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Cobalt-catalyzed oxidative annulation of aromatic tertiary amines with electron-deficient maleimides leading to tetrahydroquinoline derivatives

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ABSTRACT

Described herein is a $CoCl_2$–TBHP (*t*-butyl hydroperoxide) system that efficiently catalyzes the oxidative annulation of aromatic tertiary amines with a typical electron-deficient alkene, *N*-substituted maleimides, producing the corresponding polycyclic tetrahydroquinoline derivatives. This oxidizing system could also be applied to the annulation of an electron-rich alkene.

Introduction

The oxidative activation of a C(sp^3)–H bond on an aromatic tertiary amine combined with a subsequent annulation using electron-rich alkenes has become a useful and direct tool to construct polycyclic nitrogen-containing heterocycles, such as tetrahydroquinoline,[1] the skeletons of which are widely found in natural products and in biologically active substances.[2] Initial examples were reported by Murahashi et al. who found that a rhodium(II)-TBHP system could efficiently catalyze the oxidative intramolecular cyclization of an aromatic tertiary amine tethered with an alkene moiety, producing a hydroisoquinoline framework.[3] Also, Miura and co-workers demonstrated an iron-catalyzed oxidative coupling of *N*,*N*-dimethylanilines with vinyl ethers under an O_2 atmosphere leading to tetrahydroquinoline derivatives.[4] In the last decade, several groups reported that an association of many sorts of copper catalysts with TBHP effectively promoted an oxidative annulation of aromatic amines with unsaturated compounds to achieve a one-pot preparation of the complicated nitrogen-containing heterocycles.[5] However, due to the electron deficient nature of the intermediates, such as a cation or a radical species, generated in an oxidative annulation involving the above examples,[6] most alkenes employed as a coupling partner are limited either to electron-rich alkenes, such as a vinyl ether[5a,b] and an enamine (an enamide),[7] or to unactivated alkenes, such as styrene.[8] Hence, the metal-catalyzed oxidative annulation of an aromatic amine with an electron-deficient alkene has not been studied extensively, and a metal catalytic system that could solve this problem remains unexplored.[9,10] In 2011, Miura et al. described the copper-catalyzed annulation of *N*-methylanilines with electron-deficient alkenes, such as *N*-substituted maleimides, under an ambient atmosphere that led to tetrahydroquinolines.[6,11] In this context, we reported that cobalt(II) chloride efficiently catalyzed the α-cyanation of aromatic tertiary amines in the presence of TBHP leading to β-aminonitriles.[12] On the basis of the results described above, we expected that a Co(II)-TBHP oxidizing system could be applied to the annulation of aromatic tertiary amines with electron-deficient alkenes.[13] In this letter, we report the preliminary results.

Results and discussion

Initially, an examination of the reaction conditions of oxidative annulation was performed (Table 1). On the basis of our previous work,[12] a model coupling of *N*,*N*-dimethyl-*p*-toluidine with *N*-phenylmaleimide was performed using 10 mol% of $CoCl_2$ and *t*-butyl hydroperoxide (TBHP) as an oxidizing agent at 60 °C for 5 h in CH_3OH under an N_2 atmosphere.[14] Consequently, the expected annulation managed to proceed, producing tricyclic pyrrolo[3,4-

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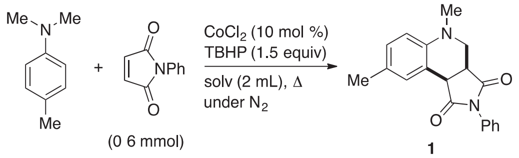
0040-4039/

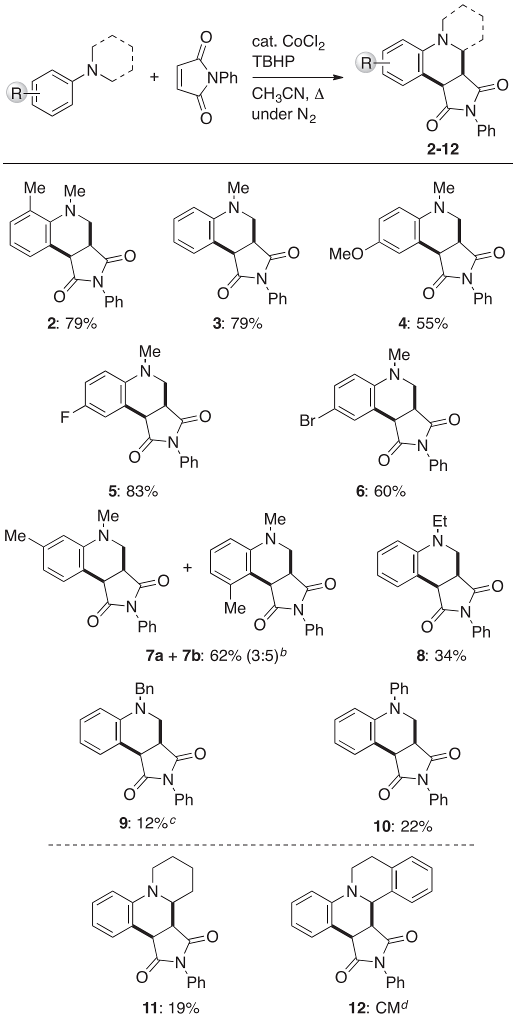
Table 1
Examinations of the reaction conditions[a]



Entry	CoX_2	Amine (equiv)	Solv	Yield (%)[b]
1	$CoCl_2$	1.0	CH_3OH	37
2	$CoCl_2$	1.0	$PhCH_3$	30
3	$CoCl_2$	1.0	1,2-DCE[c]	43
4	$CoCl_2$	1.0	CH_3CN	44
5	$CoBr_2$	1.0	CH_3CN	42
6	CoI_2	1.0	CH_3CN	13
7	$CoCl_2$	1.5	CH_3CN	87
8	$CoCl_2$	2.0	CH_3CN	94 (90)[d]
9	—[e]	2.0	CH_3CN	5
10[f]	$CoCl_2$	2.0	CH_3CN	83

[a] Standard conditions: *N*,*N*-dimethyl-*p*-toluidine (1.2 mmol), *N*-phenylmaleimide (0.6 mmol), solvent (2 mL), 60 °C, 5 h.
[b] NMR yield.
[c] 1,2-Dichloroethane.
[d] Isolated yield.
[e] Without $CoCl_2$.
[f] O_2 atmosphere.

Table 2
Scope of tertiary aromatic amines[a]



[a] Standard conditions: a tertiary amine (2 mmol), *N*-phenylmaleimide (1 mmol), $CoCl_2$ (0.1 mmol), TBHP (1.5 mmol), CH_3CN (3 mL), 60 °C, 5 h. [b] Determined by ^1H NMR. [c] 0.6 mmol scale. [d] A complicated mixture.

c]quinoline derivative **1** in a 37% yield (entry 1). The structure of tricyclic **1** was determined using the obtained spectral data, and was compared with the spectra of a relatively known compound. As a solvent effect, toluene was ineffective, but the use of 1,2-dichloroethane (1,2-DCE) and acetonitrile resulted in a slight increase in the chemical yield (entries 2–4). Acetonitrile was then used as the optimal solvent. When two types of cobalt catalysts, in addition to $CoCl_2$, were then examined, $CoBr_2$ effectively undertook the desired oxidative annulation (entries 5 and 6). But, there is no clear reason for the decrease in the product yield, when using CoI_2. From the viewpoint of economical cost, $CoCl_2$ was chosen as the optimal catalyst. Interestingly, when an equivalent of *N*,*N*-dimethyl-*p*-toluidine was increased to 2.0 equiv, the yield of **1** was finally improved to 94% (entries 7 and 8), and **1** was finally isolated at a maximum yield of 90% after a common work-up. In these cases, no by-products were observed. The case without the cobalt catalyst hardly undertook the corresponding annulation, which proved the utility of the cobalt catalyst (entry 9). Also, when the reaction was conducted under an O_2 atmosphere, the product yield was slightly decreased (entry 10).

With the optimal conditions, the scope and limitations of the Co(II)-catalyzed annulation using several aromatic tertiary amines were examined (Table 2). The substrates with either an *o*-methyl group or no substituent group on the benzene ring gave the corresponding tricyclic tetrahydroquinoline derivatives **2** and **3** in relatively good yields. In the case involving a methoxy group, the product yield of **4** was slightly decreased to the moderate level. The substrates with typical electron-withdrawing groups, such as fluoro and bromo groups, yielded annulated products **5** and **6** in satisfactory yields. Also, when the reaction was conducted with *m*-methyl-substituted *N*,*N*-dimethylaniline, a mixture of tetrahydroquinoline derivatives **7a** and **7b** was obtained in a relatively good yield. Product **7b** having a methyl group at the *ortho*-position was preferentially formed. This tendency is in agreement with the results on the basis of the stabilization of hyperconjugation.[6,15] On the other hand, when the oxidative coupling was conducted with unsymmetrical *N*-alkylated or *N*-arylated, such as an ethyl, a benzyl, or a phenyl group, *N*-methylanilines under the optimal conditions, the expected annulation selectively proceeded at the methyl group side, giving tetrahydroquinoline derivatives **8**, **9**, and **10**. This was probably due to an avoidance of a steric hindrance. However, all cases yielded the tricyclic adducts in rather low yields. Moreover, the substrate with a cyclic amino group as a piperidine ring led to a substantial decrease in the product yield, producing **11** in a 19% yield. Thus, *N*-phenyl-1,2,3,4-tetrehydroisoquinoline was employed in the hope of stabilizing the reaction intermediate with the adjacent benzene ring. Although smooth consumption of the starting amine was observed, the desired annulation did not occur to produce **12**, which finally led to a complicated mixture.

The scope and limitations of maleimide derivatives were then investigated using the optimal conditions (Table 3). For example, when the annulation was carried out with *N*-arylated maleimides with either a *p*-Me-C_6H_4 or a *p*-Cl-C_6H_4 group, the corresponding tetrahydroquinoline derivatives **13** and **14** were obtained in good yields, which led to the fact that the electronic effects of the substituents on the benzene ring had a little effect on the product yield. Also, the use of *N*-alkylated maleimides with either a benzyl or a *t*-butyl group produced annulated products **15** and **16** in satisfactory yields. Unfortunately, other electron-deficient alkenes, such as maleic anhydride, an acrylate ester, and acrylonitrile, were not applicable to the present annulation.