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CuBr-Catalyzed Reaction of *N*,*N*-Dimethylanilines and Silyl Enol Ethers: An Alternative Route to *β*-Arylamino Ketones

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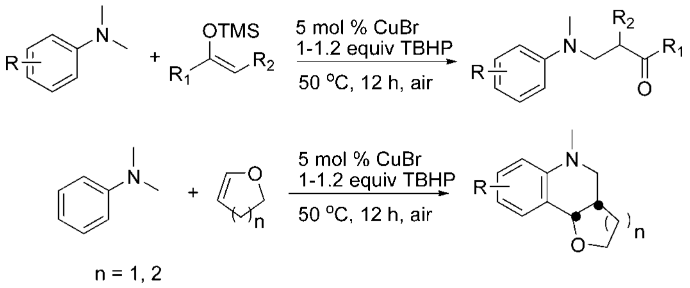
ABSTRACT



A wide range of silyl enol ethers undergo the reactions with *N*,*N*-dimethylanilines in the presence of transition metal catalysts under mild conditions to give *β*-arylamino ketones. In the cases of silyl enol ethers derived from unsymmetrical ketones, regiospecific addition of carbonyl compounds was obtained at the olefinic position of silyl enol ether.

The investigation of new reactions of C−H activation in searching for high efficiencies and high selectivities has aroused a lot of attention in recent years because of economical and environmental importance.[1] In these efforts, transition metal catalysis has featured prominently in the past decades, leading to the establishment of a range of new types of reactions that offer the powerful tools for the synthesis of complex frameworks without utilizing the prefunctionalization of C−X or C−M bonds.[2] Amines are common structural units of natural products, pharmaceuticals, and functional materials. Consequently, the selective C−H bond functionalization of amines has been extensively explored, and some promising catalytic systems for sp^3 C−H bond activation adjacent to the nitrogen atom have been reported.[3] For instance, ruthenium-catalyzed intramolecular olefin-iminium ion cyclization[4] and oxidative cyanation of tertiary amines,[5] ruthenium-catalyzed alkylation of amines from the addition of alkenes,[6] iridium-catalyzed approach of pyrroliz-

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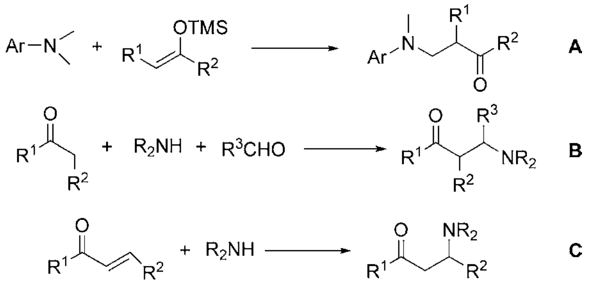
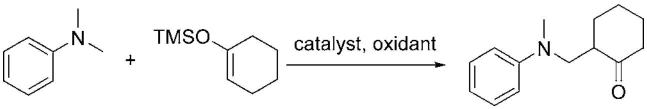
idinones from N-acylated pyrrolidines,[7] and copper-catalyzed reactions of tertiary amines with alkynes, indoles, nitromethane, and malonates[8] have been developed to synthesize α-substitued amines. Very recently, the copper-catalyzed oxidative difluoromethylation of tertiary amines was described.[9] As our ongoing research program toward the development of catalytic systems for the direct functionalization of C−H bonds,[10] we have been interested with employing amines as useful substrates. Herein, we describe our results concerning the unique copper-catalyzed coupling of silyl enol ethers with *N*,*N*-dimethylanilines to give β-arylamino ketones by the cleavage of α-sp^3 C−H bond of nitrogen in the presence of TBHP under mild conditions (Scheme 1, A).

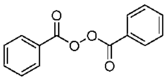
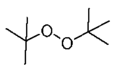
Scheme 1. Strategies for Preparation of β-Amino Ketones



β-Amino ketones are highly valuable molecules considering their numerous applications for building blocks of drugs and biologically active compounds.[11] Traditionally, β-amino ketones are synthesized by the Mannich reaction or the aza-Michael addition reaction (Scheme 1, B and C). Although these methods are widely used in organic synthesis, they often suffer from long reaction time and harsh reaction conditions.[12] In particular, it has been difficult to achieve β-arylamino ketones from Mannich reaction or aza-Michael addition reaction using arylamines because of their reduced nucleophilic reactivity.[13] Recent studies established that the coordination of nitrogen to metal and overlap of the metal obital with the α-C−H bond in amines would induce the formation of iminium ion intermediates.[14] These conclusions led us to the assumption that the nucleophilic attack of silyl enol ethers, which are widely used in organic synthesis as more reactive analogues of ketones, to these iminium ion intermediates may be feasible to give β-arylamino ketones directly, which would be extremely valuable from the synthetic point of view.

Table 1. Effect of Metals, Oxidants, and Solvents on the Reaction[a]



entry	catalyst	oxidant	solvent	yield (%)[b]
1	CuBr	-	CH_3CN	NR
2	-	TBHP	CH_3CN	NR
3	$RuCl_3$	TBHP	CH_3CN	32
4	$Pd(OAc)_2$	TBHP	CH_3CN	11
5	$FeCl_2$	TBHP	CH_3CN	20
6	$FeCl_3$	TBHP	CH_3CN	38
7	CuI	TBHP	CH_3CN	41
8	CuCl	TBHP	CH_3CN	55
9	$CuBr_2$	TBHP	CH_3CN	51
10	$CuCl_2$	TBHP	CH_3CN	48
11	CuBr	TBHP	CH_3CN	58
12	CuBr		CH_3CN	37
13	CuBr		CH_3CN	53
14	CuBr	TBHP	CH_2Cl_2	36
15	CuBr	TBHP	toluene	trace
16	CuBr	TBHP	CH_3CN	70 [c]
17	CuBr	TBHP	CH_3CN	46 [d]

[a] Reaction conditions: *N*,*N*-dimethylbenzenamine (122 mg, 1 mmol), cyclohexenyloxytrimethylsilane (85 mg, 0.5 mmol), catalyst (0.025 mmol), oxidant (1 equiv), TBHP (1−1.2 equiv), 0.10 mL, 5−6 M in decane, CH_3CN (5 mL), 50 °C, 12 h. [b] Isolated yields. [c] 1.5 mmol of *N*,*N*-dimethylbenzenamine was used. [d] 1.2 equiv of 2β-di-*tert*-butyl-4-methylphenol (BHT) was added.

To test our hypothesis, we examined the reaction of cyclohexynyloxytrimethylsilane and *N*,*N*-dimethyl- benzenamine in the presence of metal catalysts under oxidative conditions, and a selection of examples are presented in Table 1. The nature of catalysts, oxidants, and solvents was crucial for the activation of sp^3 C−H bond of dimethylbenzenamine. No reaction was examined in the absence of catalysts or oxidants (entries 1 and 2). The reaction was found to occur in the presence of TBHP with several metals such as $RuCl_3$, $Pd(OAc)_2$, $FeCl_3$, and $FeCl_2$,

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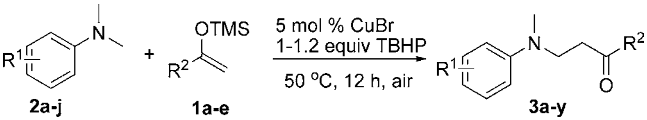
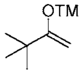
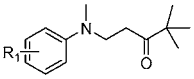
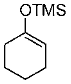
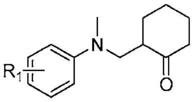
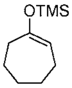
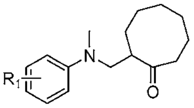
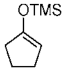
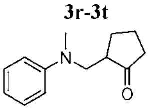
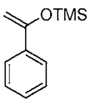
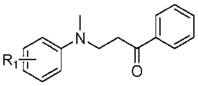
but with low yields (entries 3−6). An improvement was presented by using copper catalysts such as CuI, CuCl, $CuBr_2$, and $CuCl_2$, and the combination of CuBr and TBHP provided the best result (entries 7−11). Other oxidants including benzoic peroxyanhydride and 2-(*tert*-butylperoxyl)-2-methyl- propane were less efficient (entries 12 and 13). A study of the reaction in various solvents identified acetonitrile as suitable alternatives to CH_2Cl_2 and toluene (entries 14 and 15). The use of excess anilines could be beneficial and provided improved yield (entry 16). Cyclohexanone was inactive under the reaction conditions, showing that silyl enol ethers are better nucleophiles than corresponding carbonyl derivatives. Notably, the reaction was completely chemoselective and no traces of product resulting from second coupling were detected.

The generality of this transformation was examined under the optimized reaction conditions, and the results are summarized in Table 2. A broad range of *N*,*N*-dimethylanilines could be coupled with silyl enol ethers. *N*,*N*-Dimethylanilines bearing both electron-donating and electron-withdrawing substituents on the aryl ring could be successfully used in the direct reaction with silyl enol ethers to synthesis the desired β-arylamino ketones (Table 2, entries 1−8). However, the substituent at ortho-position drastically slowed the reaction (Table 2, entry 12). Very poor reactivity of other hindered tertiary amines and anilines such as *N*-phenyl-1,2,3,4-tetrahydroisoquinoline and *N*,*N*-diethylbenzenamine was also observed, indicating that the steric hindance successively decreased the reactivity. Both acyclic and cyclic silyl enol ethers, which were easily prepared through a stirring of ketones with CH_3SiCl in the presence of Et_3N and NaI in CH_3CN at room temperature,[15] were found to serve as good substrates (Table 2, entries 1−25). In the case of cyclic silyl enol ethers, the size of cycle has an significant effect on the efficiency of the reaction. Cyclohexenyloxytrimethylsilane and cycloheptenyloxytrimethylsilane were active substrates and gave the desired β-amino ketones efficiently (Table 2, entries 9−20). Cyclopentenyloxytrimethylsilane, however, was found to be less active to afford lower yields (Table 2, entry 21). The aryl silyl enol ether were also applicable to the present reaction to give the corresponding β-arylamino ketones smoothly (Table 2, entries 22−25).

Table 2. Reaction of *N*,*N*-Dimethylanilines with Silyl Enol Ethers[a]



2a-j **1a-e** **3a-y**

entry	silyl enol ether	R^1	product	yield %[b]
1	 **1a**	H (**2a**)	 **3a-3h**	75
2		4-Me (**2b**)		86
3		3-Me (**2c**)		60
4		4-Et (**2d**)		82
5		4-t-Bu (**2e**)		85
6		4-Br (**2f**)		64
7		4-Cl (**2g**)		75
8		3-Cl (**2h**)		60
9	 **1b**	H (**2a**)	 **3i-3q**	70
10		4-Me (**2b**)		58
11		3-Me (**2c**)		58
12		2-Me (**2i**)		trace
13		4-Et (**2d**)		50
14		4-t-Bu (**2e**)		67
15		4-Br (**2f**)		58
16		4-Cl (**2g**)		60
17		3-Cl (**2h**)		60
18	 **1c**	H (**2a**)	 **3r-3t**	79
19		4-Me (**2b**)		66[c]
20		4-Br (**2f**)		64
21	 **1d**	H (**2a**)	 **3u**	21
22	 **1e**	H (**2a**)	 **3v-3y**	67
23		4-Me (**2b**)		65
24		4-Br (**2f**)		63
25		4-OMe (**2j**)		68

[a] Reaction conditions: *N*,*N*-dimethylanilines (1.5 mmol), CuBr (4 mg, 0.025 mmol), silyl enol ethers (0.5 mmol), TBHP (1−1.2 equiv), 0.10 mL, 5−6 M in decane, CH_3CN (5 mL), 50 °C, 12 h. [b] Isolated yields. [c] 1 mmol of *N*,*N*-dimethylbenzenamine was used.

We extended the reaction to unsymmetrical silyl enol ethers. It is known that the regioselectivity of ketones in Mannich reaction is difficult to control to any significant extent. With the aid of strong lithium base (LDA),[16] we prepared the less substituent kinetically favored silyl enol ether **1f** from 2-methylcyclohexanone. In addition, under the conventional equilibrium conditions, we obtained the more stable silyl enol ether **1g** via the removing of C-2 proton in 2-methylcyclohexanone. Notably, during the course of this transformation the reaction of *N*,*N*-dimethylbenzenamine took place regioselectively at the olefinic position of the silyl enol ethers, and the regiochemical feature was retained. As we expected, the reactivity of silyl enol ether **1g** was slightly decreased due to the steric hindrance (Scheme 2). This reaction provided an alternative method for regioselective synthesis of β-arylamino ketones.

Encouraged by the successful reaction between silyl enol ethers and *N*,*N*-dimethylanilines, we next attempted the reaction of enol ethers with *N*,*N*-dimethylanilines. Significantly, *N*,*N*-dimethylbenzenamine was directly converted to

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[14] (a) Murahashi, S.-I.; Takaya, H. *Acc. Chem. Res.* **2000**, *33*, 225. (b) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069.

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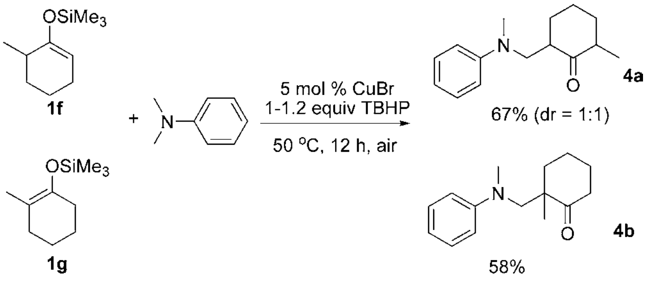
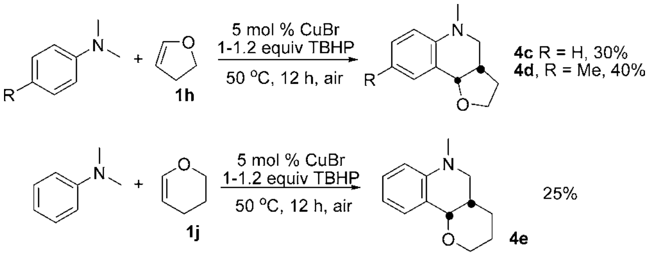
Scheme 2. Regioselective Synthesis of β-Arylamino Ketones

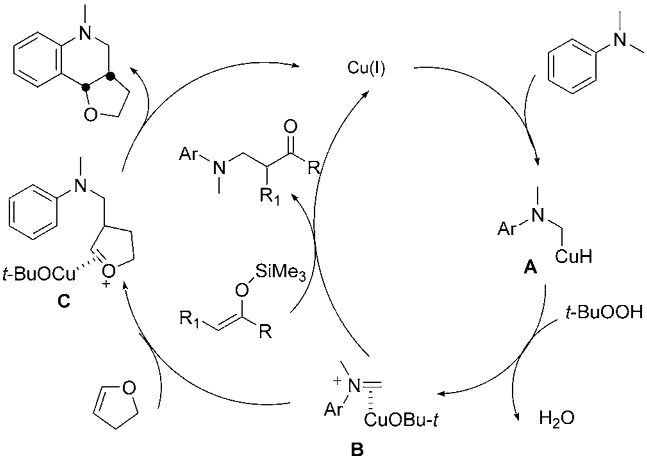


Scheme 3. Synthesis of Quinoline Derivatives



the derivatives of quinonlines via the intramolecular annulation in a single step (Scheme 3), although the efficiency of the reaction required further improvement. Thus, cyclic enol ether such as 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran underwent the annulation process to provide the fused heterocycles with *cis*-stereoisomers. The reaction demonstrates the potential power for the construction of a C−C bond in which the sp^3 C−H activation occurs with concomitant ring closure under catalytic mild conditions.

Scheme 4. Plausible Mechanism



Based on the mechanistic findings of previous studies,[5] a plausible scenario that could account for the formation of these compounds is illustrated in Scheme 4. The oxidative addition of copper to the α-C−H bond of amine to give the α-metalated intermediate **A**, which generates the η^2-iminium metal complex **B**.[14] The nucleophilic attack of silyl enol ether on iminium ion complex **B** affords the corresponding β-amino ketones and librates the copper catalyst. In the case of enol ethers, the nucleophilic attack of enol ether on the iminium ion intermediate **B** results in the intermediate **C**, which undergoes electrophilic addition to the phenyl ring to give the annulated products. Another possible pathway is that the free radicals generated by TBHP with the acceleration of transition metals result in the formation of intermediate **B**,[17] which undergoes the addition reaction to give the products. We performed the reaction in the presence of 1.2 equiv of free-radical scavenger 2β-di-*tert*-butyl-4-methylphenol (BHT) and found that the yield was decreased to 46% (Table 1, entry 17). This result illustrates that a radical pathway is not able to be fully excluded. Further research is required for the elucidation of the detailed mechanism.

In summary, we have demonstrated the application of sp^3 C−H bond activation for various *N*,*N*-dimethylanilines in the synthesis of β-arylamino ketones under mild conditions. The method is compatible with a wide range of silyl enol ethers/enol ethers and the regiospecific additions typically take place at the olefinic position of silyl enol ethers.

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Supporting Information Available: Experimental procedure and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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