Organic LETTERS

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Alkene Diamination Using Electron-Rich Amines: Hypervalent Iodine-Promoted Inter-/Intramolecular C–N Bond Formation

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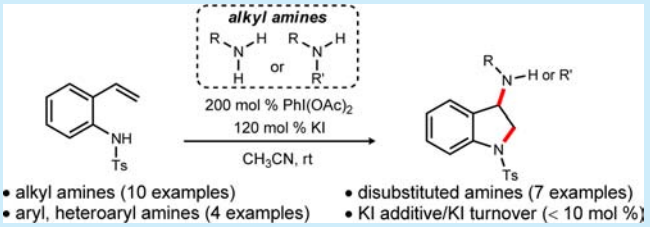
Supporting Information

ABSTRACT: A combined inter-/intramolecular oxidative diamination of terminal alkenes is described that uses a hypervalent iodine oxidant and a nucleophilic amine to produce 3-aminoindolines at room temperature. This operationally straightforward and metal-free protocol is compatible with a broad range of functional groups. A mechanism involving the conversion of the amine to an electrophilic nitrogen source is advanced and used to identify a protocol effective with substoichiometric amounts of iodide and commercially available phenyl iodobenzene diacetate (PIDA) as the stoichiometric oxidant.



The *vic*-diamine is a functional group array frequently encountered in biologically active small molecules, ligands for metallic catalysts, and organocatalysts.[1] Strategies for *vic*-diamine preparation range from the stereocontrolled formation of the central carbon–carbon bond[2,3] to the diamination of carbon–carbon π-bonds (e.g., Figure 1A).[4−8] Insofar as most *vic*-diamines are nonsymmetric, the regio- and stereocontrolled diamination of unsymmetrical alkenes is highly valued (Figure 1B).[9] Numerous nitrogen sources have been developed for this purpose, including *N*-aryl/alkyl sulfonamides,[10] nitronium/nitrile,[11] azide,[12] dialkylamine,[13] strained acyl hydrazides,[14] and amide derivatives.[15] More rare is the use of electron-rich, nucleophilic amines (chloramine formed in situ, Figure 1C).[13,16−18] To activate these nitrogen sources, protocols have been explored as a prelude for stereocontrolled catalysis, mostly reliant on metals (e.g., osmium, palladium, nickel, gold).[19] Herein, we report a metal-free alkene inter-/intramolecular diamination using electronically differentiated amines and a hypervalent iodine reagent. A method for regioselective diamination is described for the formation of 3-aminoindoline scaffolds that utilizes a combination of electron-deficient sulfonamide and electron-rich alkylamine nitrogen sources.

Recent progress in alkene diamination has involved both metal-catalyzed and metal-free intra-/intermolecular approaches (Figure 1).[19] For example, Muniz reported the Pd(II)/Pd(IV)-catalyzed intramolecular oxidative diamination of a tethered unactivated alkene with a sulfonylated urea.[20] The same method was used for the preparation of a bisindoline via the sequential transfer of two sulfonamide groups to an internal alkene.[6] Chang developed a metal-free transformation using hypervalent iodine and halide additive.[7] Diamination of unactivated alkenes using a single tethered nitrogen in combination with a second nitrogen source delivered intermolecularly was demonstrated separately by Chemler[9] and Michael.[21]

Our goal was to identify a means to effect alkene diamination using nitrogen donors that might offer complementarity in reactivity. Electron rich, Brønsted basic amines would be particularly valuable additions in this regard, but not generally considered compatible with oxidative conditions or late-transition-metal promoters. Our initial approach was directed at the formation of an electrophilic *N*-iodamine from a monosubstituted amine and *N*-iodosuccinimide (NIS), combined with a styrene bearing a sulfonamide tether (Table 1). Using cyclopentylamine, this experiment furnished the desired 3-aminoindoline **2** in 75% yield (Table 1, entry 1). As an alternative to NIS, and based on literature precedent for activation of inorganic halide by hypervalent iodine oxidant,[22] a combination of phenyl iododiacetate (PIDA) and halide source was examined next.[23] Use of stoichiometric tetrabutylammonium iodide or ammonium iodide (Table 1, entries 2 and 3) led to similar yields of indoline product. When oxidant or iodide were used alone, however, no product consumption was observed under otherwise identical conditions (Table 1, entries 4–6). Chloride or bromide in combination with PIDA was found to be inferior (Table 1, entries 7 and 8). PIDA in combination with potassium iodide was ultimately superior to NIS alone by consideration of cost and purification.

The use of PIDA (2 equiv) and KI (1.2 equiv) provided the broadest possible scope when examining a range of substrates (Table 2). While focusing on electron-rich monosubstituted alkyl amines, a wide degree of chemoselectivity was observed, highlighted by amines bearing a terminal alkene (Table 2, entry 2), a pyridine (Table 2, entry 4), and an oxetane (Table 2, entry 8). A series of aliphatic amines also provided similar results (Table 2, entries 1, 5–7), although *tert*-butylamine resulted in

Received: June 11, 2014
Published: July 1, 2014

dx.doi.org/10.1021/ol501693j | *Org. Lett.* 2014, 16, 3804–3807

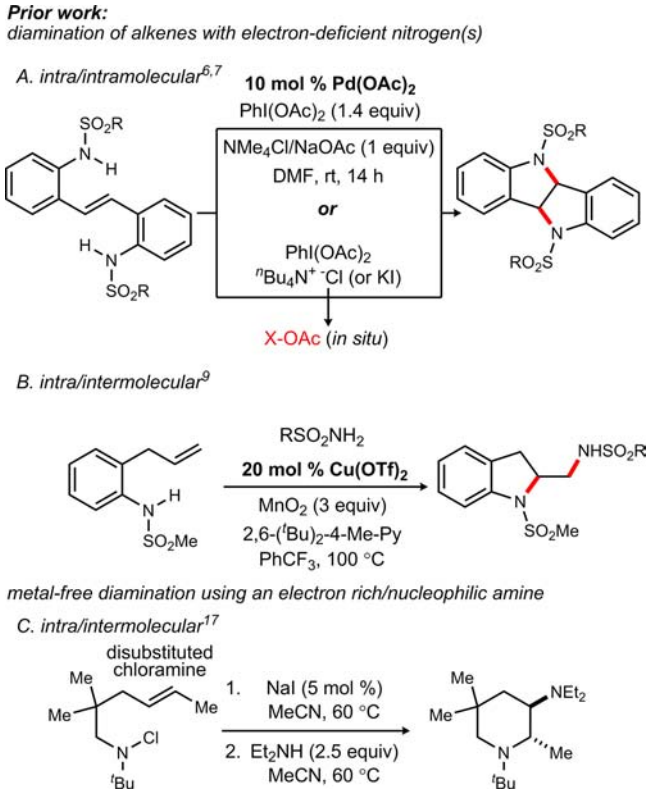
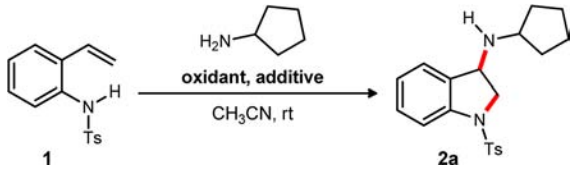


Figure 1. Overview of alkene diamination using metal or metal-free conditions.

Table 1. Hypervalent Iodine-Mediated Diamination



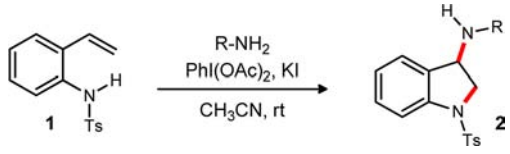
entry[a]	oxidant (equiv)	additive (equiv)	conversion[b] (%)	yield[c] (%)
1	–	NIS (1.2)	100	75
2	$PhI(OAc)_2$ (2)	nBu_4NI (1)	100	64
3	$PhI(OAc)_2$ (2)	NH_4I (1)	100	66
4	$PhI(OAc)_2$ (2)	–	10	–
5	–	nBu_4NI (1)	0	–
6	–	KI (1)	0	–
7	$PhI(OAc)_2$ (2)	nBu_4NCl (1)	16	–
8	$PhI(OAc)_2$ (2)	KBr (1)	14	–
9	**$PhI(OAc)_2$ (2)**	**KI (1.2)**	**100**	**83**

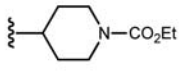
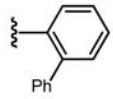
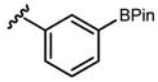
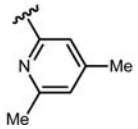
[a]All reactions were performed on an 0.18 mmol scale (0.1 M) and a standard 18 h reaction time. [b]Conversion was determined by ^1H NMR using CH_2Br_2 as an internal standard. [c]Isolated yield.

only 20% yield of **2j** (Table 2, entry 9). Also notable is the ability to engage arylamines (anilines) in efficient diamination (Table 2, entries 10−12), although 2-aminolutidine provided the product in only 42% yield (Table 2, entry 13). The reaction with aniline gave the desired indoline **2k** in 68% yield (Table 2, entry 10).

Disubstituted amines were also examined (Table 3). Cyclic amines, including pyrrolidine, isoindoline, and an isoquinoline, were tolerated (Table 3, entries 1−3), with yields ranging from 64 to 73%. Representative heterocycles also tolerated the oxidative conditions (Table 3, entries 4 and 5), providing a 78%

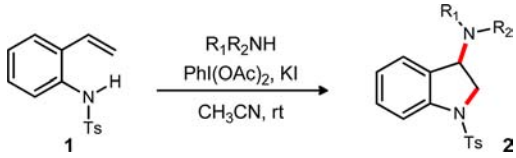
Table 2. Alkene Diamination Using Monosubstituted Amines[a]



entry	2	R	yield (%)[b]
1	**b**	Bn	64
2	**c**	allyl	78
3	**d**	$CH_2CH_2CH_2OMe$	72
4	**e**	C_7H_9N	62
5	**f**	cyclohexyl	73
6	**g**	Ph_2CH	57
7	**h**		91
8	**i**	C_3H_5O (3-oxetanyl)	94
9	**j**	*tert*-Bu	20
10	**k**	Ph	68
11	**l**		79
12	**m**		79
13	**n**		42

[a]All reactions were performed on a 0.18 mmol scale using 1 equiv of the olefin, 2.0 equiv of PIDA, 1.2 equiv of KI, and 2.0 equiv of amine in CH_3CN (0.1 M) at rt for 18 h. [b]Isolated yield.

Table 3. Alkene Diamination Using Disubstituted Amines[a]



entry	2	R	yield[b] (%)
1	**o**	C_4H_8 (pyrrolidine)	67
2	**p**	C_8H_8 (isoindoline)	73
3	**u**	C_9H_{10} (tetrahydroisoquinoline)	64
4	**q**	C_4H_8O (morpholine)	78
5	**r**	C_4H_8S (thiomorpholine)	72
6	**s**	$C_{14}H_{14}$ (dibenzylamine)	82
7	**t**	C_9H_{10} (*N*-allylaniline)	59

[a]All reactions were performed on a 0.18 mmol scale using 1 equiv of the olefin, 2.0 equiv of PIDA, 1.2 equiv of KI, and 2.0 equiv of amine in CH_3CN (0.1 M) at rt for 18 h. [b]Isolated yield.

and 72% yield for morpholine and thiomorpholine, respectively. Dibenzylamine and *N*-allylaniline resulted in an 82% and

dx.doi.org/10.1021/ol501693j | Org. Lett. 2014, 16, 3804−3807

59% yield, respectively, for the diaminated alkene (Table 3, entries 6 and 7).

A plausible reaction mechanism is depicted in Figure 2. A key question is the source of synergism between iodide and I(III)

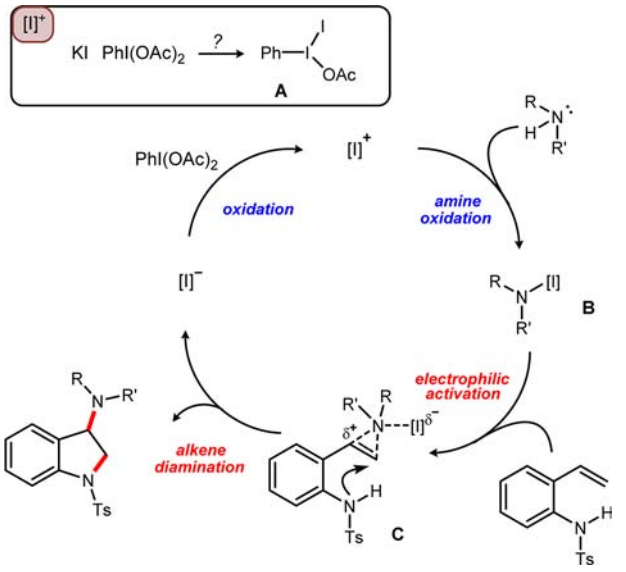


Figure 2. Proposed mechanistic pathway.

oxidant. One possibility is the formation of an electrophilic iodinating agent (e.g., **A**). The success of NIS in this transformation suggests that formation of an iodamine or similarly electrophile-activated amine (**B**) is a key pathway in the reaction. Association of **B** with the alkene would lead to **C**, an intermediate that could succumb to cyclization and formation of 3-aminoindoline.[24] Control experiments do not clearly support a canonical cyclic iodonium intermediate or an alkene amino-halogenation.[13,17] In contrast to prior work with electron-rich alkenes, neither diamination product nor a *vic*-aminoiodide were detected when a non-nucleophilic amine was used.[13] Instead, a 3-acetoxyindoline was isolated and determined to be noncompetent as an intermediate to **2a**.[25] Further evidence in support of a mechanism somewhat unique to prior metal-free oxidative approaches is the broad amine scope[17] and use of a nonactivated alkene.[13,22] No evidence for amine → imine or indoline → indole oxidation was observed in these studies.

One consequence of this general mechanistic outline is the consumption of iodide and its subsequent regeneration, implying the existence of a catalytic cycle. Indeed, experiments to probe the relationship of iodide loading to isolated yield clearly indicate turnover under these conditions (Figure 3, eq 1). This alluring behavior notwithstanding, the general use of stoichiometric potassium iodide in the studies outlined above valued equally the yield and scope of the reaction over a common, generally effective time. Whether the iodide activates the iodonium reagent through the formation of a complex, or is itself recycled through an iodide−iodonium couple, is a question that will be addressed by future studies.

In summary, we have developed a hypervalent iodine(III)-assisted, combined inter-/intramolecular diamination reaction. The transformation provides direct entry to diverse 3-aminoindoline derivatives and engages both mono- and disubstituted amines. This unique approach effects metal-free diamination of alkenes using a combination of electron-rich and

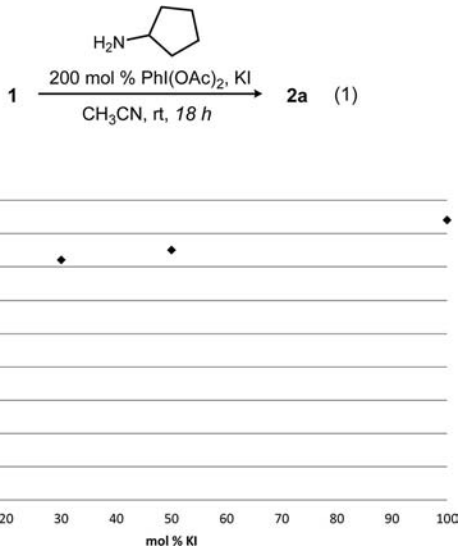


Figure 3. Evidence for iodide turnover in the PIDA-promoted diamination of **1**. (a) A standard reaction time of 18 h was established. Note: Data points in red are estimated yields using CH_2Br_2 as an internal standard (^{1}H NMR, crude reaction mixture); black diamonds refer to isolated yields.

electron-deficient (aryl sulfonamide) nitrogen sources without amine preactivation or protection.

■ ASSOCIATED CONTENT

Supporting Information

Complete preparatory and analytical data for all new compounds. 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.

■ ACKNOWLEDGMENTS

We are grateful to the National Science Foundation (CHE 1153003) for support of this work.

■ DEDICATION

This paper is dedicated to Professor Tae Hee Hong (Daejeon Health Sciences College) on the occasion of his 70th birthday.

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(25) See the Supporting Information for this and other control experiments.

NOTE ADDED AFTER ASAP PUBLICATION

Figure 1 contained errors in the version published ASAP on July 2, 2014, the correct version reposted on July 3, 2014.