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Molecular Iodine Catalyzed Cross-Dehydrogenative Coupling Reaction between Two sp^3 C−H Bonds Using Hydrogen Peroxide

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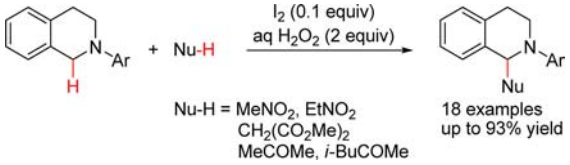
ABSTRACT



A useful method for molecular iodine catalyzed oxidative C−C bond formation between tertiary amines and a carbon nucleophile using hydrogen peroxide as the terminal oxidant is reported. This is the first report of a molecular iodine catalyzed cross-dehydrogenative coupling (CDC) reaction between two sp^3 C−H bonds.

Iodine source catalyzed C−H oxidation with various stoichiometric oxidants has attracted great interest because iodine sources have low toxicity and are inexpensive compared with transition metal catalysts. Ishihara et al.[1] and others[2] have reported novel C−H oxidations using a catalytic amount of quaternary ammonium iodide with aq H_2O_2 or *tert*-butyl hydroperoxide as terminal oxidants, which generate only water or *tert*-butanol waste products. This mild C−H oxidation can produce C−O or C−N bonds, or both. C−C bond formation is one of the most fundamental reactions in organic synthesis because most organic molecules are made up of C−C bonds. Cross-dehydrogenative coupling (CDC) reactions between two C−H bonds are powerful C−C bond forming methods, and various types of CDC reactions have been developed in recent years.[3] The oxidation of a C−H bond adjacent to a nitrogen atom of tertiary amines to iminium ions has attracted great interest because a synthetically and biologically useful Mannich-type product is obtained from relatively simple precursors. Murahashi et al. have pioneered the Ru catalyzed oxidative cyanation of tertiary amines,[4] and Li et al. have reported copper catalyzed CDC reactions.[5] Recently, various CDC methods have been reported, using transition metal catalysts, such as Fe,[6]

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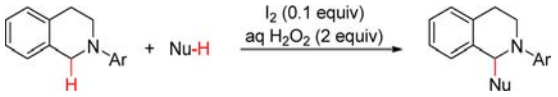
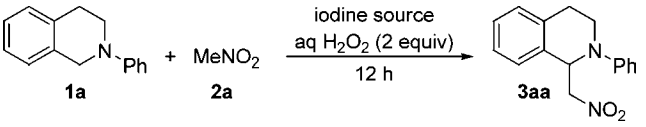
Scheme 1. Molecular Iodine Catalyzed CDC Reaction with aq H_2O_2



V,[7] Rh,[8] Au,[9] or Pt,[10] or photocatalysts, such as $Ir(ppy)_2(dtbbpy)^+$,[11] $Ru(bpy)_3^{2+}$,[12] or eosin Y.[13] In addition, metal-free methods using a stoichiometric amount of an oxidant, such as $PhI(OAc)_2$,[14] DDQ,[15] or the tropylium ion,[16] have been reported. However, the catalytic metal-free oxidative CDC reaction of tertiary amines with a carbon nucleophile, without photoirradiation, has not been reported. From our study of oxidation with iodine sources,[17] we found that tertiary amines can be oxidized with catalytic molecular iodine in the presence of hydrogen peroxide. Here we report the first molecular iodine catalyzed oxidative C−C bond formation through the CDC reaction between two sp^3 C−H bonds, using hydrogen peroxide as the terminal oxidant (Scheme 1).

Table 1 shows the reaction conditions for oxidative C−C bond formation from *N*-phenyl tetrahydroisoquinoline (**1a**), as the substrate, in nitromethane (**2a**). We obtained the corresponding aza-Henry product **3aa** in good yield when we used 0.05 equiv of molecular iodine and 2 equiv of aq H_2O_2 at 40 °C (entries 1−3), and we found that both of the reagents were necessary (entries 4 and 5). By increasing the amount of molecular iodine to 0.1 equiv, we obtained **3aa** in 93% yield (entry 6). We found that molecular iodine was the most effective of the iodine sources tested for this oxidation, and when we used other iodine sources we obtained only low yields of **3aa** (entries 6−12). Interestingly, C−C bond formation proceeded in good yield when we used 5 equiv of **2a** in MeCN (entry 13).

Table 1. Study of Reaction Conditions[a]



entry	iodine source (equiv)	temp (°C)	**3aa** (%)[b]
1	I_2 (0.05)	rt	67
2	I_2 (0.05)	40	89 (82)
3	I_2 (0.05)	60	87
4	–	40	4
5[c]	I_2 (0.05)	40	10
6	I_2 (0.1)	40	96 (93)
7	$^nBu_4NI$ (0.1)	40	24
8	MgI_2 (0.1)	40	17
9	CaI_2 (0.1)	40	14
10	KI (0.1)	40	15
11	NaI (0.1)	40	6
12	LiI (0.1)	40	6
13[d]	I_2 (0.1)	40	76 (67)

[a] Reaction conditions: **1a** (0.3 mmol), iodine source, and 35% aq H_2O_2 (2 equiv) in **2a** (3 mL) were stirred for 12 h. [b] ^1H NMR yields. Numbers in parentheses are isolated yields. [c] The reaction was performed without aq H_2O_2. [d] The reaction was performed with 5 equiv of **2a** in MeCN (3 mL).

Scheme 2 presents the scope and limitations of CDC reactions between *N*-aryl tetrahydroisoquinolines (**1**) and nitroalkanes **2** under the optimized reaction conditions. In general, the corresponding aza-Henry products (**3aa**, **3ba**, **3ca**, **3da**, **3ea**, **3fa**) were obtained in good yields with nitromethane (**2a**) as the coupling partner, regardless of whether there was an electron-donating or -withdrawing group on the *N*-aryl group aromatic ring. Using nitroethane (**2b**), C−C bond formations proceeded smoothly to afford the desired products (**3ab**, **3bb**, **3eb**, **3fb**) in moderate to good yields. Unfortunately, *N*,*N*-dimethyl-*p*-toluidine was a poor substrate.

In addition to oxidative aza-Henry reactions, we applied our method to oxidative Mannich reactions (Scheme 3). The corresponding Mannich products (**5aa**, **5ca**) were obtained in good yields using activated methylene compounds such as dimethyl malonate. Next, we attempted oxidative coupling between tertiary amines and nonactivated ketones. Under the optimized conditions shown in Table 1, the corresponding oxidative Mannich product was not obtained in acetone. However, in the presence of 5 equiv of acetic acid, C−C bond formation proceeded smoothly. In general, using acetone and 4-methyl-2-pentanone, the desired products (**5ab**, **5bb**, **5cb**, **5db**, **5eb**, **5ac**) were obtained in good yields, regardless of whether there was an electron-donating or -withdrawing group on the *N*-aryl group aromatic ring.

We performed several control experiments to attempt to resolve the reaction mechanism. It has been known that tetrahydroisoquinolines can be oxidized to

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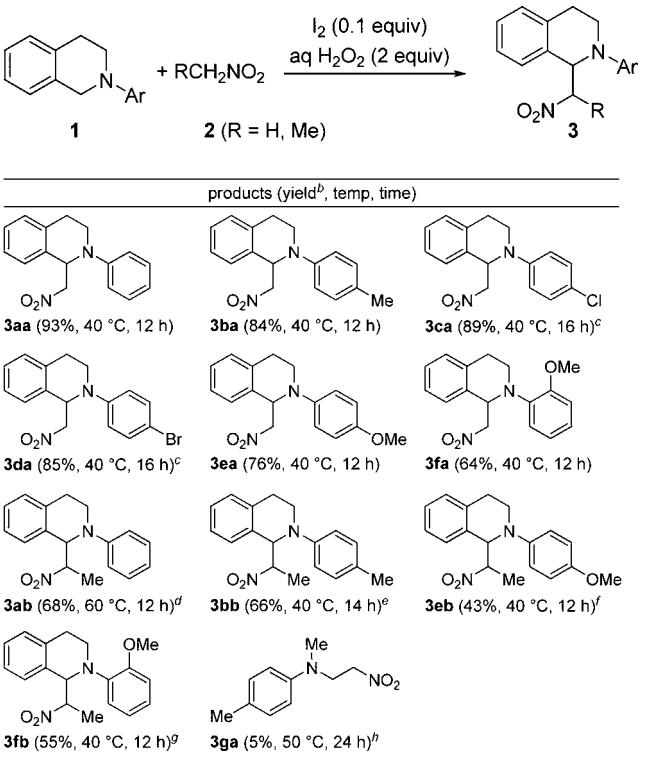
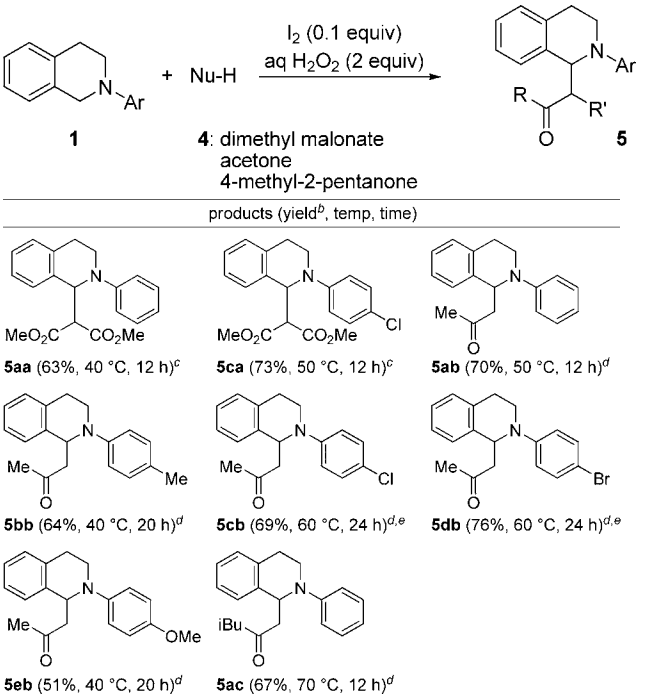
Scheme 2. CDC Reaction of Amines with Nitroalkanes[a]



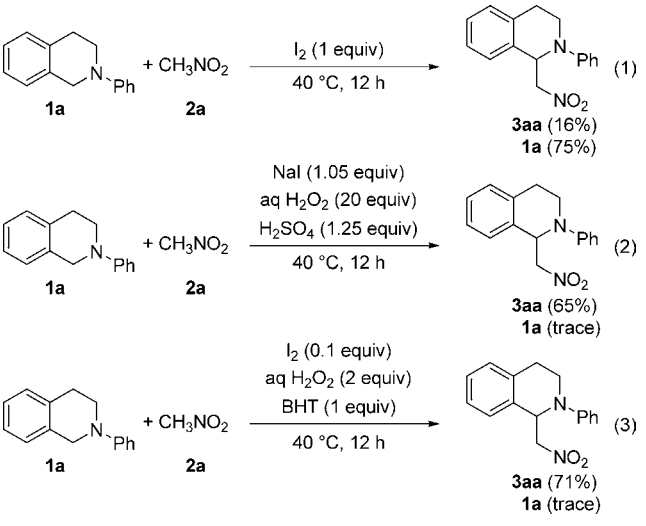
[a] Reaction conditions: **1** (0.3 mmol), I_2 (0.1 equiv), and 35% aq H_2O_2 (2 equiv) in **2** (3 mL) were stirred. [b] Isolated yields. [c] **2**/MeOH (2/1 mL) was used. [d] dr = 61:39. [e] dr = 65:35. [f] dr = 64:36. [g] dr = 60:40. [h] *N*,*N*-Dimethyl-*p*-toluidine was used as substrate.

Scheme 3. CDC Reaction of Amines with Carbonyl Compounds[a]



[a] Reaction conditions: **1** (0.3 mmol), I_2 (0.1 equiv) and 35% aq H_2O_2 (2 equiv) in **4** (3 mL) was stirred. [b] Isolated yields. [c] **4a** (1 mL) was used. [d] AcOH (5 equiv) was added. [e] **4**/MeOH (2/1 mL) was used.

Scheme 4. Study of Reaction Mechanism



3,4-dihydroisoquinolines with a stoichiometric amount of molecular iodine in ethanol.[18,19] However, when we used 1 equiv of molecular iodine in the absence of aq hydrogen peroxide, we obtained **3aa** only in 16% yield and recovered 75% of **1a** (Scheme 4, eq 1). This result suggests that the oxidation of amines requires both molecular iodine and hydrogen peroxide. The iodination of several compounds, including electron-rich aromatics, olefins, and ketones, with molecular iodine is accelerated by hydrogen peroxide,[20] and in one of these reactions, hypoiodous acid (HOI)[21] has been considered to be an active species.[20f] In fact, the NaI/H_2O_2/acid system[22] that is known to generate HOI or its protonated form was effective in the oxidation of tertiary amines, and the desired products were obtained in 65% yield (Scheme 4, eq 2). Furthermore, BHT, a radical inhibitor, scarcely suppressed our CDC reaction (Scheme 4, eq 3).

Scheme 5 shows a plausible path for this oxidation, which we postulate after considering all of the results

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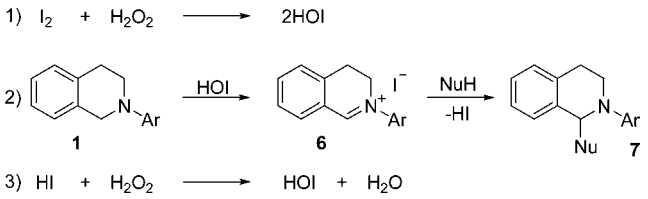
Scheme 5. Plausible Path



presented above. The active species are not yet clear, but we suppose that the tertiary amine **1** is oxidized to the iminium ion **6** by HOI,[23,24] which is generated from molecular iodine and hydrogen peroxide.[20f] The iminium ion **6** undergoes the addition of a carbon nucleophile, such as a nitroalkane **2** or a carbonyl compound **4**, to form the desired product **7**. Hydrogen iodide, generated by the addition of a nucleophile to **6**, is reoxidized to HOI by hydrogen peroxide.[22]

In conclusion, we report molecular iodine catalyzed oxidative C−C bond formation by a CDC reaction between tertiary amines and a carbon nucleophile. This novel reaction is interesting because it uses catalytic molecular iodine and aq H_2O_2 as the terminal oxidant. The application of this oxidation to other reactions is now in progress in our laboratory.

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

The authors declare no competing financial interest.

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