## Intramolecular Oxidative Diamination and Aminohydroxylation of Olefins under Metal-Free Conditions

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ABSTRAC

A metal-free procedure that is simple to operate and convenient to handle was developed for the facile intramolecular oxidative diamination of olefins using an iodobenzene diacetate oxidant and a halide additive to furnish bisindolines at room temperature. The present reaction is featured by mild conditions, a broad substrate scope, and excellent functional group tolerance. The same protocol was successfully extended to the aminohydroxylation.

Preparative route to compounds having a diamino- or aminohydroxy unit from readily available reactants is of high importance since it constitutes a key component of natural products, bioactive pharmaceuticals, and electronic materials (Scheme 1).<sup>1</sup> Over the past decade, various metal-mediated approaches have been developed to afford vicinal diamines in either an intra- or intermolecular manner. For instance, Muñiz et al. reported the Pd(II)catalyzed intramolecular oxidative diamination of  $\omega$ -alkenyl-substituted ureas.<sup>2</sup> They used a hypervalent iodine(III) reagent such as PhI(OAc)<sub>2</sub> as the efficient terminal oxidant to operate the postulated the Pd(II)/Pd(IV) catalytic cycle under mild conditions. The bisindolines, annelated indoles, and bipyrrolidines were also prepared by the same

Scheme 1. Bioactive Compounds Bearing Diamino- or Aminohydroxy Units

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catalytic system via the sequential transfer of two sulfonamido groups into bridging internal olefins.<sup>2b</sup>

Lloyd-Jones and Booker-Milburn developed the Pd(II)catalyzed intermolecular 1,2-diamination of conjugated dienes with ureas using oxygen or benzoquinone as the terminal oxidant.<sup>3</sup> The reaction proceeded with excellent

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regioselectivity under mild conditions (60 °C).<sup>3</sup> The Muñiz group also reported the Pd(II)-catalyzed intermolecular diamination of nonactivated terminal olefins to react with two different nitrogen sources such as saccharin and dibenzenesulfonamides using the iodobenzene dipivalate oxidant.<sup>2e</sup> Shi et al. elegantly demonstrated that Cu(I) species can catalyze highly regio- and stereoselective diaminations of conjugated dienes or terminal olefins with a diaziridinone derivative.<sup>4</sup> In addition, Chemler et al. showed that copper(II) acetate promotes the intramolecular diamination of unactivated alkenes to furnish a number of cyclic sulfamides.<sup>5</sup>

Despite the significant advances made in the metalcatalyzed synthesis of vicinal diamines, only a few examples of the corresponding metal-free procedures have been revealed.<sup>6</sup> For instance, Muñiz et al. reported iodonuim  $IPy_2BF_4$  (Py = pyridine)-mediated diamination of alkenes with tethered ureas to afford cyclic ureas at relatively high temperatures (120 °C).<sup>6a</sup> Widenhoefer et al. showed that *N*-iodosuccinimide (NIS) works as an efficient reagent for the intramolecular difunctionalization of *N*-alkenyl ureas.<sup>6b</sup> It is noteworthy that a high level of chemoselectivity was attained by the choice of additives: diamination was operative in the presence of sodium bicarbonate while a AgOTf additive led to alkoxyamination to provide isoureas.

In our continuing efforts to develop efficient, selective C-N bond-forming reactions,<sup>7</sup> we recently investigated the synthetic utility of hypervalent iodine(III) species in the oxidative amination reactions.<sup>8</sup>

In those studies, we found that the reactivity of iodine-(III) oxidants was significantly increased by the action of additives such as Cu(II) species in the intramolecular synthesis of carbazoles starting from *N*-amidobiphenyls.<sup>8b</sup> We also developed intermolecular chemoselective imidation of aryl sp<sup>2</sup> or benzylic sp<sup>3</sup> C–H bonds using the PhI(OAc)<sub>2</sub> oxidant.<sup>8a</sup> In this context, we describe herein *a new advance in the oxidative diamination and aminohydroxylation of the alkenes tethered with disulfonamides, ureas, or hydroxysulfonamides using hypervalent iodine and a halide additive under ambient metal-free conditions.* 

Optimal diamination conditions were sought using **1a**, stilbene bearing two sulfonamido groups at the *ortho*-position,

Table 1. Optimization of the Reaction Conditions<sup>a</sup>



<sup>*a*</sup> Reaction conditions: **1a** (0.1 mmol), iodine(III) oxidant (1.5 equiv), and additive (1.0 equiv) in DMF (1.0 mL) at rt. <sup>*b*</sup> <sup>1</sup>H NMR yield (internal standard: 1,1,2,2-tetrachloroethane).

as a model substrate (Table 1). When 1.5 equiv of PhI- $(OAc)_2$  was added alone in DMF, the desired bisindoline product (**2a**) was observed to form in 32% NMR yield at rt (entry 1) to suggest that a metal-free pathway would indeed be possible. This result was surprising in that the role of iodobenzene diacetate (IBDA) was hypothesized to operate in only the Pd(II)/Pd(IV) cycle in the diamination method developed by Muñiz et al.<sup>2</sup> Therefore, this result lead us to postulate a different role of IBDA in the present case.

We tried to search for a more satisfactory diamination procedure, especially under metal-free conditions. Unlike our previous studies wherein electronically more electrophilic bis(trifluoroacetoxy)iodobenzene (PIFA) displayed higher reactivity compared to IBDA in the cabazole synthesis,<sup>8b</sup> PIFA was ineffective in the present reaction (entry 2). Different sources of iodine oxidants or *m*-CPBA resulted in lower efficiency (entries 2–5).

To improve the reaction efficiency, we subsequently investigated the additive effects of Lewis acids or other plausible promotors. Although certain Lewis acids were previously known to increase the reactivity of hypervalent iodine(III) oxidants,<sup>9</sup> metallic or nonmetallic Lewis acids were almost ineffective in our case (entries 6–7). In contrast, the addition of NaCl or NaI resulted in a notable enhancement of the reaction efficiency (entries 8–9)

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whereas the effect of NaF or NaOAc was negligible (entries 10-11).<sup>10</sup> The highest additive effect was observed with tetrabutylammonium chloride (entry 12) or KI (entry 13). No conversion was achieved with *n*-Bu<sub>4</sub>NCl alone in the absence of the iodine(III) oxidant (entry 14).



Scheme 2. Reactivity Dependence on the N-Substituent Groups

As anticipated, it was observed that the choice of N-substituents of substrates dramatically influenced the reaction efficiency (Scheme 2). While unsubstituted 2,2'-diamino-(E)-stilbene was totally inert, substrates bearing N-acetyl or N-(*tert*-butyloxycarbonyl) (Boc) groups were partially decomposed under the employed conditions. In contrast, N-sulfonamido stilbenes were readily cyclized to afford the corresponding bisindolines, and the reactivity was dependent on the type of sulfonamides. Among those examined, the highest product yield was obtained with a substrate bearing a N-benzenesulfonamido group followed by N-Ts and N-Ns compounds.

Stereochemical assignment of the obtained compounds was based on the <sup>1</sup>H NMR coupling constants. The coupling constants of the isolated bisindoline products (2a-2c) were measured to be 6.9–8.5 Hz, matching the values of known *syn*-isomers (J = 7-10 Hz). In the case of the corresponding *trans*-isomers, *J*-values are known to be in the range 0–2 Hz.<sup>12</sup> In addition, other spectroscopic data of the isolated bisindolines and ureas completely matched those previously reported.<sup>2a,b</sup>

Under the above optimized conditions using the PhI- $(OAc)_2$  oxidant (1.5 equiv) and *n*-Bu<sub>4</sub>NCl additive (1.0 equiv), a range of substrates were subsequently examined to study the feasibility of the present reaction (Table 2). The position of substituents in the arene part did not significantly influence the reaction efficiency as demonstrated by entries 2 and 3. The bisindoline products were isolated in high yields regardless of the electronic variation on substrates employed. Indeed, the introduction of electron-withdrawing substituents such as fluoro or ester groups did not diminish the reaction efficiency (entries 4 and 5, respectively). With the use of a naphthalene-derived substrate, the cyclization took place smoothly to furnish the corresponding product in good yield (entry 6). An unsymmetrical bisindoline skeleton having

Table 2. Diamination and Aminohydroxylation of Alkenes<sup>*a,b*</sup>



<sup>&</sup>lt;sup>*a*</sup> Reaction conditions: substrate (0.1 mmol), PhI(OAc)<sub>2</sub> (0.15 mmol), and *n*-Bu<sub>4</sub>NCl (0.1 mmol) in DMF (1.0 mL) at rt for 6 h. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) was used as solvent. <sup>*d*</sup> KI (1.0 equiv) was used instead of ammonium salt.

two different aryl parts was obtained without difficulty in high yield (entry 7).

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A urea functional group was widely used as a nitrogen source in the intra- or intermolecualr olefin diamination reactions under Pd catalysis<sup>3,6a</sup> or Lewis acid mediated conditions.<sup>11</sup> We, therefore, prepared several alkenyl ureas, and those substrates were subjected to the optimized conditions. We were pleased to observe that the desired diamination reactions occurred readily to afford 5,5- and 5,6fused bicyclic urea products in satisfactory yields (entries 8-11). Not only terminal olefins but also internal double bonds particiapted in the oxidative cyclization with similar efficiency (entry 11).

With our great delight, the above diamination protocol was successfully applied to the aminohydroxylation reaction of stilbenes substituted with a hydroxyl and sulfonamide group at the *ortho*-position. Under identical reaction conditions, saturated benzofuroindole products were obtained in moderate to high yields (entries 12-14). To the best of our knowledge, this example represents the first aminohydroxylation reaction of those substrates under metal-free conditions.<sup>13</sup>

## Scheme 3. In Situ IOAc Generation Test



In the oxidative olefin aziridination using the iodine(III) oxidant and halide additives, it was postulated that acetyl hypohalite was generated under *in situ* conditions and the species was assumed to activate the substrate's double bonds more efficiently.<sup>10,14</sup> To examine the validity of this mode of activation in our present reactions, preliminary studies were next performed (Scheme 3).<sup>15</sup> While no conversion was observed by the single action of I<sub>2</sub> (conditions A), the addition of PhI(OAc)<sub>2</sub> resulted in significantly increased reactivity (conditions B) which was much higher than that obtained from conditions C using PhI(OAc)<sub>2</sub> alone.

A proposed pathway of the present diamination and aminohydroxylation reactions is shown in Scheme 4. It is Scheme 4. Proposed Mechanistic Pathway



assumed that  $PhI(OAc)_2$  initially reacts with a halide to give a halide-exchanged halonium species **A** which is subsequently converted to active acetyl hypohalite **B**.<sup>14</sup> It is postulated that olefin is halogenated upon electrophilic addition of the double bond by **B** to afford a halonium intermediate **C**. However, instead of forming the hypohalite species **B**, the possibility that Ph-I-OAc generated by IBDA can react with olefin to afford the halonium intermediate **C** cannot be completely ruled out at this stage.<sup>16</sup> An intramolecular addition of a sulfonamido group into the halonium carbon center yields an aminohalogenated intermediate **D** which subsequently undergoes an S<sub>N</sub>2 replacement reaction finally leading to *syn*-products with complete selectivity.

In conclusion, we have developed a facile procedure for intramolecular oxidative diamination of olefins. The reaction proceeds at ambient temperature under metal-free conditions. For the first time, aminohydroxylation was also achieved using alkenes tethered with nitrogen and oxygen atom sources. The halide additive was crucial for exerting the high reactivity of the iodobenzene diacetate oxidant to generate an active hypohalite species.

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**Supporting Information Available.** Experimental details, and <sup>1</sup>H and <sup>13</sup>C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.