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Sulfuryl Chloride as an Efficient Initiator for the Metal-Free Aerobic Cross-Dehydrogenative Coupling Reaction of Tertiary Amines

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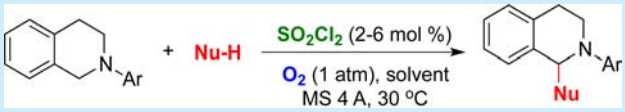
Supporting Information

ABSTRACT: A metal-free cross-dehydrogenative (CDC) reaction of tertiary amines was developed using a catalytic amount of sulfuryl chloride (SO_2Cl_2) under mild aerobic conditions. On the basis of the nature of SO_2Cl_2, it was assumed that the reagent acts as a radical initiator to induce the metal-free CDC reaction via a radical-initiated autoxidation mechanism.



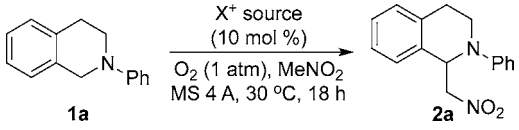
With increased awareness of the environmental impact of current chemical process, the development of new green and sustainable synthetic methodologies has grown substantially.[1] In this context, the direct use of carbon−hydrogen (C−H) bonds in cross-coupling reactions has emerged as a potentially powerful strategy to streamline synthetic methods by bypassing the necessity of synthesizing activated nucleophiles and/or electrophiles prior to the coupling event. A successful class of C−H functionalization reactions is the cross-dehydrogenative (CDC) reaction of the α-C−H bond of tertiary amines.[2] Pioneered by Murahashi[3] and Li,[4] who employed ruthenium and copper catalysts, respectively, using peroxides as oxidants, rapid improvement upon the original conditions has led to a CDC reaction that can be performed under mild aerobic conditions.[5] Despite the progress made thus far, most protocols rely upon the use of toxic metal salts as catalysts, and examples of metal-free aerobic CDC reactions are relatively scarce.[6]

During the course of our investigations to develop a metal-free CDC reaction in air by using aminium radical cations as redox-active organocatalysts, we found that the $SbCl_6^-$ counteranion was the active catalyst. On the basis of this discovery, we recently reported a unique catalytic system composed of $NaSbCl_6$ and *N*-hydroxyphthalimide (NHPI) that enabled the CDC reaction of *N*-aryl tetrahydroisoquinolines with various pronucleophiles under mild aerobic conditions.[7] Although the exact nature of the active catalytic species and its mode of activation are unknown at this stage, one working hypothesis is that the $SbCl_6^-$ acts as a reservoir of $SbCl_5$.[8] Since $SbCl_5$ is a well-known strong oxidant and an excellent electrophilic chlorinating reagent,[9] we assumed that a metal-free aerobic CDC reaction with tertiary amines could be realized with the catalytic use of organo-based electrophilic halogenating reagents.

In this communication, we wish to report the use of sulfuryl chloride (SO_2Cl_2) as a metal-free initiator for the CDC reaction of tertiary amines and various pronucleophiles under mild conditions with oxygen gas as the terminal oxidant.

On the basis of our working hypothesis, we examined the oxidative nitro-Mannich reaction between *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**) and nitromethane in the presence of catalytic amounts of various electrophilic halogenating reagents (Table 1, Figure 1).

Table 1. Investigation of Electrophilic Halogen Sources[a]



entry	X^+ source	conv[b] (%)	yield[b] (%)
1	NCS	68	60
2	SO_2Cl_2	>95	75
3	^{t}BuOCl	9	10
4	chloramine T	5	8
5	dichloramine T	5	4
6	trichloroisocyanuric acid	<5	4
7	NBS	5	3
8	NIS	18	11
9	I_2	15	15
10[c]	SO_2Cl_2	>95	93
11[c,d]	SO_2Cl_2	>95	90
12[c,e]	SO_2Cl_2	<5	1

[a]Reaction conditions: amine **1a** (0.25 mmol), X^+ source (0.025 mmol, 10 mol %), MS 4 Å (50 mg) in $MeNO_2$ (0.6 mL) at 30 °C for 18 h under a balloon of dry oxygen. [b]Determined by ^{1}H NMR analysis. [c]6 mol % catalyst was used. [d]Protected from light. [e]Under argon atmosphere.

When we utilized a catalytic amount of *N*-chlorosuccinimide (NCS), the desired CDC adduct **2a** was obtained in a moderate yield (entry 1). Surprisingly, in contrast to our previously reported $NaSbCl_6$/NHPI system, the addition of NHPI was found to slightly suppress the reaction. We examined various electrophilic chlorinating reagents and found that SO_2Cl_2, which is known as a surrogate of chlorine gas, provided the

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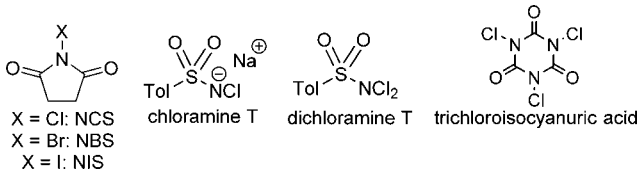
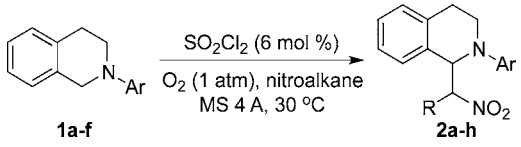


Figure 1. Electrophilic halogen sources.

desired product in 75% yield (entry 2). On the other hand, various electrophilic chlorinating sources were screened, but the results for the CDC reaction was quite poor (entries 3−6). In addition, other electrophilic halogen reagents, such as *N*-bromosuccinimide (NBS), *N*-iodosuccinimide (NIS), and iodine, were examined, but in all cases the reaction hardly proceeded (entries 7−9). On the basis of these results, we determined SO_2Cl_2 as the optimal catalyst and examined other conditions to improve the yield of **2a**. Since SO_2Cl_2 fully converted the *N*-aryl amine **1a** to provide the CDC adduct **2a** in a good yield, we assumed that the electrophilic chlorinating reagent may cause some decomposition of the starting material and/or product to decrease the overall yield. To our delight, when we lowered the catalyst loading to 6 mol %, the oxidative nitro-Mannich product **2a** was obtained in an excellent yield (entry 10). In addition, we examined the possibilty of light being involved in the CDC reaction and found that by protecting the reaction vessel from ambient light, the reaction proceeded smoothly (entry 11). We also performed the reaction in the absence of O_2 gas and found the reaction hardly proceeded (entry 12).

With the optimized conditions in hand, the substrate generality was investigated (Table 2). In addition to simple

Table 2. Substrate Scope of Amines and Nitroalkanes[a]



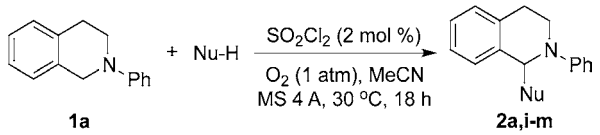
entry	Ar	nitroalkane	time (h)	yield[b] (%)
1	Ph (**1a**)	$MeNO_2$	18	93 (80)
2	4-Me-C_6H_4 (**1b**)	$MeNO_2$	18	88 (84)
3	3-Me-C_6H_4 (**1c**)	$MeNO_2$	18	86 (70)
4	2-Me-C_6H_4 (**1d**)	$MeNO_2$	72	12 (4)
5	4-MeO-C_6H_4 (**1e**)	$MeNO_2$	18	60 (44)
6	4-Cl-C_6H_4 (**1f**)	$MeNO_2$	53	90 (75)
7	Ph (**1a**)	$EtNO_2$	48	82 (71)[c]
8	Ph (**1a**)	$^nPrNO_2$	54	70 (62)[d]

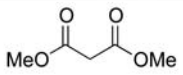
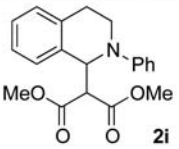
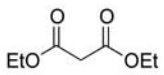
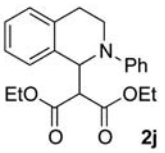
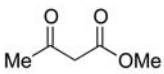
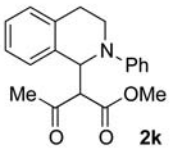
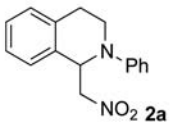
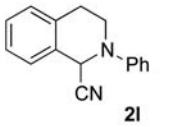
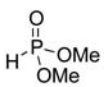
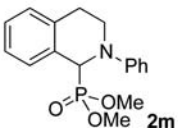
[a]Reaction conditions: amine **1a-f** (0.25 mmol), SO_2Cl_2 (0.015 mmol, 6 mol %), MS 4 Å (50 mg) in nitroalkenes (0.6 mL) at 30 °C under a balloon of dry oxygen. [b]Determined by ^{1}H NMR analysis; the isolated yields are shown in parentheses. [c]dr = 1.8:1. [d]dr = 1.5:1.

N-phenyl-substituted tetrahydroisoquinoline **1a** (entry 1), other *N*-aryl tetrahydroisoquinolines **1b−f** were examined (entries 2−6). When various tolyl-substituted tetrahydroisoquinolines **1b−d** were subjected to our optimized catalyst system, the *para*- and *meta*-substituted tolyl substrates **1b,c** underwent the CDC reaction smoothly (entries 2 and 3). On the other hand, *ortho*-substituted tertiary amine **1d** reacted sluggishly, and CDC product **2d** was obtained in a low yield (entry 4).[10] When a 4-methoxylphenyl substrate **1e** was employed, the desired product **2e** was obtained in a moderate yield (entry 5). In addition to the electron-rich *N*-aryl amines, an electron-deficient 4-chlorophenyl substrate **1f** reacted slowly, but the desired CDC adduct **2f** was obtained in a relatively high yield (entry 6). We also examined different nitroalkanes and found that nitroethane and nitropropane were applicable nucleophiles that provided the expected CDC products **2g,h** in good yields, despite the fact that the reactions proceeded more slowly (entries 7 and 8). In contrast to the *N*-aryl tetrahydroisoquinolines, other tertiary amines such as *N*,*N*-dimethyl-*p*-toluidine (**3**) and *N*-benzyl tetrahydroisoquinoline were found to be unreactive in our metal-free system.

Next, other pronucleophiles were examined as substrates (Table 3). After further optimization using dimethyl malonate as a model substrate, we found that only 2 mol % of SO_2Cl_2 and 1 equiv of the nucleophile were required when the reaction was performed in acetonitrile. Similarly, when diethyl malonate was utilized as a substrate, the desired product **2i** was obtained

Table 3. Substrate Scope of Nucleophiles[a]



entry	nucleophile	product	yield (%)[b]
1		 **2i**	92 (77)
2		 **2j**	89 (76)
3[c]		 **2k**	68 (67)
4[d]	$MeNO_2$	 **2a**	84 (70)
5[e]	TMSCN	 **2l**	93 (85)
6[e]		 **2m**	87 (85)

[a]Reaction conditions: *N*-phenyl tetrahydroquinoline **1a** (0.25 mmol), nucleophiles (0.25 mmol), SO_2Cl_2 (0.005 mmol, 2 mol %), MS 4 Å (50 mg) in acetonitrile (0.6 mL) at 30 °C under a balloon of dry oxygen. [b]Determined by ^{1}H NMR analysis; the isolated yields are shown in parentheses. [c]dr = 1.6:1. [d]10 equiv of the nucleophile was used. [e]5 equiv of the nucleophile and 6 mol % SO_2Cl_2 were used.

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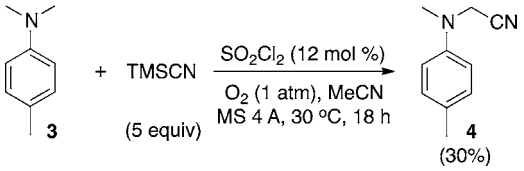
in a good yield. When methyl acetoacetate was employed, the CDC adduct **2j** was obtained in a good yield with a modest diastereoselectivity. We also examined the oxidative nitro-Mannich reaction and found that with an excess of nitromethane the desired product **2a** was formed in a high yield.

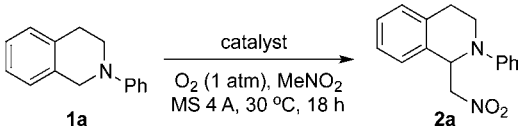
With increased amounts of both SO_2Cl_2 and the nucleophile, the oxidative cyanation with trimethylsilyl cyanide was also successful. In addition to carbon-based nucleophiles, a phosphine-based nucleophile, such as dimethyl phosphite, was found to react smoothly to furnish α-amino phosphonate **2m** with an excellent yield. To further broaden the substrate scope, the oxidative cyanation reaction was attempted with *N*,*N*-dimethyl-*p*-toluidine (**3**), and the desired CDC product was obtained in a modest yield (Scheme 1).

Scheme 1. Oxidative Cyanation of *N*,*N*-Dimethyl-*p*-Toluidine



To elucidate the role of SO_2Cl_2 for the metal-free CDC reaction with *N*-aryl tetrahydroisoquinolines, we conducted additional experiments (Table 4). Although most metal-catalyzed aerobic CDC reactions occur through the reoxidation of the catalyst by oxygen gas, such a scenario is improbable for SO_2Cl_2 due to the high oxidation potential of electrophilic chlorine.[11] Thus, we assume that the CDC reaction occurs through an autoxidation mechanism initiated by either an acid[6a] or a radical species.[6f] Indeed, when we utilized methanesulfonic acid (entry 1) and 2,2′-azobis(4-methoxy-2,4-dimethyl valeronitrile) (V-70) (entry 2) as initiators, the oxidative aza-Mannich reaction proceeded in moderate yields. Since sulfuric acid could be generated from the hydrolysis of SO_2Cl_2, we examined the possibility of an acid-initiated mechanism by performing the CDC reaction using a catalytic amount of sulfuric acid (entry 3). On the basis of the poor conversion, we believe that the CDC reaction with SO_2Cl_2 does not proceed through the acid-initiated pathway. To exclude the possibility of a synergistic effect between SO_2Cl_2 and sulfuric acid, we examined the oxidative coupling reaction using a catalytic amount of a 1:1 SO_2Cl_2/H_2SO_4 mixture (entries 4 and 5).

Table 4. Comparison of Catalysts[a]



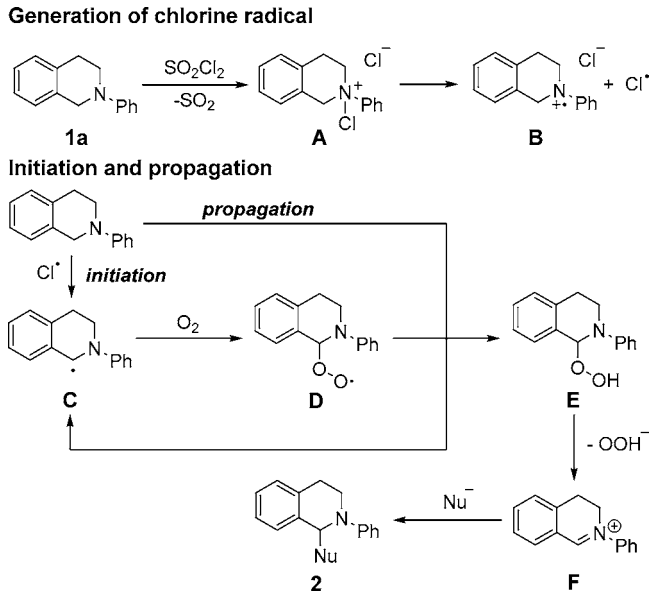
entry	initiator (mol %)	conv[b] (%)	yield[b] (%)
1	$MeSO_3H$ (6)	43	40
2	V-70 (6)	45	38
3	H_2SO_4 (6)	7	7
4	SO_2Cl_2 (3)	93	73
5	H_2SO_4 (3), SO_2Cl_2 (3)	33	10
6	SO_2Cl_2 (6), BHT (100)	30	22

[a]Reaction conditions: amine **1a** (0.25 mmol), initiator (0.015 mmol, 10 mol %), MS 4 Å (50 mg) in $MeNO_2$ (0.6 mL) at 30 °C for 18 h under a balloon of dry oxygen. [b]Determined by ^{1}H NMR analysis.

Although the CDC adduct was obtained in a good yield using only 3 mol % of SO_2Cl_2 (entry 4), the addition of sulfuric acid inhibited the oxidative aza-Mannich reaction, and the possibility of a synergistic effect was ruled out (entry 5). Thus, we assume that the CDC reaction proceeds through a radical-initiated autoxidation mechanism. To confirm the radical-initiated mechanism, we introduced a stoichiometric amount of a radical inhibitor, 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT), and found that the oxidative nitromethylation reaction was significantly suppressed (entry 6).[12]

Based on our control studies, our proposed reaction mechanism is depicted in Scheme 2. Although a radical-initiated autoxidation mechanism is most probable, the mechanism of the initiation step still remains unclear. Initially, we speculated that SO_2Cl_2 undergoes homolytic cleavage to generate chlorine radicals to initiate the CDC reaction. However, based on the bond dissociation energy of $ClSO_2-Cl$ (46 ± 4 kcal/mol),[13] it is highly unlikely that the homolytic cleavage occurs at room temperature. In addition, the possibility of a light-mediated chlorine radical formation is denied since the SO_2Cl_2-initiated CDC reaction occurs in the absence of light (Table 1, entry 11). One plausible pathway to generate the radical initiator is through the chlorination reaction of tertiary *N*-aryl amines to form the ammonium cation **A**, followed by the homolytic cleavage of the N−Cl bond to generate aminium cation **B** and the chlorine radical.[14] Once the chlorine radical is formed, it can abstract the hydrogen atom from **1** to generate the carbon-centered radical intermediate **C**,[15] and this radical intermediate can react with molecular oxygen to provide the oxygen-centered radical **D**. Subsequently, intermediate **D** can abstract the hydrogen atom from **1** to form alkyl hydroperoxide **E** and intermediate **C** to propagate the autoxidation. Elimination of the hydroperoxide anion, followed by the nucleophilic addition to iminium intermediate **F**, would furnish the desired CDC adduct.[16]

Scheme 2. Proposed Reaction Mechanism



In summary, we developed a metal-free CDC reaction of tertiary amines that could proceed under very mild aerobic

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conditions. On the basis of our control studies, we assume that the SO_2Cl_2-initiated CDC reaction occurs through a radical-initiated autoxidation mechanism. Although the reaction mechanism is classic and simple, the SO_2Cl_2-initiated aerobic CDC reaction represents one of the most efficient and green C−H bond functionalization reactions since a catalytic amount (2−6 mol %) of an inexpensive reagent is required and the decomposition products of SO_2Cl_2 (HCl, SO_2, and H_2SO_4) can be easily removed by evaporation or aqueous workup.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) An alternative mechanistic pathway to access intermediate **C** is through the deprotonation of aminium radical **B** with **1a**.

(16) ^{1}H NMR spectra of the crude reaction mixture of **1a** and SO_2Cl_2 in MeCN under an atmosphere of O_2 suggests the presence of alkyl peroxide intermediate **E**. Please see the Supporting Information for additional details.