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Letter

Cobalt(II)-Catalyzed Oxidative Coupling of Aromatic Tertiary Amines with Enol Silyl Ethers Leading to β-Aminoketone Derivatives

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Abstract We demonstrated that a cobalt(II)-TBHP (*tert*-butyl hydroperoxide) oxidizing system efficiently catalyzes the coupling of aromatic tertiary amines with enol silyl ethers, producing the corresponding β -aminoketones.

Key words cobalt, oxidation, aromatic tertiary amine, enol silyl ether, β -aminoketone

β-Aminoketone derivatives have occupied one of the central positions of nitrogen-containing valuable compounds, because their structure is commonly found in the central structure of natural products, biologically active substances, and functional materials.¹ Thus far, conventional approaches to the production of β -aminoketones have generally amounted to either a Mannich-type reaction involving amines, aldehydes, and enolizable carbonyl compounds,^{1a,2} or the aza-Michael-type reaction using α , β -unsaturated carbonyl compounds and amines or their analogues.³ On the other hand, over the past two decades, the direct introduction of a variety of functional groups at $C(sp^3)$ -H that is adjacent to a nitrogen atom on the amine has been demonstrated through the transition-metal-catalyzed oxidative coupling of tertiary amines with nucleophiles in the presence of an appropriate organic oxidizing agent and molecular oxygen.⁴ With this procedure in hand, several groups have achieved the one-pot preparation of βaminoketone derivatives through the association of tertiary amines and a representative carbon nucleophile, an enol silyl ether.⁵ However, most of the reported methods have been limited to an oxidizing catalytic system using either a copper(I) or a copper(II) catalyst. The only reported examples other than a copper catalyst have involved either a visible-light photoredox system using Ru(bpy)Cl₂ or NaSbCl₆ in



the presence of N-hydroxyphthalimide (NHPI), which catalyzed a similar oxidative coupling of tertiary amines with enol silvl ethers leading to β -aminoketones.^{6,7} Therefore, we believe that there is ample room to further explore this type of oxidative coupling using other metal catalysts and oxidants. Among transition metals, it has been recently reported that a variety of cobalt complexes contain a high potential to induce useful molecular conversions, such as a C-H functionalization,^{8a} hydrosilylation,^{8b} hydroformylation,^{8c} and an enantioselective transformation,^{8d} as well as a classical Pauson-Khand reaction.^{8e} In this context, we reported a cobalt(II)–TBHP oxidizing system whereby α -cyanation of aromatic tertiary amines leads to β-aminonitriles,⁹ and as a further extension, attempted to apply this simple cobaltoxidizing system to the direct preparation of β-aminoketones using aromatic tertiary amines and enol silyl ethers.¹⁰ In this letter, we report the preliminary results.

On the basis of our previous work, when the coupling of *N*,*N*-dimethylaniline with an enol silvl ether (2 equiv per the amine), which was derived from acetophenone, was examined using a catalytic amount of CoCl₂ (5 mol% per the aniline) and TBHP (1.5 equiv per the aniline) in methanol at 60 °C for two hours under an ambient atmosphere, the expected oxidative coupling proceeded smoothly to produce β -aminoketone **1** in a 62% yield (Table 1, entry 1).¹¹ When a similar reaction with two equivalents of dimethylaniline for the nucleophile was then examined, the yield of 1was slightly increased (Table 1, entry 2). The coupling was then examined under conditions involving a cobalt catalyst (5 mol% per the enol silvl ether) and an oxidant (1.5 equiv per the enol silvl ether). Attempts were made using several oxidants, most of which led to a decrease in the product yield (Table 1, entries 3-6). Molecular oxygen was also ineffective for the oxidative coupling (Table 1, entry 7). Gratifyingly, the use of CoBr₂, instead of CoCl₂, slightly improved the product yield (Table 1, entry 8). Moreover, the coupling

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with $CoBr_2$ could be extended to an acetonitrile solution (Table 1, entry 10). When the reaction was conducted at 40 °C, the oxidative coupling proceeded without a drastic loss of β -aminoketone **1** (Table 1, entry 11).

Table 1	Examination of the Reaction Conditions ^a
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Entry	[Co]	Oxidant	Solvent	Temp (°C)	NMR yield (%)
1 ^b	CoCl ₂	TBHP	MeOH	60	62
2	CoCl ₂	TBHP	MeOH	60	73
3	CoCl ₂	DTBP ^c	MeOH	60	trace
4	$CoCl_2$	MCPBA ^d	MeOH	60	4
5	$CoCl_2$	$H_2O_2^e$	MeOH	60	38
6	$CoCl_2$	DDQ ^f	MeOH	60	n.r.
7	$CoCl_2$	O ₂	MeOH	60	18
8	CoBr ₂	TBHP	MeOH	60	79 (75) ^g
9	CoBr ₂	TBHP	MeOH	40	58
10	CoBr ₂	TBHP	MeCN	60	79
11	CoBr ₂	TBHP	MeCN	40	75

^a Standard conditions: amine (1 mmol), enol silyl ether (0.5 mmol), [Co]

(0.025 mmol), TBHP (0.75 mmol), solvent (0.5 mL).

^b The molar ratio: aromatic amine/enol silyl ether = 1:2.

^c Di*-tert*-butyl peroxide. ^d *m*-Chloroperoxybenzoic acid.

^e 30% Aqueous solution.

^f 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone.

⁹ Isolated yield.

Then, the oxidative catalytic system was applied to aromatic tertiary amines possessing several functional groups (Scheme 1). When substrates had an electron-donating group, such as a methyl group, on the aromatic ring, the oxidative coupling proceeded smoothly to produce the expected β -aminoketones **2–4** in relatively good yields, regardless of the location of the methyl group. Also, the amines with a methoxy group yielded aminoketone 5 in a practical yield. In contrast, the substrates with an electronwithdrawing group, such as bromo and nitro groups, managed to undertake the coupling to produce the corresponding β -aminoketones **6** and **7** in rather low yields. On the other hand, for N-phenyltetrahydroisoquinoline, the expected aminoketone 8 was obtained in a good yield, in which the carbon nucleophile was introduced at the benzyl position next to a nitrogen atom. In contrast, a trialkylamine-type substrate, N-methyltetrahydroisoquinoline hardly undertook the coupling. These results strongly implied that a phenyl group requires stabilizing the reaction intermediate. Unfortunately, the oxidative introduction of a phenacyl group onto the substrates with an N,N-diethylamino group and a cyclic amino moiety, such as piperidine, did not occur.



Scheme 1 Substrate scope of tertiary aromatic amines. *Reagents and conditions*: aromatic amine (1 mmol), enol silyl ether (0.5 mmol), CoBr₂ (0.025 mmol), TBHP (0.75 mmol), MeCN (0.5 mL).

The substrate effect of several enol silyl ethers was then investigated using the optimal conditions (Scheme 2). Any sort of substituent next to the carbonyl moiety, such as a 4-MeC₆H₄ group, a *tert*-butyl group, or a methyl group, did not show the direct effect on the yield in production of the corresponding β -aminoketone derivatives **12–14** in 50–60% yields. Also, in the case with an α -methyl-substituted enol silyl ether, although a decrease in the product yield was ob-





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served, the desired coupling proceeded to give β -aminoketone **15**. Moreover, the couplings with six- or seven-membered cyclic enol silyl ethers yielded β -aminoketones **16** and **17** in satisfactory yields.

In contrast, two ketene silyl acetals with either a branched reaction site or an unsubstituted reaction moiety led to a drastic decrease in the product yields (Scheme 3). However, there was no reasonable reason for these results. The low yield from the use of the ketene silyl acetal was in agreement with a similar coupling using $CuCl_2 \cdot 2H_2O$ under an O_2 atmosphere.^{5b}



Then, to show the utility of the present oxidative coupling, a direct coupling using acetophenone was attempted (Scheme 4). For example, when the mixture of *N*,*N*-dimethylaniline and acetophenone (2 equiv per *N*,*N*-dimethylaniline) was treated with the Co(II)–TBHP oxidizing system in the presence of L-proline (1 equiv) as an additive, the expected oxidative coupling proceeded, but afforded **1** in only an 8% yield.^{12,13} In addition, when a similar reaction was conducted in the presence of Me₃SiOTf and Hünig's base (*i*-Pr₂NEt) in an effort to realize the in situ formation of the corresponding enol silyl ether, β -aminoketone **1** was obtained in a 16% yield.



To better understand the reaction pathway for the series of preparations of β -aminoketones, a control experiment was conducted (Scheme 5). When the coupling was carried out in the presence of a radical scavenger, 2,6-di(*tert*butyl)-*p*-cresol (BHT) and 2,2,6,6-tetramethylpiperidin-1yl)oxyl (TEMPO), the formation of **1** was half restrained. This result suggested that a coupling with the cobalt–TBHP system would mainly proceed through a single-electron transfer (SET) rather than an ionic path.



Scheme 5 Control experiment with a radical inhibitor

Scheme 6 shows the plausible reaction path for the Co(II)–TBHP oxidative coupling of a tertiary aromatic amine with an enol silvl ether. On the basis of the report by Dovle et al.,¹⁴ we assume that the oxidation coupling series would proceed via two key steps involving (i) the generation of the *tert*-butylperoxy radical derived from a cobalt(II) catalyst and TBHP and (ii) the formation of an iminium intermediate via the oxidation of an aromatic amine with an in situ generated *tert*-butylperoxy radical. An aromatic amine would be oxidized with a *tert*-butylperoxy radical through both single-electron transfer (SET) and proton transfer (PT) to produce the corresponding iminium intermediate. Then, the iminium intermediate would be coupled with the enol silvl ether, which would lead to the production of a β -aminoketone derivative. The oxidized cobalt(III) species would be reduced again with the formed *t*-BuOOH to regenerate a cobalt(II) complex.



 $\label{eq:scheme f} \begin{array}{l} \mbox{Scheme 6} & \mbox{Plausible reaction path for oxidative coupling using the} \\ \mbox{CoBr}_2\mbox{-TBHP system} \end{array}$

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588097.

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- (11) General Procedure for a Cobalt-Catalyzed Oxidative Coupling of Aromatic Tertiary Amines with Enol Silyl Ethers To a screw-capped test tube (5 mL) under ambient atmosphere containing freshly distilled MeCN (0.5 mL) were successively added 0.5 M MeCN solution of CoBr₂ (50 µL, 0.025 mmol), aniline (1.0 mmol), enol silyl ether (0.50 mmol), and 5.5 M tertbutyl hydroperoxide in decane (136 µL, 0.750 mmol). After the tube was sealed with a cap that contained a PTFE septum, the mixture was heated at 40 °C (bath temperature) and monitored by GC and TLC analysis. The reaction was quenched with a Na_2CO_3 aq solution (5 mL). The aqueous layer was extracted with CHCl₃, the organic phases were dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure. The crude product was purified by silica chromatography (hexane-EtOAc = 4:1) to give the corresponding β -aminoketone. (3-Methylphenylamino)-1-phenyl-1propanone (1)

White solid; 75% (90 mg). ¹H NMR (300 MHz, CDCl₃): $\delta = 8.00-8.02$ (m, 2 H), 7.64–7.51 (m, 3 H), 7.37–7.31 (m, 2 H), 6.85–6.79 (m, 3 H), 3.95–3.90 (t, *J* = 6.9 Hz, 2 H), 3.34–3.30 (t, *J* = 6.9 Hz, 2 H), 3.01 (s, 3 H). ¹³C NMR (75 MHz, CDCl₃): $\delta = 199.4$, 148.5, 136.8, 133.1, 129.3, 128.6, 128.0, 116.5, 112.3, 47.9, 38.5, 35.1. MS (EI): *m/z* (%) = 239 (100) [M⁺].

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