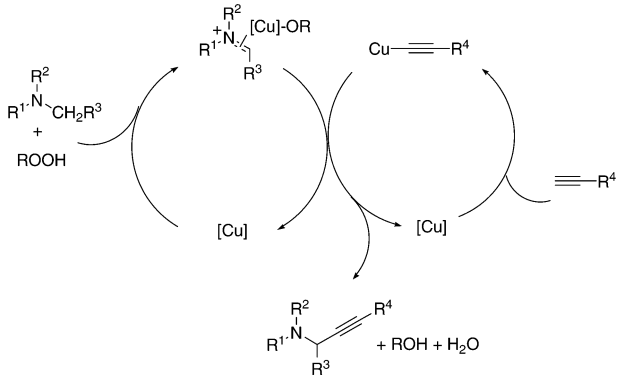
Scheme 3. Reaction of Cyclic Benzylamine



Scheme 4. Reaction of Simple Cyclic Amine



Scheme 5. Tentative Mechanism for the Direct Oxidative Coupling of Amine with Alkyne



A tentative mechanism for the product formation is proposed in Scheme 5. Copper catalyzed the formation of an imine-type intermediate (coordinated to copper) through activation of sp^3 C−H adjacent to nitrogen. Copper also activated the terminal alkyne. Subsequently, coupling of the two intermediates resulted in the desired product and regenerated the copper catalyst.[14] Alternatively, it is possible that *tert*-butylperoxide products were involved as intermediates,[15] which were further converted into the corresponding alkynylation amine via CuBr.[16]

In summary, we report here a simple and effective catalytic method to form propargylamine by using copper bromide via a combination of sp^3 C−H bond and sp C−H bond activations and C−C bond formations. Because piperidine derivatives and 1,2,3,4-tetrahydro-isoquinoline derivatives are important structural features of natural products and pharmaceuticals, this catalytic reaction will be an efficient method for the synthesis of such compounds. The scope, mechanism, and synthetic application of this reaction is under investigation.

Acknowledgment. We are grateful to the Canada Research Chair (Tier I) foundation (to C.J.L.), the CFI, NSERC, Merck Frosst, and McGill University for support of our research.

Supporting Information Available: Representative experimental procedure and characterization of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA0460763