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Selective Functionalization of sp^3 C−H Bonds Adjacent to Nitrogen Using (Diacetoxyiodo)benzene (DIB)

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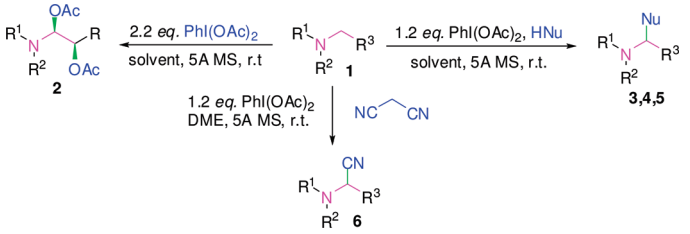

A $PhI(OAc)_2$ mediated selective functionalization of sp^3 C−H bonds adjacent to a nitrogen atom has been reported. When piperidine derivates were used, direct diacetoxylation of α and β sp^3 C−H adjacent to a nitrogen atom were observed to afford various *cis*-2,3-diacetoxylated piperidines. On the other hand, tetrahydroisoquinoline derivatives gave various α-C−H functionalized products in the presence of $PhI(OAc)_2$. Nitroalkanes, dialkyl malonates, and β-keto ester are active participants in this coupling reaction. Meanwhile, α-amino nitriles can also be obtained by oxidative coupling of amines with malononitrile.

Introduction

Direct formation of C−C, C−O, and C−N bonds from unactivated carbon−hydrogen bonds is one of the most challenging projects in organic synthesis.[1] In this content, selective functionalization of C−H bonds adjacent to a nitrogen atom is of great importance due to the fact that important building blocks can be formed in a single step using this approach.[2] Various methods such as lithiation, radical method, and transition metal catalysis have been developed to achieve this functionalization.[2] Our effort is to achieve this transformation by oxidative method using hypervalent iodine(III) reagents. Hypervalent iodine(III) reagents have recently received much attention due to their low toxicity, easy handling, and high reactivity.[3] The most well-known representative of this class is (diacetoxyiodo)benzene (DIB), which is found to be useful for the oxidative functionalization of various functional groups.[3] We envision that iminium ions **II** could be formed in the presence of DIB. β-Hydrogen elimination of **II** and further transformation should afford the difunctionalized products (Scheme 1a). On the other hand, direct capture of iminium ions **II** with nucleophiles should lead to the monofunctionalized products (Scheme 1b). Herein we report our research on the selective functionalization of sp^3 C−H bonds adjacent to a nitrogen atom using DIB as the oxidant.

Results and Discussion

Selective *cis*-Diacetoxylation of Tertiary Amines Using (Diacetoxyiodo)benzene (DIB). Recently, direct formation of C−O bonds based on α-C−H activation of amines has received great attention. One of the earliest strategies was disclosed by Brown and further developed by Shono. It utilizes electrochemical, anodic oxidation of tertiary amines to deliver the corresponding α-aminals (Scheme 2a).[4] Weinreb developed an alternative to the electrochemical

(1) For recent reviews on C-H activation and functionalization, see: (a) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731.

(2) For recent reviews on activation of sp^3 C-H bonds adjacent to a nitrogen atom, see: (a) Li, C. J. *Acc. Chem. Res.* **2009**, *42*, 335. (b) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069. (c) Doye, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3351. (d) Murahashi, S.-I. *Angew. Chem., Int. Ed.* **1995**, *34*, 2443.

(3) (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (c) Togo, H.; Katohgi, M. *Synlett* **2001**, 565. (d) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123.

(4) (a) Shono, T.; Matsumura, Y.; Onomura, O.; Ogaki, M.; Kanazawa, T. *J. Org. Chem.* **1987**, *52*, 536. (b) Shono, T.; Matsumura, Y.; Tsubata, K. *Org. Synth.* **1985**, 206. (c) Shono, T. *Tetrahedron* **1984**, 811. (d) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264. (e) Weinberg, N. L.; Brown, E. A. *J. Org. Chem.* **1966**, *31*, 4058.

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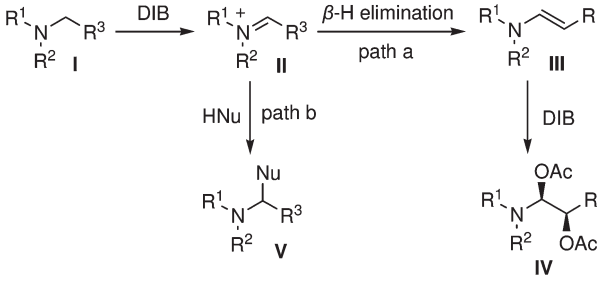
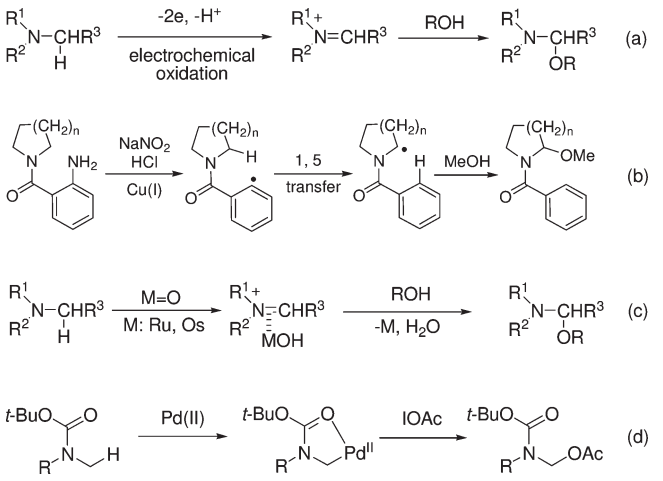
SCHEME 1. Selective Functionalization of Tertiary Amine



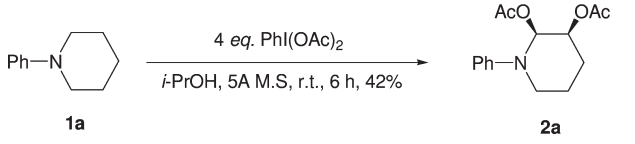
SCHEME 2. General Strategies for C−O Formation Adjacent to Nitrogen



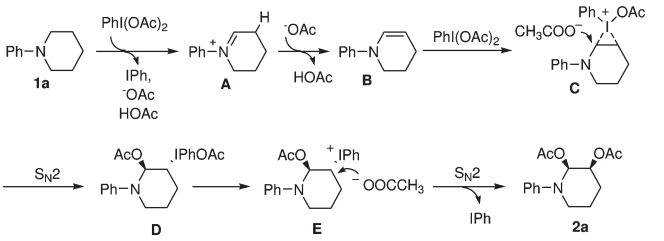
oxidation, which take advantage of the 1,5-hydrogen atom transfer, to achieve α-methoxylation of N-heterocycles (Scheme 2b).[5] Murahashi mimicked cytochrome P-450 type reactivity using Ru(II) and Os(III) catalysts to afford various α-oxygenated compounds (Scheme 2c).[6] Very recently, Yu and Corey reported a similar pathway, in the presence of directing groups, to achieve the selective acetoxylation of α-CH_3 and β-CH_2, respectively (Scheme 2d).[7] Despite these significant progress on the C−O bond formation via C−H bond functionalization adjacent to nitrogen atom, direct functionalization of β-C−H still remains a great challenge. To the best of our knowledge, there are no generally effective methods for dioxygenation of the both positions.[8]

On the other hand, dioxygenation continues to be a fascinating and useful area of research since Sharpless and

SCHEME 3. *cis*-Diacetoxylation of 1-Phenylpiperidine 1a



SCHEME 4. Proposed Mechanism



co-workers reported the OsO_4-catalyzed *cis*-dihydroxylation of alkenes and its asymmetric version.[9] Because of the high cost and toxicity of OsO_4, various alternative metal catalysts for alkene *cis*-dihydroxylations have been developed in the past years.[10] Currently, Celik reported that hypervalent iodine compound can also mediate this transformation in the absence of metal.[11] However, an efficient method for the direct dioxygenation of less reactive methylene group is not disclosed so far. Herein, we report a direct 2,3-diacetoxylation of α,β-C−H of piperidine derivates promoted by hypervalent iodine(III).

We focused our studies on the acetoxylation of piperidine derivates using DIB. To a mixture of 1-phenylpiperidine **1a** (0.2 mmol) and 5 Å molecular sieves (50 mg) in *i*-PrOH (2 mL), DIB (4 equiv) was added in one portion. After stirring at room temperature for 6 h, *cis*-2,3-diacetoxylated product **2a** was isolated in a 42% yield (Scheme 3).[12] The proposed mechanism of the formation of **2a** is shown in Scheme 4. Similar to strategies of the oxidation of tertiary amines by either electrochemical pathway (Scheme 2a) or metal-catalyzed pathway (Scheme 2c), intermediate iminium

(5) (a) Sun, P.; Sun, C.; Weinreb, S. M. *J. Org. Chem.* **2002**, *67*, 4337. (b) Han, G.; LaPorte, M.; McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1996**, *61*, 9483.

(6) (a) Murahashi, S.-I.; Naota, T.; Miyaguchi, N.; Nakato, T. *Tetrahedron Lett.* **1992**, *33*, 6991. (b) Murahashi, S.-I.; Saito, T.; Naota, T.; Kumobakashi, H.; Akutogaua, S. *Tetrahedron Lett.* **1991**, *32*, 5991. (c) Murahashi, S.-I.; Saito, T.; Naota, T.; Kumobayashi, H.; Akutapxwa, S. *Tetrahedron Lett.* **1991**, *32*, 2145. (d) Murahashi, S.-I.; Naota, T.; Kuwzbara, T.; Saito, T.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1990**, *1l2*, 7820. (e) Murahashi, S.-I.; Naota, T.; Yonemura, K. *J. Am. Chem. Soc.* **1988**, *110*, 8256.

(7) (a) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391. (b) Wang, D.-H.; Hao, X.-S.; Wu, D.-F.; Yu, J.-Q. *Org. Lett.* **2006**, *8*, 3387.

(8) The only example was achieved by electrochemical oxidation, see ref 3a.

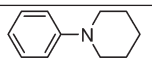
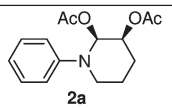
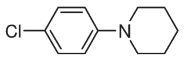
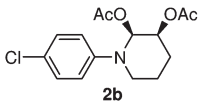
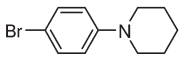
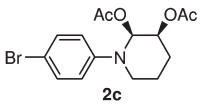
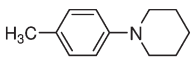
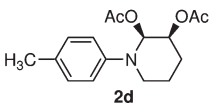
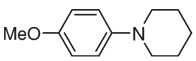
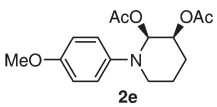
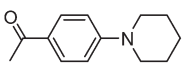
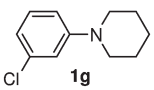
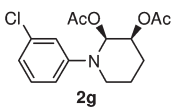
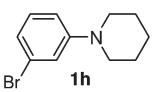
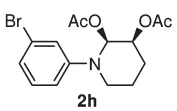
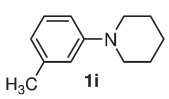
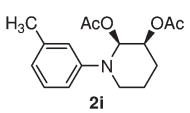
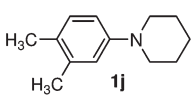
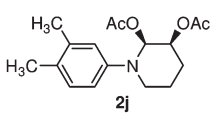
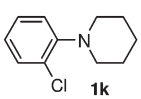
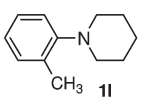
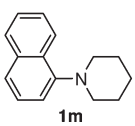
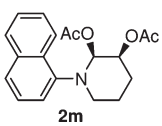
(9) (a) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. (b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; VCH: New York, 2000.

(10) For Fe-catalyzed dihydroxylations: (a) Fujita, M.; Costas, M.; Que, L., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 9912. (b) Chen, K.; Costas, M.; Kim, J.; Tipton, A. K.; Que, L., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 3026. (c) Chen, K.; Que, L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2227. For Mn-catalyzed dihydroxylations: (d) Brinksma, J.; Schmieder, L.; Van Vliet, G.; Boaron, R.; Hage, R.; De Vos, D. E.; Alsters, P. L.; Feringa, B. L. *Tetrahedron Lett.* **2002**, *43*, 2619. (e) De Vos, D. E.; De Wildeman, S.; Sels, B. F.; Grobet, P. J.; Jacobs, P. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 980. For Ru-catalyzed dihydroxylations: (f) Yip, W.-P.; Yu, W.-Y.; Zhu, N.; Che, C.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14239. (g) Ho, C.-M.; Yu, W.-Y.; Che, C.-M. *Angew. Chem., Int. Ed.* **2004**, *43*, 3303. (h) Plietker, B.; Niggemann, M. *Org. Lett.* **2003**, *5*, 3353. (i) Shing, T. K. M.; Tai, V. W. F.; Tam, E. K. W. *Angew. Chem., Int. Ed.* **1994**, *33*, 2312. For Pd-catalyzed dihydroxylations: (j) Wang, A.; Jiang, H.; Chen, H. *J. Am. Chem. Soc.* **2009**, *131*, 3846. (k) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179.

(11) Celik, M.; Alp, C.; Coskun, B.; Gültekina, M. S.; Balci, M. *Tetrahedron Lett.* **2006**, *47*, 3659.

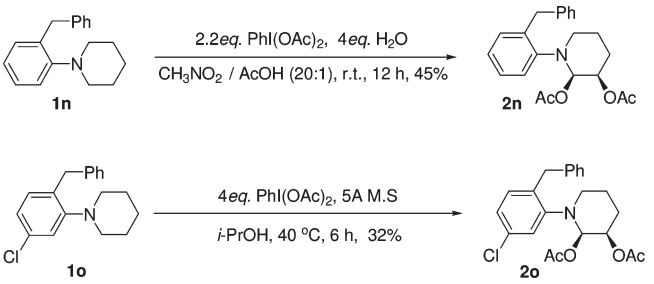
(12) The *cis*-geometry was confirmed by the ^{1}H NMR spectrum. The observed coupling constants, $J_{2,3}$ = 4.8 Hz for products **2a**−**2c**, **2g**, and $J_{2,3}$ = 4.4 Hz for product **2d**, are within the coupling constant of the two *cis*-hydrogen of cyclohexane [J_{HH} (ax−ex, cis): 0−5 Hz, J_{HH} (ax−ax, trans): 6−14 Hz]. The coupling constants of similar structure, such as (*cis* and *trans*)-2,3-dihydroxypyrans and substituted tetrahydroquinoline, can also be used for reference. For detail, see: (a) Levecque, P.; Gammon, D.; Kinfe, H. H.; Jacobs, P.; De Vos, D.; Sels, B. *Org. Biomol. Chem.* **2007**, *5*, 1800. (b) Sugai, T.; lkeda, H.; Ohta, H. *Tetrahedron* **1996**, *52*, 8123. (c) Sridharan, V.; Avendaño, C.; Menéndez, J. C. *Tetrahedron* **2007**, *63*, 673. Furthermore, hypervalent iodine(III) reagents promoted dioxygenation of alkenes always afford the *cis*-products. The mechanism of the formation of the *cis*-products have been proposed before. For detail, see (d) Rebrovic, L.; Koser, G. F. *J. Org. Chem.* **1984**, *49*, 2462. Also see ref 11.

TABLE 1. DIB Promoted 2,3-Diacetoxylation of Amines[a]

entry	amine	product	conditions	yield
1[b]	 **1a**	 **2a**	*i*-PrOH, r.t., 6h	42%
2	 **1b**	 **2b**	CH_3CN, r.t., 6h	35%
3	 **1c**	 **2c**	CH_3CN, 40 °C, 6h	42%
4	 **1d**	 **2d**	*i*-PrOH, 5-10 °C, 4.5h	41%
5	 **1e**	 **2e**	*i*-PrOH, 0 °C, 6h	44%
6	 **1f**	_	*i*-PrOH, r.t., 6h or CH_3CN, r.t., 6h	decomposed
7	 **1g**	 **2g**	CH_3CN, r.t., 5.5h	26%
8	 **1h**	 **2h**	CH_3CN, 40 °C, 6h	45%
9	 **1i**	 **2i**	CH_3CN, r.t., 6h	44%
10	 **1j**	 **2j**	*i*-PrOH, 5-10 °C, 4.5h	46%
11	 **1k**	_	*i*-PrOH, r.t., 6h or CH_3CN, r.t., 6h	decomposed
12	 **1l**	_	*i*-PrOH, r.t., 6h or CH_3CN, r.t., 6h	decomposed
13	 **1m**	 **2m**	CH_3CN, r.t., 6h	20%

[a]Unless noted, reaction was carried out with **1** (0.2 mmol), $PhI(OAc)_2$ (2.2 equiv), and 5 Å molecular sieves (50 mg) in 2 mL of solvent. [b]$PhI(OAc)_2$ (4 equiv) used.

SCHEME 5. DIB Promoted 1,2-Diacetoxylation



ion **A** was formed in the presence of $PhI(OAc)_2$. β-Hydrogen elimination afforded α,β-unsaturated compound **B**, which underwent electrophilic addition of $PhI(OAc)_2$ to the double bond to afford trans-compound **D**. Subsequent elimination of iodobenzene via S_N2 type nucleophilic substitution gave *cis*-2,3-diacetoxylated product **2a**.[11,12d]

Piperidine with various aryl substituents at the nitrogen were investigated, as shown in Table 1. Substituent effect on aryl groups was evident for both para- and meta-substituted 1-arylpiperidines and the desired products were obtained with moderate yields, whereas ortho-substituents always led to the decomposition of substrates. Tertiary amines with electron-rich substituents were relatively more reactive and afforded the product with increased yields and in the meantime, the reaction could be carried out at lower temperature (entries 4, 5, 9, and 10). On the contrary, substrates with electron-withdrawing substituents were less reactive (entries 2, 3, 7, and 8). A more electron-withdrawing group such as acetyl did not give any diacetoxylated product, contrarily, piperidine **1j** with two donating groups afforded **2j** in a 46% yield (entries 6 and 10). 1-(Naphthalen-1-yl)piperidine **1m** was also oxidized to desired product **2m** in a low yield (entry 13).

Although 1-phenylpiperidines, containing chlorine and methyl substituents at the ortho position led to decomposition in the oxidative system, a benzyl group was tolerated. Amines **1n** and **1o** were oxidized to diacetoxylated products in 45% and 32% yields, respectively (Scheme 5).

DIB Mediated Cross-Dehydrogenative Coupling (CDC) Reaction. CDC reaction involving α-C−H bonds in amines has attracted great attention recently due to its atom- and step-economy, high efficiency, and low cost.[13−17] Murahashi,[13] Doyle,[14] Li,[15] and others[16] have developed this oxidative coupling reaction via transition metal catalysis in the presence of oxidants. Very recently, Todd developed a metal-free CDC reaction using DDQ as oxidant with limited reaction scope.[17] Herein, we report our study in this area by using hypervalent iodine(III) reagents.

SCHEME 6. DIB Mediated Cross Coupling Reaction and Proposed Mechanism

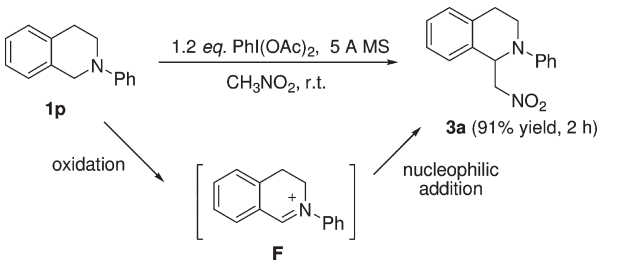
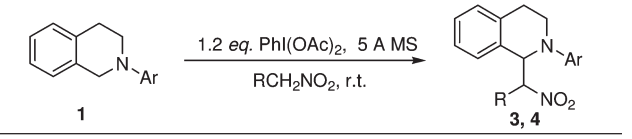
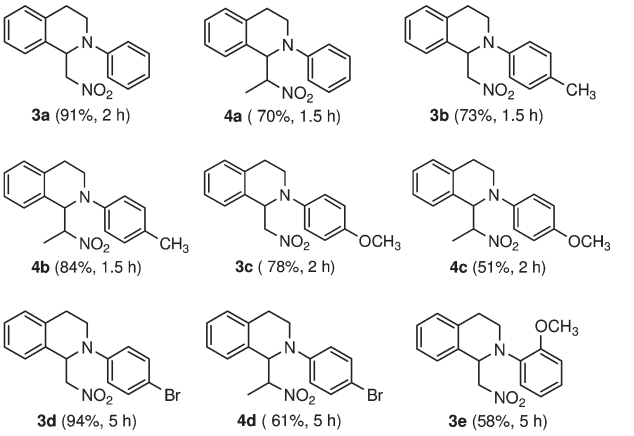


TABLE 2. DIB Mediated Cross Coupling of Tertiary Amines with Nitroalkanes[a]



products (yield, time)



[a]The reaction was run with **1p**−**1t** (0.2 mmol), $PhI(OAc)_2$ (1.2 equiv), and 5 Å molecular sieves (50 mg) in 1 mL of RCH_2NO_2 at rt.

When tetrahydroisoquinoline **1p** was used to investigate the oxidative functionalization in CH_3NO_2, a cross-dehydrogenative coupling (CDC) product **3a** was isolated in a 91% yield after 2 h. The formation of **3a** can be explained by the mechanism that oxidation of tertiary amine **1p** affords the intermediate iminium ion **F**, subsequently, it is captured by a nucleophile to generate the coupling product **3a** (Scheme 6).

Various β-nitroamine derivatives were generated in good to high yields under the above conditions, as shown in Table 2. The steric effect of nucleophiles was obvious. CH_3NO_2 always gave better results than $CH_3CH_2NO_2$ (**3** vs **4**). The electronic nature of aryl substituents of tetrahydroisoquinolines also affected the reactivities too. Electron-rich aryl groups gave slightly lower yields of desired products, whereas electron-poor substituent afforded the best yield (up to 94%) among all results (**3b** and **3c** vs **3d**).

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(14) Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648.

(15) For select examples, see: (a) Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7075. (b) Basle, O.; Li, C.-J. *Org. Lett.* **2008**, *10*, 3661. (c) Basle, O.; Li, C.-J. *Green Chem.* **2007**, *9*, 1047. (d) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928. (e) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672. (f) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (g) Li, Z.; Li, C.-J. *Eur. J. Org. Chem.* **2005**, *15*, 3173. (h) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (i) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997.

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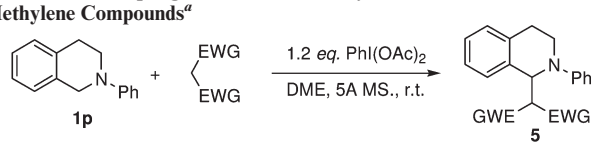
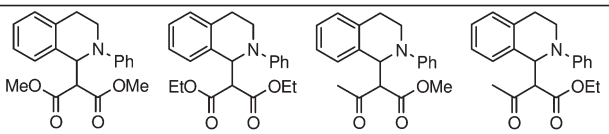
(17) Tsang, A. S.-K.; Todd, M. H. *Tetrahedron Lett.* **2009**, *50*, 1199.

TABLE 3. Coupling Reaction of Tertiary Amines with Activated Methylene Compounds[a]



1p 5

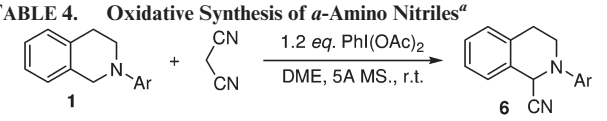
products (yield, time)



5a (57% 5.5 h) **5b** (69%, 5 h) **5c** (78%, 6 h) **5d** (80%, 5 h)

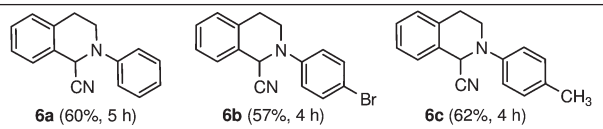
[a]The reaction was run with **1p** (0.2 mmol), activated methylene compounds (2 equiv), $PhI(OAc)_2$ (1.2 equiv), and 5 Å molecular sieves (50 mg) in 2 mL of 1,2-dimethoxyethane (DME) at rt.

TABLE 4. Oxidative Synthesis of *a*-Amino Nitriles[a]



1 6

products (yield, time)



6a (60%, 5 h) **6b** (57%, 4 h) **6c** (62%, 4 h)

[a]The reaction was run with **1** (0.2 mmol), malononitrile (2 equiv), $PhI(OAc)_2$ (1.2 equiv), and 5 Å molecular sieves (50 mg) in 2 mL of 1,2-dimethoxyethane (DME) at rt.

In addition to nitroalkanes, this metal-free CDC reaction was also applicable to activated methylene compounds (Table 3). Dialkyl malonate derivatives and β-keto esters reacted smoothly with tertiary amine under very mild conditions, affording the desired products in good to high yields.

Oxidative Synthesis of *a*-Amino Nitriles. When malononitrile was used as the pronucleophile to investigate the coupling reaction with tertiary amine, instead of β-dicyano-substituted tetrahydroisoquinoline derivate, α-amino nitrile **6a** was obtained as the sole product.

α-Amino nitriles are extremely useful synthetic intermediates. The nitrile functionality can be hydrolyzed easily to produce α-amino acids, and nucleophilic additions to the nitrile group provide access to α-amino aldehydes, α-amino ketones, α-amino alcohols, and 1,2-diamines. An attractive way to α-amino nitriles is achieved by oxidative cross coupling reactions. However, toxic cyanides were always needed.[13,18] As a result, an alternative nitrile-saving source, malononitrile, should be encouraged in this efficient route.

Then we investigated various tetrahydroisoquinolines in the synthesis of α-amino nitriles. The results were shown in table 4. α-Amino nitriles **6** were always obtained in moderate to good yields. Tetrahydroisoquinolines with an electron-rich group gave slightly better results. The detailed mechanism of this transformation was still unclear. A probably pathway is that a certain oxidative degradation of malononitrile with the cleavage of the C−CN bond by $PhI(OAc)_2$ takes place and gives the corresponding products **6**.[15g] According to this way, 2 equiv of $PhI(OAc)_2$ are needed at least to complete this transformation. However, 1.2 equiv of $PhI(OAc)_2$ was enough in this reaction.

(18) North, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4126.

Conclusions

In conclusion, we have reported a $PhI(OAc)_2$ mediated selective functionalization of sp^3 C−H bonds adjacent to a nitrogen atom. For piperidine derivates, various *cis*-2,3-diacetoxylated piperidines were synthesized via direct diacetoxylation of α and β sp^3 C−H adjacent to a nitrogen atom. On the other hand, for tetrahydroisoquinoline in the presence of nucleophiles, such as nitroalkanes, dialkyl malonates, and β-keto ester, α-C−H functionalized products were obtained. Furthermore, α-amino nitriles can also be obtained from the oxidative coupling of amines with malononitrile.

Experimental Section

General Procedure for the Preparation of 1-Arylpiperidine-2,3-diyl Diacetate. To a stirred solution of 1-(4-chlorophenyl)-piperidine **1b** (0.2 mmol) and 5 Å molecular sieve (50 mg) in CH_3CN (2 mL), $PhI(OAc)_2$ (0.44 mmol, 2.2 equiv) was added. After completion of the addition, the solution was stirred at room temperature. When the reaction was considered complete as determined by TLC analysis, sodium thiosulfate was added and the mixture was stirred for several minutes. After removal of the solvent under reduced pressure, the residue was flash chromatographed on silica gel to give desired product **2b** in a 35% yield.

***cis*-1-(4-Chlorophenyl)piperidine-2,3-diyl Diacetate (2b)**, solid; mp 102−104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16−7.19 (m, 2 H), 6.84−6.85 (d, J = 4.8 Hz, 1 H), 6.70−6.73 (m, 2 H), 3.98−4.01 (m, 1 H), 3.45−3.49 (m, 1 H), 3.09−3.16 (m, 1 H), 1.90−2.24 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 168.8, 146.0, 128.8, 121.6, 113.6, 89.2, 59.7, 49.2, 26.6, 23.8, 20.9, 20.7. IR (neat, cm^{-1}) 3263, 3045, 2957, 2926, 2853, 1763, 1674, 1596, 1497, 1372, 1238, 1205, 1094, 1010, 813, 717, 667, 602, 507. HRMS (EI) m/z: calcd for $C_{15}H_{18}ClNO_4$ M + H = 312.0997; found 312.1004.

***cis*-1-(2-Benzyl-phenyl)piperidine-2,3-diyl Diacetate (2n)** was obtained according to the above method using 2.2 equiv of $PhI(OAc)_2$ and 4 equiv of H_2O in CH_3CN/AcOH (20:1) at room temperature. The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 28 mg (45%) of the indicated compound as a solid after 12 h; mp 76−78 °C. ^{1}H NMR (400 MHz, CD_3COCD_3): δ 7.26−7.31 (m, 3 H), 7.15−7.20 (m, 4 H), 6.95−6.97 (m, 2 H), 6.69−6.70 (d, J = 4.8 Hz, 1 H), 4.01−4.09 (m, 3 H), 3.27−3.32 (m, 1 H), 2.71−2.76 (m, 1 H), 2.11−2.19 (m, 1 H), 1.81−2.06 (m, 6 H), 1.74 (s, 3 H). ^{13}C NMR (100 MHz, CD_3COCD_3): δ 169.7, 169.6, 150.3, 143.1, 138.9, 131.8, 130.6, 129.6, 128.3, 127.1, 124.8, 123.2, 91.4, 63.1, 57.2, 38.4, 27.7, 25.7, 21.3, 21.0. IR (neat, cm^{-1}) 3486, 3060, 3026, 2960, 2925, 2871, 1763, 1597, 1490, 1451, 1371, 1241, 1205, 1009, 987, 762, 734, 700, 607, 561, 532. HRMS (EI) m/z: calcd for $C_{22}H_{25}NO_4$ M + H = 368.1856; found 368.1851.

General Procedure for the Preparation of β-Nitroamine Derivatives 3a−3e, 4a−4d. To a stirred solution of tetrahydroisoquinolines (0.2 mmol) and 5 Å molecular sieves (50 mg) in 1 mL of RCH_2NO_2, $PhI(OAc)_2$ (1.2 equiv) was added in one portion. Then the mixture was allowed to stir at room temperature.

When the reaction was considered complete as determined by TLC analysis, the reaction mixture was then filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on alkalescence silica gel to afford corresponding products.

1,2,3,4-Tetrahydro-1-(nitromethyl)-2-phenylisoquinoline (3a). The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford 48.9 mg (91%) of the indicated compound as a solid after 2 h; mp 84−86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28−7.16 (m, 6 H), 7.12−7.10 (d, J = 7.2 Hz, 1 H), 6.97−6.95 (d, J = 8.4 Hz, 2 H), 6.85−6.81 (t, J = 7.2 Hz, 1 H)), 5.55−5.51 (t, J = 7.2, 1 H), 4.86−4.81 (m, 1 H), 4.56−4.51 (m, 1 H), 3.66−3.55 (m, 2 H), 3.10−3.02 (m, 1 H), 2.80−2.73 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 135.2, 132.9, 129.5, 129.1, 128.1, 126.9, 126.6, 119.4, 115.1, 78.7, 58.1, 42.0, 26.4. HRMS (EI) m/z: calcd for $C_{16}H_{16}N_2O_2$ M + H = 269.1285; found 269.1281.

1,2,3,4-Tetrahydro-1-(1-nitroethyl)-2-phenylisoquinoline (4a). The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford 39.6 mg (70%) of the indicated diastereoisomers (2:1) as an oil after 1.5 h. ^{1}H NMR (400 MHz, CD_3COCD_3, 2:1 mixture of diastereoisomers): δ 7.36−7.00 (m, 8 H), 6.78−6.70 (m, 1 H), 5.33−5.09 (m, 2 H), 3.93−3.55 (m, 2 H), 3.10−2.88 (m, 2 H), [1.67−1.65 (d, J = 6.8 Hz), 1.60−1.58 (d, J = 6.4 Hz), 3 H]. ^{13}C NMR (100 MHz, CD_3COCD_3, 2:1 mixture of diastereoisomers): δ 150.8, 150.6, 137.3, 136.8, 135.5, 133.9, 130.7, 130.6, 130.4, 130.2, 129.4, 128.7, 127.5, 127.1, 120.2, 119.8, 116.8, 115.8, 89.9, 87.0, 63.6, 62.4, 44.4, 43.2, 27.5, 26.8, 18.2, 17.9. HRMS (EI) m/z: calcd for $C_{17}H_{18}N_2O_2$ M + H = 283.1441; found 283.1437.

General Procedure for the Coupling Reaction of Tertiary Amines with Activated Methylene Compounds. To a stirred solution of tetrahydroisoquinoline **1p** (0.2 mmol), activated methylene compounds (2 equiv) and 5 Å molecular sieves (50 mg) in 2 mL of 1,2-dimethoxyethane (DME), $PhI(OAc)_2$ (1.2 equiv) was added in one portion. Then the mixture was allowed to stir at room temperature. When the reaction was considered complete as determined by TLC analysis, the reaction mixture was then filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on alkalescence silica gel to afford corresponding products.

Dimethyl 2-(1,2,3,4-Tetrahydro-2-phenylisoquinolin-1-yl)-malonate (5a). The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 38.6 mg (57%) of the indicated compound as an oil after 5.5 h. ^{1}H NMR (400 MHz, CD_3COCD_3): δ 7.23−7.09 (m, 6 H), 7.02−7.00 (d, J = 8.4 Hz, 2 H), 6.74−6.70 (t, J = 7.2 Hz, 1 H), 5.68−5.66 (d, J = 9.6 Hz, 1 H), 4.01−3.98 (d, J = 9.6 Hz, 1 H), 3.74−3.68 (m, 2 H), 3.63 (s, 3 H), 3.53 (s, 3 H), 3.10−3.02 (m, 1 H), 2.92−2.85 (m, 1 H). ^{13}C NMR (100 MHz, CD_3COCD_3): δ 169.4, 168.5, 150.6, 137.1, 136.6, 130.5, 130.4, 129.0, 128.4, 127.3, 119.9, 116.7, 60.2, 59.6, 53.4, 53.3, 53.2, 43.3, 26.9. HRMS (EI) m/z: calcd for $C_{20}H_{21}NO_4$ M + H = 340.1550; found 340.1554.

General Procedure for the Synthesis of α-Amino Nitriles 6a−6c. To a stirred solution of tetrahydroisoquinoline **1p** (0.2 mmol), malononitrile (2 equiv), and 5 Å molecular sieves (50 mg) in 2 mL of 1,2-dimethoxyethane (DME), $PhI(OAc)_2$ (1.2 equiv) was added in one portion. Then the mixture was allowed to stir at room temperature. When the reaction was considered complete as determined by TLC analysis, the reaction mixture was then filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on alkalescence silica gel to afford corresponding products **6**.

1,2,3,4-Tetrahydro-2-phenylisoquinoline-1-carbonitrile (6a). The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford 28.1 mg (60%) of the indicated compound as a solid after 5 h; mp 99−101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.22 (m, 6 H), 7.09−7.07 (m, 2 H), 7.03−6.99 (t, J = 7.6 Hz, 1 H), 5.51 (s, 1 H), 3.80−3.75 (m, 1 H), 3.52−3.46 (m, 1 H), 3.20−3.12 (m, 1 H), 3.00−2.94 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 134.6, 129.6, 129.6, 129.4, 128.8, 127.1, 126.9, 121.9, 117.6, 53.2, 44.2, 28.5. IR (KBr, cm^{-1}) 3627, 3461, 2983, 2925, 2853, 1888, 1739, 1598, 1374, 1242. Anal. Calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.11; H, 6.23; N, 11.89.

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Supporting Information Available: Detailed experimental procedure and ^{1}H NMR and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.