DOI: 10.1002/adsc.201200999

Antimony/*N*-Hydroxyphthalimide as a Catalyst System for Cross-Dehydrogenative Coupling Reactions under Aerobic Conditions

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Received: November 13, 2012; Revised: January 14, 2013; Published online: February 1, 2013

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200999.

Abstract: In the course of our investigations to find a novel catalyst for the cross-dehydrogenative coupling (CDC) reaction, it was discovered that antimony(V) serves as a co-catalyst with *N*-hydroxyphthalimide (NHPI) under aerobic conditions. This is a rare example of a catalytic use of antimony for an oxidative coupling reaction.

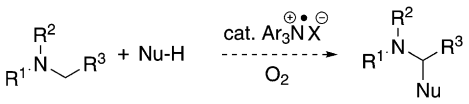
Keywords: aerobic oxidation; antimony; CDC; cross-dehydrogenative coupling; *N*-hydroxyphthalimide (NHPI)

Catalytic carbon-carbon bond forming reactions are among the most valuable processes in synthetic organic chemistry, since they can constitute key steps in the syntheses of complex molecules. Among these reactions, cross-dehydrogenative coupling (CDC) reactions of amines have emerged as an attractive means of forming carbon-carbon bonds,[1] because nitrogen-containing compounds are ubiquitous in natural products and pharmaceuticals, and their direct transformations into more complex compounds would be synthetically useful.

After the pioneering work by Murahashi,[2] who reported the ruthenium-catalyzed CDC reactions in 2003, and the subsequent development by Li using copper catalysts,[3] the CDC has emerged as the reaction of choice to examine new catalyst systems for oxidative coupling reactions. Despite a large number of transition metal-catalyzed (V,[4] Mo,[5] Fe,[6] Ru,[7] Ir,[8]) CDC reactions reported to date, examples of metal-free systems are still rare.[9]

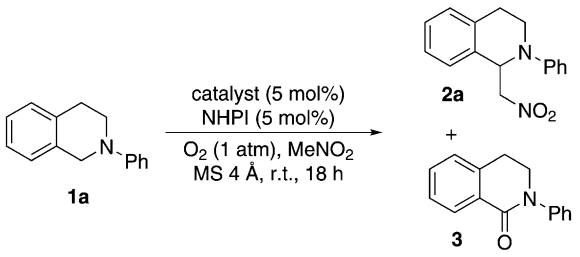
Thus, we planned to explore the use of redox-active organocatalysts to facilitate the aerobic oxidative coupling reaction of amines with pronucleophiles. In the course of our investigations into the use of aminium radical cations as catalysts for the aerobic CDC reaction, we found an interesting phenomenon in which the Sb(V) counteranion can act as a catalyst for the oxidative coupling reaction.

Although aminium radicals are known to serve as stoichiometric single electron oxidants,[10] there are only a few examples in which catalytic use of the aminium radical cation were reported for an aerobic oxidation reaction.[11] Initially, we examined the commercially available tris(*p*-bromophenyl)aminium hexachloroantimonate as a catalyst for the CDC reaction (Scheme 1). Even though antimony is classified as a semi-metal in the periodic table, we expected that the replacement of the counteranion would be possible at a latter stage of our optimization process. When *N*-phenyltetrahydroisoquinoline (**1a**) was reacted with nitromethane in the presence of tris(*p*-bromophenyl)aminium hexachloroantimonate (5 mol%), and MS 4 Å[12] under oxygen atmosphere at room temperature, the desired product was obtained in a low yield (Table 1, entry 1). We hypothesized that the problem in its catalytic use for oxidation reactions is due to the difficulty in the hydrogen radical abstraction process. Therefore, we speculated that the addition of *N*-hydroxyphthalimide (NHPI) as an N–O radical source for the hydrogen abstraction would facilitate the aerobic oxidation.[13,14] Gratifyingly, when we added NHPI (5 mol%), the cross-coupling product was obtained in a good yield, accompanied with the formation of a small amount of amide **3** (entry 2). To determine the best aminium radical catalyst, several aminium radical salts were examined. Although hexafluoroantimonate salt was an active catalyst (entry 3), surprisingly, the catalytic activity of tetrafluoroborate and hexafluorophosphate salts was very poor (entries 4 and 5). Thus, we hypothesized that the counteranion must play an important role in the catalytic



Scheme 1. Aminium radical-catalyzed CDC reaction.

Table 1. Screening of the catalysts.[a]



Entry	Catalyst[b]	Yield [%][c]	
		2a	**3**
1[d]	Ar_3NSbCl_6	29	24
2	Ar_3NSbCl_6	64	6
3	Ar_3NSbF_6	41	<5
4	Ar_3NBF_4	6	<5
5	Ar_3NPF_6	11	<5
6	Et_4NSbCl_6	51	<5
7	Ph_3CSbCl_6	41	<5
8	$NaSbCl_6$(α-$NaphNO_2$)	>95	<5
9	$SbCl_5$	53	6
10	–	3	<5
11[d]	$NaSbCl_6$(α-$NaphNO_2$)	22	<5

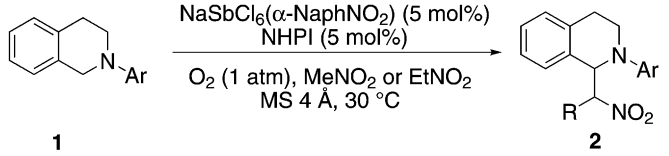
[a] *Reaction conditions:* amine **1a** (0.25 mmol), catalyst (5 mol%), NHPI (5 mol%), MS 4 A (50 mg) in $MeNO_2$ (0.5 mL) under O_2 (1 atm) at room temperature for 18 h.
[b] Ar = *p*-Br-C_6H_4.
[c] Yield based on **1a** and determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.
[d] In the absence of NHPI.

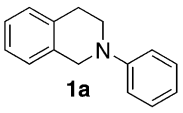
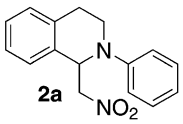
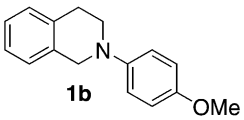
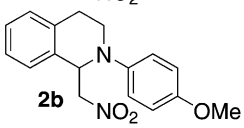
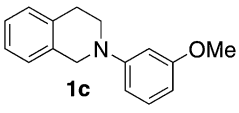
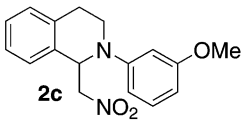
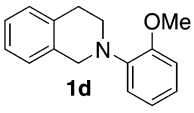
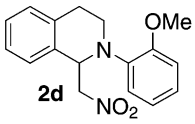
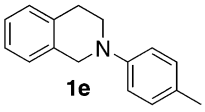
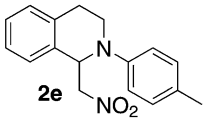
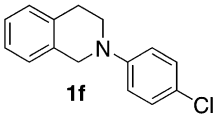
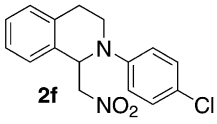
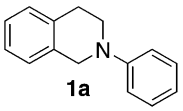
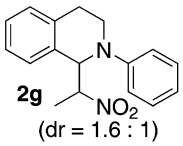
cycle. When we tested this hypothesis by replacing the countercation of the catalyst from the aminium radical to tetraethylammonium or trityl cation, moderate yields were obtained (entry 6 and 7). Thus, it was most likely that the real active catalyst was not the aminium radical cation, but the antimonate counteranion.

Antimony oxide has been previously reported as a catalyst for oxidation reactions, such as dehydrogenation or selective oxidation of alkanes.[15,16] However, in most cases, antimony served as an additive for other transition metal catalysts (V, Mo, Fe, etc.) and very high temperatures were required for these reactions.[17] Although antimony is not strictly a nonmetal, we decided to investigate this catalyst further, since the catalytic use of antimony for the CDC reactions of tertiary amines has not been reported.[18] In addition, the investigation of $SbCl_6^-$ anion as an oxidation catalyst would dispel the notion of these species as just innocent non-coordinating counteranions. After screening various antimonate salts, we found that the α-nitronaphthalene-ligated sodium hexachloroantimonate was the most active catalyst (entry 8).[19] Although it would be desirable to employ commercially available antimony pentachloride as a catalyst, its activity was only moderate (entry 9). Finally, we confirmed that both the sodium antimonate catalyst and NHPI work in a synergistic manner to facilitate the oxidative transformation. (entries 10 and 11).

Next, we examined the substrate generality of this oxidative coupling reaction (Table 2). Under the optimized reaction conditions, the oxidative aza-Henry reaction of **1a** at 30 °C provided the coupling product in a high yield (entry 1). While electron-rich *o*- and *p*-methoxyphenyl-substituted amines afforded high yields, the *m*-methoxyphenyl-substituted substrate

Table 2. Substrate generality.[a]



Entry	Substrate	Product	Time [h]	Yield [%][b]
1			4	90 (85)
2			5	>95 (82)
3			39	73 (74)
4			48	89 (86)
5			13	87 (83)
6			11	57 (53)
7[c]		 (dr = 1.6 : 1)	24	73 (64)

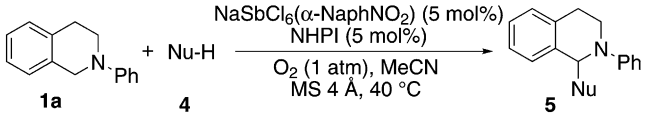
[a] *Reaction conditions:* amine **1** (0.25 mmol), $NaSbCl_6$(α-$NaphNO_2$) (5 mol%), NHPI (5 mol%), MS 4 A (50 mg) in $MeNO_2$ (0.5 mL) under O_2 (1 atm) at 30 °C.
[b] NMR yields are based on **1** and determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields are given in parentheses.
[c] $EtNO_2$ as a solvent.

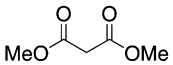
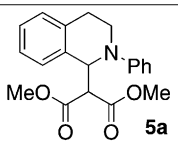
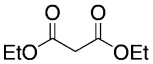
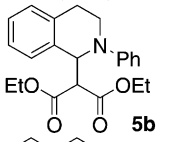
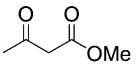
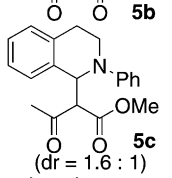
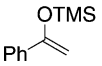
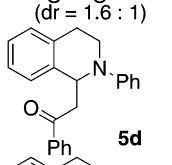
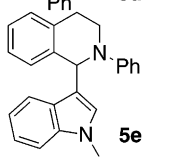
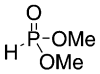
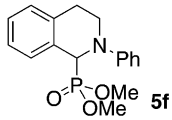
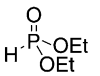
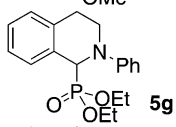
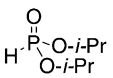
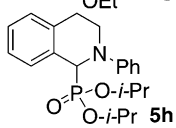
was slightly less reactive (entries 2–4). Also, a *p*-tolyl-substituted compound reacted smoothly to afford the desired product with an excellent yield (entry 5). On the other hand, an electron-deficient *p*-chlorophenyl-substituted substrate afforded only a moderate yield (entry 6). In addition, when nitroethane was used as a solvent, the corresponding product was obtained in a good yield and moderate diastereoselectivity (entry 7). We also examined other amines such as tetrahydroisoquinoline, *N*-benzyltetrahydroquinoline, and *N*,*N*-dimethyltoluidine as substrates, but the desired products were obtained in very low yields.[20,21]

Then, the scope of nucleophiles was examined (Table 3). Initially, we screened different solvents and found acetonitrile was best at 40 °C in the presence of 3 equivalents of the pronucleophiles. While dimethyl and diethyl malonates afforded the desired coupling products in high yields (entries 1 and 2), the reactivity of β-keto esters was surprisingly lower (entry 3). We also examined sp^2-hybridized nucleophiles such as silyl enol ether **4d** (entry 4) and *N*-methylindole (entry 5) and found them to be viable substrates for this aerobic oxidative coupling reaction. Similar to the previous report by Li,[3b] the latter substrate required higher reaction temperature. In addition to the carbon-based nucleophiles, phosphine nucleophiles could also be applied. Methyl, ethyl and isopropyl phosphites reacted smoothly with **1a** (entries 6–8) to afford the desired products in excellent yields.

Although the reaction mechanism for the copper-catalyzed aerobic and peroxide-mediated CDC reaction has been recently clarified by Klussmann, the roles of antimonate and NHPI in our system remain unclear. However, since the reaction does not proceed with only NHPI as a catalyst and that catalyst turnover is observed for the antimonate salt, we assume that the antimony catalyst is responsible for the single electron oxidation step and NHPI facilitates the hydrogen radical abstraction process (Scheme 2).[22] Initially, the reaction begins from a single electron oxidation of the tertiary amine by high valent antimony(V or IV). The resulting low valent antimony(IV or III) is oxidized with molecular oxygen to regenerate antimony(V or IV) and form an oxygen radical anion.[23] Next, the oxygen radical anion abstracts the hydrogen from NHPI to form PINO (phthalimide *N*-oxide) radical and hydrogen peroxide anion. Hydrogen abstraction of aminium radical cation **I** by PINO affords iminium intermediate **II** and subsequently, the nucleophile, deprotonated by the hydrogen peroxide anion, is trapped to furnish the aerobic oxidative coupling product. It should be noted that both the high valent antimony and PINO could be interchanged for either oxidation steps. We also performed the CDC reaction in the presence of a radical inhibitor and the desired product was still obtained, albeit with a low yield (21%).[24] Since the yield obtained parallels the reaction in the absence of the NHPI co-catalyst, the most likely explanation is that a second antimonate-mediated two-electron oxidation pathway exists in our CDC reaction.

Table 3. Scope of nucleophiles.[a]



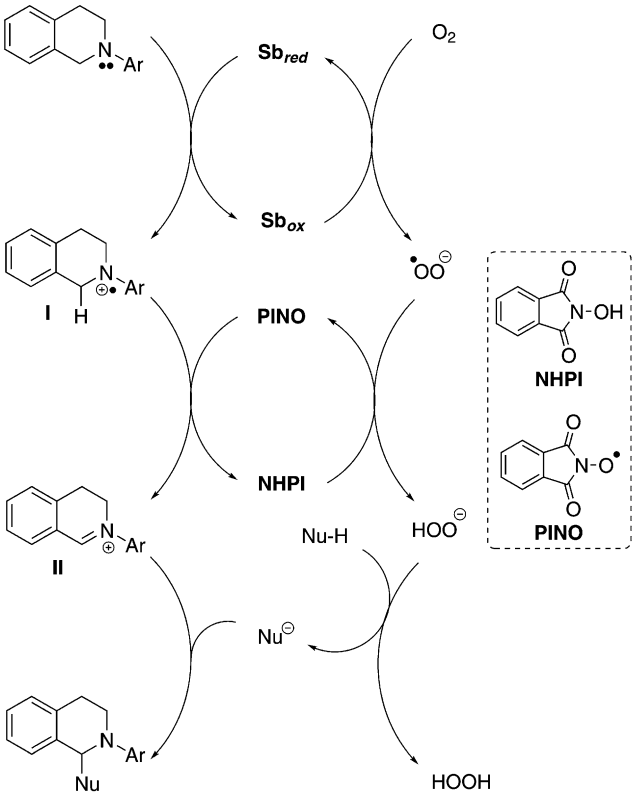
Entry	Nucleophile	Product	Time [h]	Yield [%][b]
1	 **4a**	 **5a**	4	95 (69)
2	 **4b**	 **5b**	21	87 (64)
3	 **4c**	 **5c** (dr = 1.6 : 1)	4	69 (41)
4	 **4d**	 **5d**	4	76 (53)
5[c,d]	 **4e**	 **5e**	31	57 (43)
6	 **4f**	 **5f**	42	>95 (90)
7	 **4g**	 **5g**	5	90 (81)
8	 **4h**	 **5h**	12	91 (82)

[a] *Reaction conditions:* amine **1a** (0.25 mmol), nucleophile **4** (3 equiv), $NaSbCl_6$(α-$NaphNO_2$) (5 mol%), NHPI (5 mol%), MS 4 A (50 mg) in MeCN (0.5 mL) under O_2 (1 atm) at 40 °C.

[b] NMR yields are based on **1a** and determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields are given in parentheses.

[c] 1.5 equivalents of the nucleophile were used.

[d] 80 °C.



Scheme 2. Plausible reaction mechanisms.

In summary, an antimonate anion, with the assistance of NHPI, was found to serve as an excellent catalytic system for the CDC reactions between a variety of tertiary arylamines and pronucleophiles under mild aerobic oxidative conditions. Although there is no significant advantage of this catalyst system for the CDC reaction when compared to other reported methods, we have demonstrated that the antimonate counteranion possesses non-innocent, catalytic oxidative properties that have gone unrecognized until this point.

Experimental Section

Typical Procedure for the CDC Reaction of *N*-Aryltetrahydroisoquinolines

To a dried 10-mL round-bottomed flask, equipped with an oxygen balloon, was added MS 4 A (50 mg), $MeNO_2$ (0.5 mL) and **1a** (52.2 mg, 0.249 mmol). Then, NHPI (2.0 mg, 0.0123 mmol) and $NaSbCl_6$(α-NaphNO_2) (6.8 mg, 0.0128 mmol) were successively added. After stirring the reaction mixture for 4 h at 30 °C, the solvent was removed under reduced pressure and the NMR yield was determined with 1,1,2,2-tetrachloroethane (13 μL) as an internal standard (90% yield). The crude mixture was filtered through silica gel, and the filtrate was concentrated under reduced pressure. Flash chromatography on silica gel with hexane/ethyl acetate (15:1) afforded **2a**; yield: 56.6 mg (85%).

Acknowledgements

This work was partially supported by a Grant-in-Aid for Science Research from the Global COE Program of the Japan Society for the Promotion of Science (JSPS), The University of Tokyo, the Ministry of Education, Culture, Sports, Science and Technology (MEXT) Japan, the New Energy and Industrial Technology Development Organization (NEDO) and Japan Science and Technology Agency (JST).

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