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Org Lett. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

Org Lett. 2015 May 1; 17(9): 2190–2193. doi:10.1021/acs.orglett.5b00828.

An Umpolung Strategy for the Synthesis of β-Aminoketones via Copper-Catalyzed Electrophilic Amination of Cyclopropanols

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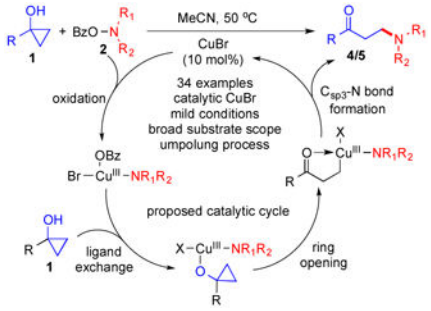
Abstract

A novel copper-catalyzed electrophilic amination of cyclopropanols with *O*-benzoyl-*N*,-*N*-dialkylhydroxylamines to synthesize various β-aminoketones via a sequence of C-C bond cleavage and C_{sp3}-N bond formation is reported. The reaction conditions are mild and tolerate a wide range of functional groups including benzoate, tosylate, expoxide, and α,β-unsaturated carbonyls, which are incompatible in the traditional amine nucleophilic conjugate addition and the Mannich reaction conditions. Preliminary mechanistic studies and a proposed catalytic cycle of this umpolung β-aminoketone synthesis process have been described as well.

Abstract



Nitrogen-containing groups are indispensable moieties of pharmaceuticals, agrochemicals and materials. Transition-metal-catalyzed C_{sp2}-N bond formations,[1] particularly the Buchwald-Hartwig amination, [2] Chan-Lam coupling,[3] and C_{sp2}-H amination,[4] have significantly advanced the installation of nitrogen-containing groups on aromatic and olefinic substrates. However, transition metal catalyzed C_{sp3}-N bond formation at non-activated C_{sp3}-centers for the syntheses of aliphatic amines are still very limited. Significant advances of C_{sp3}-H animation reaction and amination of double bonds[6] have been made

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ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization for new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

Notes

The authors declare no competing financial interests.

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recently to synthesize aliphatic nitrogen-containing compounds. Our interest in using cyclopropanols and the related systems as useful alkyl cross-coupling partners to form important C_{sp3}-C_{sp3} and C_{sp3}-heteroatom bonds (Figure 1A and 1B)[7] as well as using polysubstituted amines as potential selective adenylyl cyclase 1 inhibitors for treating inflammatory and neuropathic pain[8] prompted us to develop an efficient copper-catalyzed electrophilic amination[9] of cyclopropanols to synthesize various β-aminoketones,[10] which are commonly prepared by the conjugation addition of amine nucleophiles to α,β-unsaturated carbonyls[11] or the Mannich-type reactions between azomethines and enolates.[12]

Cyclopropanols are important and useful functional groups in organic synthesis and can be readily prepared via the Kulinkovich protocol or cyclopropanation (Simmons-Smith reaction) of enol ethers.[13] Currently, most of the transition metal catalyzed cyclopropanol homoenolate chemistry focus on palladium-catalyzed C-C bond formation at the β-position (Scheme 1A).[14] Copper-promoted or copper-catalyzed cyclopropanol ring-opening cross-coupling reactions have been very rare despite the low-cost and sustainable feature of copper catalyst.[15] Ryu, Murai, and co-workers have discovered that Cu(II)-homoenolates derived from the treatment of 1-alkoxy-1-siloxycyclopropanes with a stoichiometric amount $Cu(BF_4)_2$ could undergo homodimerziation to form 1,6-diketones or be trapped by highly electron-deficient acetylenes to form cross-coupling products.[16] Recently, Cha, and co-workers have developed elegant S_N2' alkylations of the metal-lo-homoenolate derived from treating cyclopropanols with more than stoichiometric amount CuCN and one equivalent of $ZnEt_2$ as well as their applications in complex natural product synthesis.[17]

Electrophilic ring-opening amination of cyclopropanols could provide an umpolung and complementary strategy to synthesize β-amino carbonyls. We hypothesized that Cu(I) catalyst could be oxidized to Cu(III) by an *O*-benzoyl-*N*,-*N*-dialkylhydroxylamine[18] (cf. **2**, Figure 1C); the resulting Cu(III) species would promote a cyclopropanol ring opening reaction to generate copper-homoenolate **3**, which would undergo reductive elimination to form a C_{sp3}-N bond and regenerate the Cu(I) catalyst. We were also hoping that the use of catalytic amount of copper catalyst and the close interaction between the NR_1R_2 group and the copper-homoenolate could potentially suppress the homo-coupling, further oxidation, and other undesired reaction pathways. Herein, we report the first copper-catalyzed electrophilic amination of cyclopropanols with *O*-benzoyl-*N*,-*N*-dialkylhydroxylamines.

Our exploration started with model substrates **1a** and *O*-benzoyl-morpholine **2a** (Table 1). When a mixture of **1a** and **2a** were treated with a catalytic amount of CuI (0.1 equiv) in THF at 80 °C, the desired β-morpholinylketone **4a** was produced in 85= yield. Further reaction condition optimization showed that (i) MeCN is superior to other solvents such as THF, toluene, DCE, and 1,4-dioxane presumably due to its coordinating capacity with the copper catalyst and (ii) CuBr works slightly better than CuCl and CuI. The reaction proceeds efficiently at 50 °C, but the yield dropped significantly when the reaction was conducted at room temperature. Increasing the amount of **2a** to 1.5 equiv gave reduced reaction yield while using 1.5 equiv of **1a** was beneficial for the production of **4a**. Nitrogen-based bidentate ligand phenanthroline inhibited the product formation. Overall, we were able to obtain β-morpholinylketone **4a** in 98= yield with CuBr (0.1 equiv) in MeCN at 50 °C (entry 11).

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With the optimized reaction conditions, we then investigated the substrate scope of this electrophilic β-amination process in terms of both cyclopropanols (Figure 2) and *O*-benzoyl-*N*,*N*-dialkylhydroxylamines (Figure 3). To our satisfactory, both aryl and alkyl substituted cyclopropanols underwent the desired ring opening cross-coupling reaction to provide various aryl and alkyl β-aminoketones, respectively, in good to excellent yield. Ether (**4a** and **4h**), bromide (**4b**), fluoride (**4c**), cyclopropyl (**4f**), TBS-ether (**4k** and **4q**), terminal olefin (**4p**), free alcohol (**4j**), and diene (**4r**) functional groups are well tolerated under the reaction conditions. *Notably*, *functional* conjugate amine addition conditions and the Mannich reaction conditions to synthesize β-amino ketones survived the mild electrophilic amination conditions very well. In addition to *O*-benzoyl-morpholine (**2a**), many other *O*-benzoyl-*N*,-*N*-dialkylhydroxylamines work smoothly as the nitrogen-containing group donors (Figure 3). Benzyl (**5a** and **5b**), allyl (**5d**), sulphonamide (**5h**), Boc-carbamate (**5i** and **5l**), urea (**5j**) and amide (**5k**) groups are compatible with the reaction conditions. Notably, azitidine (**5f**), azepane (**5g**), 1,4-diazepane (**5h**), piperazine (**5i-k**), and indole or tryptoline (**5m**)-containing β-aminoketones could be obtained in good to excellent yields. The reaction could also be conducted in gram-scale as well (**4a**, Figure 2).

We then started to probe the reaction mechanism. When the reaction was conducted in the absence of *O*-benzoyl-*N*,-*N*-dialkylhydroxylamines, only a trace amount of ring opened product **6** was produced from **1a** (Figure 4, Eq.1). Increasing the amount of CuBr to 1.0 equiv resulted in a 17/1 ratio of **1a**/**6**. These results indicate that CuBr alone is not effective enough to induce cyclopropanol ring opening and a higher oxidation level of copper catalyst, Cu(II) or Cu(III), is required. When *O*-benzoyl-*N*,-*N*-dialkylhydroxylamine **2o** was employed, desired product **5o** was obtained in 69= yield and we didn't observe the formation of pyrrolidine product **7** (Figure 4, Eq.2), which suggests that a nitrogen radical is not likely involved during the oxidation of Cu(I) catalyst. Similarly, cyclopropanol **1s** gave desired product **4s** in 76= yield and no cyclized product **8** was isolated indicating a non-radical cyclo-propanol ring-opening process (Figure 4, Eq.3).[19] These two notions are further supported by the insensitivity of the reaction to the addition of 1.0 equiv of TEMPO (Figure 4, Eq.4).

With these preliminary experimental results, we proposed the following reaction mechanism based on a Cu(I)/Cu(III) catalytic cycle (Figure 5). Cu(I) catalyst was first oxidized to Cu(III) complex **A** by *O*-benzoyl-*N*,-*N*-dialkylhydroxylamine **2**.[20] The latter would undergo ligand exchange and coordinate with cyclopropanol **1** to produce intermediate **B**, which then underwent β-carbon elimination to open the cyclopropane ring by breaking the Walsh bond and provide Cu(III) homoenolate **C.** Reductive elimination would form the desired C_{sp3}-N bond, produce β-aminoketone **4**/**5**, and regenerate Cu(I) catalyst.

In summary, we have developed a novel copper-catalyzed electrophilic amination of cyclopropanols with *O*-benzoyl -*N*,-*N*-dialkylhydroxylamines as oxidant. Various β-aminoketones can be synthesized in good to excellent yield. This novel synthetic transformation features mild reaction conditions, broad substrate scope, and excellent functional group compatibility, particularly those functional groups that are problematic in the traditional nucleophilic conjugate addition conditions and the Mannich reaction

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conditions. The reaction can also be conducted on gram-scale and in complex natural product and drug settings. Preliminary mechanism studies have been conducted and led us to propose a Cu(I)/Cu(III) catalytic cycle to account for the observed outcomes. While further mechanistic investigations are necessary to understand this reaction, it does open a new gate for the development of novel synthetic transformations involving the use of cyclopropanols and related systems as C_{sp3} cross-coupling partners.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

We thank Prof. Y. Xia's group at Purdue University for assistance with mass spectrometry and Purdue University for startup support. The NIH for supporting shared NMR resources to the Purdue Center for Cancer Research is acknowledged (P30CA023168). This work is also partially supported by the ACS Petroleum Research Foundation (PRF# 54896-DNI1).

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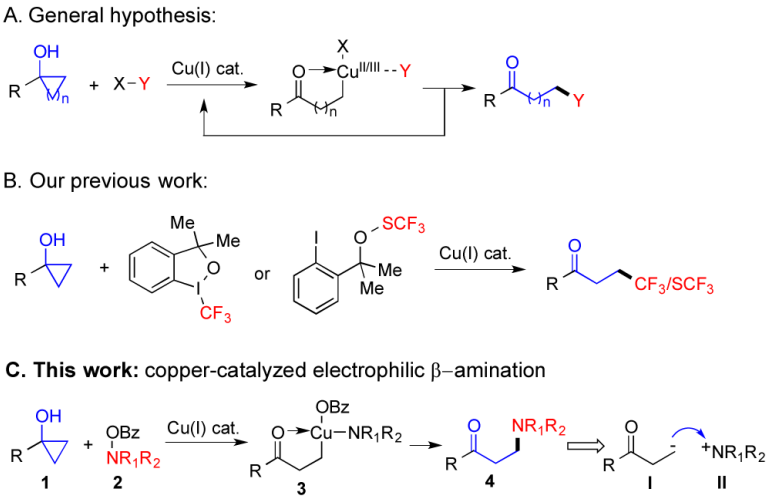

Figure 1.

Our general hypothesis and work of copper-catalyzed ring-opening cross-coupling reactions.

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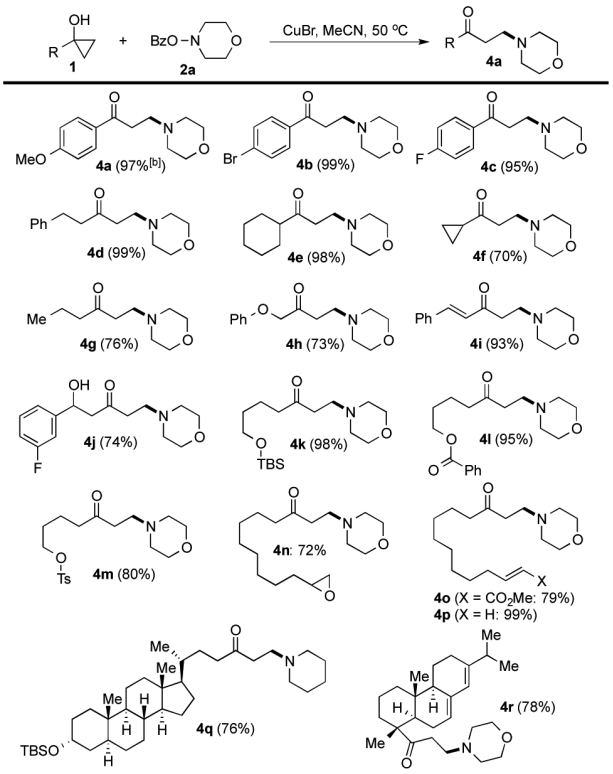

Figure 2.

Cyclopropanol substrate scope.[a]

[a] Yield of isolated products; [b] Gram-scale reaction.

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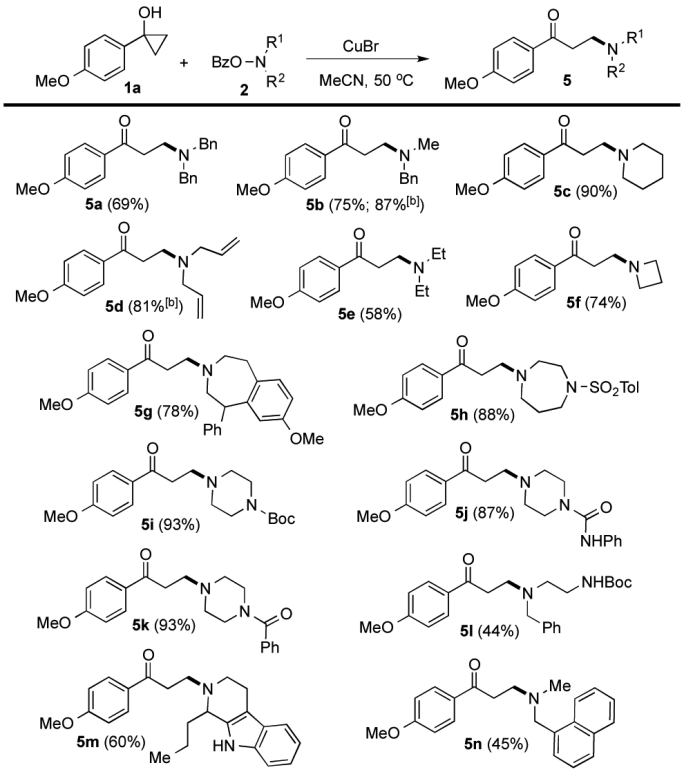

Figure 3.

O-benzoyl-*N*,-*N*-dialkylhydroxylamine scope.[a]

[a] Yield of isolated products; [b] 80 °C.

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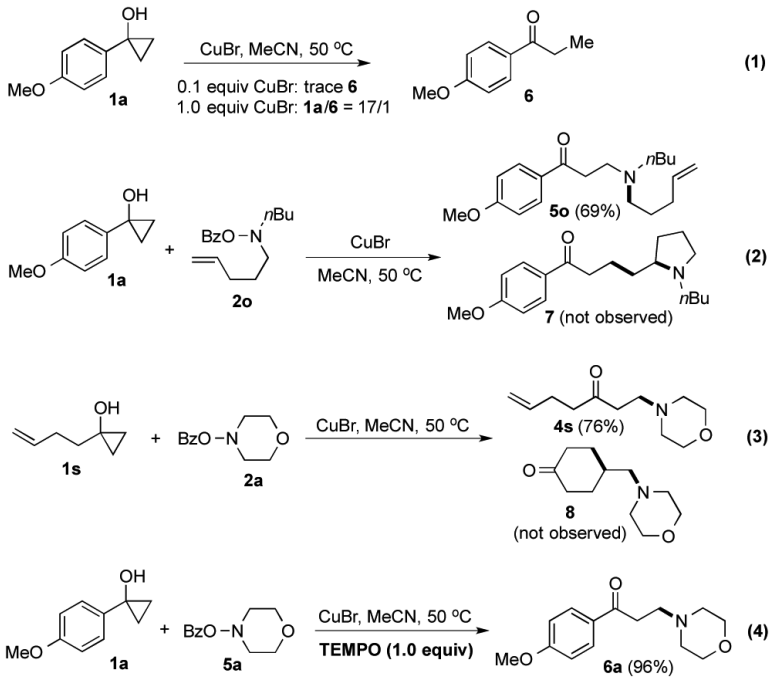

Figure 4.
Preliminary probe of reaction mechanisms.

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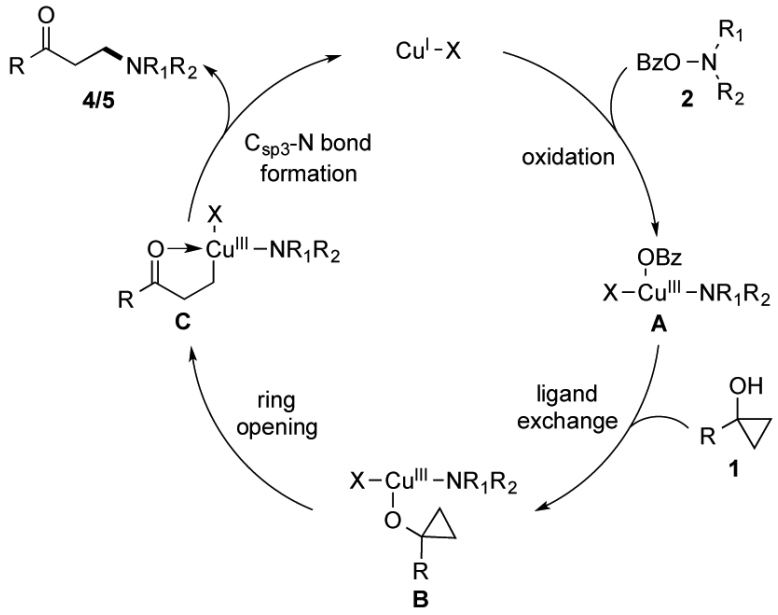

Figure 5.
Proposed catalytic cycle.

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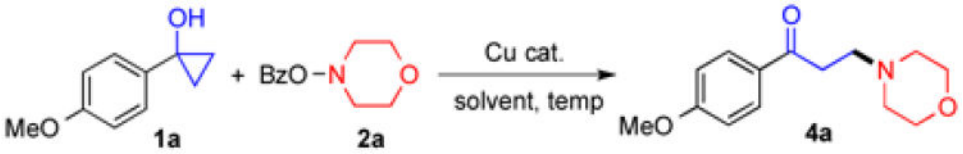
Table 1

Reaction condition optimization.[a]



entry	Cu cat.	solvent	temp (°C)	yield (%)[a]
1	CuI	THF	80	85[b]
2	CuI	THF	80	88
3	CuI	toluene	80	75
4	CuI	DCE	80	65
5	CuI	1,4-dioxane	80	82
6	CuI	MeCN	80	90
7	-	MeCN	80	0
8	CuI	MeCN	rt	39
9	CuI	MeCN	50	93
10	CuCl	MeCN	50	88
11	**CuBr**	**MeCN**	**50**	**98**
12	CuBr	MeCN	50	93[b]
13	CuBr	MeCN	50	80[c]
14	CuBr	MeCN	50	trace[d]

[a] General reaction conditions: A solution of **1a** (0.15 mmol), **2a** (0.1 mmol), and Cu(I) catalyst (0.1 equiv) were stirred until no more starting material left. The reaction process was monitored by thin-layer chromatography. Isolated yield from flash chromatography was given;

[b] 1/1 of **1a**/**2a** (0.1 mmol);

[c] **1a** (0.1 mmol) and **2a** (0.15 mmol);

[d] Phenanthroline (0.1 equiv).