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Oxidative Inter-/Intermolecular Alkene Diamination of Hydroxy Styrenes with Electron-Rich Amines

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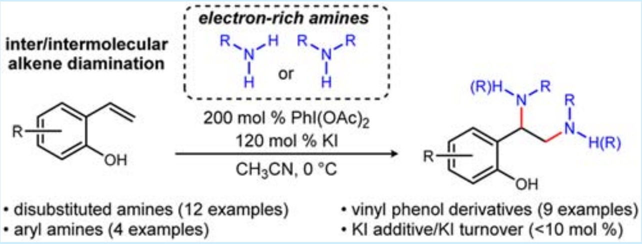
Supporting Information

ABSTRACT: Doubly intermolecular alkene diamination is achieved with electron-rich, terminal alkenes through the use of a hypervalent iodine ($PhI(OAc)_2$) reagent, iodide, and electron-rich amines. Mono- and disubstituted amines combine with electron-rich alkenes, particularly *o*-hydroxystyrenes, to achieve the greatest level of generality. This operationally straightforward protocol, unreliant on conventional metal-based activation, is compatible with a broad range of functional groups.



- disubstituted amines (12 examples)
- aryl amines (4 examples)
- vinyl phenol derivatives (9 examples)
- KI additive/KI turnover (<10 mol %)

As a general approach to *vicinal* diamines, alkene diamination is particularly expedient.[1] Activation methods directed at either alkene or amine have been dominated by transition-metal-based protocols, including palladium, copper, nickel, and gold.[2] Notably, Muñiz demonstrated the diamination of unactivated alkene employing high-oxidation-state palladium catalysis and the use of saccharin and bistosylamine (an imide) as nitrogen sources (Figure 1).[3] More recently, metal-free protocols have emerged, and halonium[4] and hypervalent iodine reagents are becoming more broadly effective.[5,6] The latter are particularly effective in aminations using non-nucleophilic amine sources, such as sulfonamide or sulfonimide, including a single enantioselective method.[7] Natural products exhibiting the *vic*-diamine functionality are often either alkyl- or arylamines. Moreover, nucleophilic, electron-rich amines are plentiful from a commercial standpoint. Their use, however, in doubly intermolecular carbon−nitrogen bond formation without metal coordination is rare.[8] Based on the finding that suitably electron-rich alkenes are effective partners for I(III)-based amine activation, we report the first doubly intermolecular homo-diamination of terminal alkenes (Figure 1).

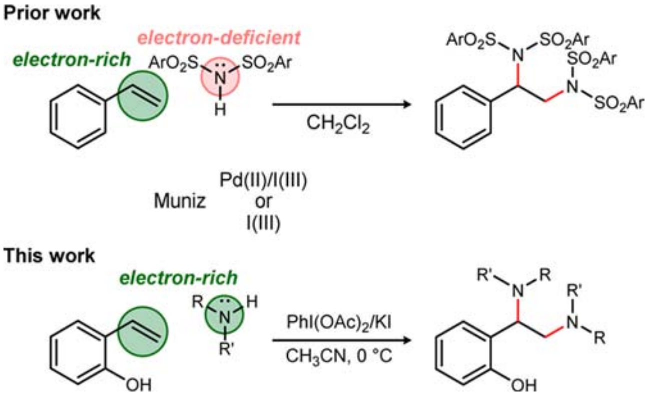


Figure 1. State-of-the-art approaches: intermolecular alkene diamination.

A key motivation to investigate electron-rich alkene/nucleophilic amine combinations was the selectivity achieved by an iodine(III) reagent with two substrates in an inter-/intramolecular alkene diamination.[9] Further extension of this selectivity to three substrates (one alkene, two amines, each capable of direct oxidation[10,11]) would demand more exquisite control.

Doubly intermolecular diamination could leverage PIDA-mediated electrophilic activation of amines to generate the putative *N*-iodamine or an electrophilic amine equivalent. However, nucleophilic amine must remain available to intercept the alkene−*N*-halamine complex. The specific strategic aim in this instance was to explore the possibility of an intermolecular alkene diamination using iodide as a precursor to iodonium, in combination with PIDA as a stoichiometric oxidant (Table 1, method A). These exploratory studies used stoichiometric iodide to ensure the highest concentration of electrophilic iodine and, vis-à-vis, the putative electrophilic amine. Although nucleophilic alkenes would be preferred on the basis of this mechanistic hypothesis, the potential for their direct oxidation by PIDA oriented these investigations first to terminal aliphatic alkenes. In the event, benzylethylene (**1a**) returned only thiopmorpholine after exposure to PIDA/KI (Table 1, entry 1).[12] Although NIS (Table 1, method B) was inferior to PIDA/KI by direct comparison in previous studies, it remains an ideal reagent for the production of *N*-iodamine.[13] Unfortunately, it also failed to effect conversion of **1a** (Table 1, entry 2). Nitrostyrene (**2a**) was evaluated as an alkene that benefits from conjugation while being resistant to direct oxidation by PIDA. This, too, failed to convert

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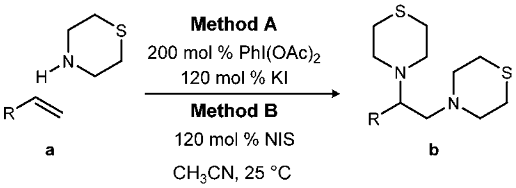
Table 1. Diamination of Terminal Alkenes[a]



entry	R	a/b	method	modified *T* (°C)	yield[b] (%)
1	$PhCH_2$	**1**	**A**	→ 65	–
2	$PhCH_2$	**1**	**B**	→ 65	–
3	*o*-$NO_2C_6H_4$	**2**	**A**	→ 65	–
4	*o*-$NO_2C_6H_4$	**2**	**B**	→ 65	–
5	Ph	**3**	**A**	→ 65	–
6	Ph	**3**	**B**	→ 65	–
7	*o*-HO-C_6H_4	**4**	**A**	–	78
8	*o*-HO-C_6H_4	**4**	**A**	0	99
9	*o*-HO-C_6H_4	**4**	**B**	–	74
10	*o*-HO-C_6H_4	**4**	**B**	0	91
11	*p*-HO-C_6H_4	**5**	**A**	–	51
12	*p*-HO-C_6H_4	**5**	**A**	0	62
13	*p*-HO-C_6H_4	**5**	**B**	–	40
14	*p*-HO-C_6H_4	**5**	**B**	0	50
15	*o*-MeO-C_6H_4	**6**	**A**	→ 65	–
16	*o*-MeO-C_6H_4	**6**	**B**	→ 65	–

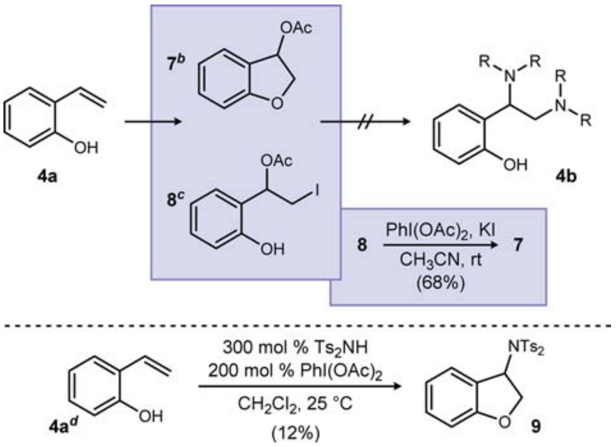
[a] All reactions were performed on a 300 μmol scale using 3 equiv of amine in CH_3CN (0.1 M) with a standard 18–24 h reaction time. [b] Isolated yield. In cases where no yield is listed, unreacted thiomorpholine was observed and could be recovered, except for entries 15 and 16 (thiomorpholine decomposition observed).

(Table 1, entries 3 and 4). Styrene (**3a**) and *o*-hydroxystyrene (**4a**) were then evaluated using these protocols, increasing the nucleophilicity of the alkene. While styrene appeared unreactive (Table 1, entries 5 and 6), *o*-hydroxystyrene provided the desired diamination product **4b** in 78% yield (Table 1, entry 7). The yield could be further improved by lowering the reaction temperature (Table 1, entry 8).

Each method (A and B) delivered **4b** in good yield, with no evidence for direct oxidation or iodination of **4a**. As a result, increasingly electron-rich alkenes were explored. *p*-Hydroxystryene also delivered the inter/inter diamination product (**5b**) using both methods (Table 1, entries 11 and 13) and with improved yield at lower temperature (Table 1, entries 12 and 14). This reactivity was mitigated, however, when *o*-vinylanisole (**6a**) was used, with no conversion despite the application of higher temperature (Table 1, entries 15 and 16). Several experiments differentiated PIDA/KI from the existing oxidative methods. In this respect, it is noteworthy that *ortho*-substituted styrenes generally performed poorly using Muniz's diamination conditions.[6,14] Additionally, the electron-deficient amine bis(tosylimide) was unreactive using either method A or B.

Several potential key intermediates in the conversion of **4a** to **4b** were isolated in small quantities throughout the course of these exploratory and optimization studes. Chief among these are the bis(oxygenation) (**7**) and iodoacetoxylation (**8**) products (Scheme 1). Neither of these is observed directly during the use of method A or B for the conversion of **4a** to **4b**. When no amine is used with method A, acetate **7** is the major product, isolated in 68% yield. Iodide **8** was first isolated (12% yield) when method A was combined with the electron-deficient Ts_2NH. These products were observed alongside unreacted **4a** and other minor unidentified decomposition products (^1H NMR).

Scheme 1. Isolation of Potential Intermediates and Study of Their Behavior[a]



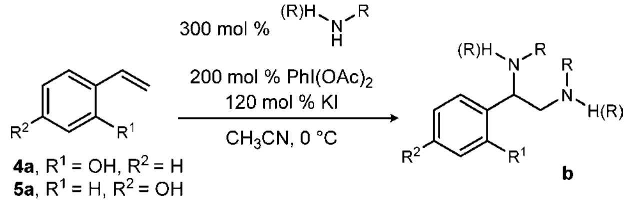
[a] All reactions were performed on a 300 μmol scale at room temperature with a standard 18–24 h reaction time. [b] 2.0 equiv of PIDA and 1.2 equiv of KI used in CH_3CN (0.1 M). [c] 2.0 equiv of PIDA, 1.2 equiv of KI, and 3.0 equiv of Ts_2NH in CH_3CN (0.1 M). [d] 1.2 equiv of PIDA and 2.4 equiv of Ts_2NH in CH_2Cl_2 (0.1 M).

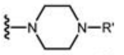
Importantly, neither **7** nor **8** generates the diamination product **4b** when subjected to method A conditions. Phenol **8** converts to **7** when exposed to PIDA/KI in the absence of amine or when treated with amine alone.

These products appear to collectively arise from electrophile addition to the terminal carbon, followed by nucleophile addition to the benzylic carbon. We speculate that carbon—nitrogen bond formation via an electrophilic amine formed in situ is a key aspect of the actual mechanism leading to diamine **4b**. Non-nucleophilic amines such as Ts_2NH, those used in palladium-mediated diamination, did not provide diamination product, instead leading to monoamination product **9**, perhaps through a pathway analogous to **4a** → **8** → **7**. This result is also consistent with the unique reactivity of an electrophilic amine using the PIDA/KI protocol.[14]

Subsequent studies specifically applied the protocol using KI/PIDA (Table 2) and the most reactive styrene to explore the amine scope of the intermolecular diamination; NIS yields were consistently 5−10% lower than PIDA/KI, although often still high. A broad range of di- and monosubstituted amines (Table 2) were included, and preliminary experiments reaffirmed the superiority of acetonitrile solvent, relative to CH_2Cl_2, toluene, THF, and dioxane. Diamination with morpholine led to **10b** in 79% yield (Table 2, entry 2). Piperidine led to *vic*-diamine **11b**, but with depressed yield (Table 2, entry 3). Isoindoline, a pyrrolidine derivative, performed similarly (Table 2, entry 4). *N*-Protected piperazines led to diamination products in moderate (59%) to good (90%) yield (Table 2, entries 5−7), allowing for subsequent unmasking of the piperazine under neutral, acidic, or basic conditions. *N*-Arylpiperazines, however, led to complex mixtures exhibiting signs of amine decomposition (Table 2, entries 8 and 9). This may be related to the presence of an electron-rich aniline, since *N*-cinnamylpiperazine (Table 2, entries 10) provided a 94% yield of diamine **18b**. Acyclic disubstituted amines engaged in diamination in low to moderate yield (Table 2, entries 11 and 12). A hypothesis about the elecron-rich nature of *N*-arylpiperazines (Table 2, entries 8 and 9) was weakened by the finding that anilines would lead to diamines **21b−24b** in 47−60% yield (Table 2, entries 13−16). *p*-

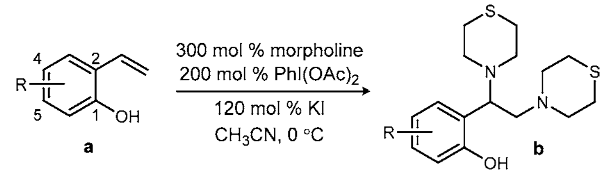
Table 2. Intermolecular Alkene Diamination: Amine Scope[a]



entry	a	b	R	yield (%)[b]
1	4	4	C_4H_8S (thiomorpholine)	99
2	4	10	C_4H_8O (morpholine)	79
3[c]	4	11	C_5H_{10} (piperidine)	29
4	4	12	C_8H_8 (isoindoline)	30
5	4	13	 R′ = Cbz	62
6[d]	4	14	R′ = Boc	59
7	4	15	R′ = CO_2Et	90
8	4	16	R′ = Ph	31
9	4	17	R′ = ${}^{m}MeOC_6H_4$	16
10	4	18	R′ = $CH_2CHCHC_6H_5$	94
11	4	19	$C_{14}H_{14}$ (dibenzylamine)	35
12	4	20	Me, Bn (*N*-methylbenzylamine)	65
13[e]	4	21	Ph	60
14[e]	4	22	4-F-C_6H_4	47
15[e]	4	23	4-^{t}Bu-C_6H_4	53
16[e]	4	24	3,5-dimethyl-C_6H_3	60
17	5	5	C_4H_8S (thiomorpholine)	62
18	5	25	C_4H_8O (morpholine)	59
19[e]	5	26	Ph	85

[a] All reactions were performed on a 300 μmol scale using 1 equiv of the olefin, 2.0 equiv of PIDA, 1.2 equiv of KI, and 3.0 equiv of amine in CH_3CN (0.1 M) at 0 °C for 18 h. [b] Isolated yield. [c] 3.0 equiv of PIDA used. [d] 2.1 equiv of amine used. [e] Reaction temperature = 25 °C.

Table 3. Alkene Diamination: Additional Styrene Scope[a]



entry	a/b	R	yield[b] (%)
1	**27**	4-F	83
2[c]	**28**	4-Cl	64
3[c]	**29**	4-Br	70
4	**30**	4-NO_2	50
5	**31**	4-MeO	54
6	**32**	4-HO	23
7	**33**	5-MeO	57
8	**34**	6-MeO	83

[a] All reactions were performed on a 300 μmol scale using 1 equiv of the alkene in CH_3CN (0.1 M) at 0 °C for 18 h. [b] Isolated yield. [c] 3.0 equiv of PIDA used.

Hydroxystyrene was also an effective precursor to *vic*-diamines, exemplified by reactions with thiomorpholine (62% yield), morpholine (59% yield), and aniline (85% yield) (Table 2, entries 17−19).

Modifications to the vinylphenol were explored further, specifically with thiomorpholine, exposing further generality (Table 3). Halogen substituents at the 4-position (**27a**−**29a**) were tolerated, leading to the diamination products **27b**−**29b** in good yield (Table 3, entries 1−3). Substituents serving to withdraw (**30a**) and donate (**31a**) electronically at the 4-position led to similar yields of diamination (50% and 54%, respectively, Table 3, entries 4 and 5). Diamination of hydroquinone **32a** was possible, albeit in low yield (23%, Table 3, entry 6). Two additional electron-rich styrenes (**33a**−**34a**) delivered their diamination product (**33b**−**34b**) in moderate to good yields (Table 3, entries 7 and 8).

While these studies employed a full equivalent of KI in order to apply general conditions to a broad collection of substrates, a series of experiments were designed to vary KI loading in a diamination of **4a** with thiomorpholine. This revealed once again that 10 mol % KI can be sufficient to achieve a good yield (74%) of **2**.[14]

The hydroxy substituent is clearly enabling, but short of essential.[15] The success with *p*-hydroxystyrene argues against a directing effect, and other functional groups that might direct amination, such as a benzyl alcohol or carboxylic acid, were explored. These led to recovery of the alkene unchanged.[14]

Overall, the electronic picture of an *o*-quinone methide intermediate may be optimal for the experimental protocol used in this transformation,[16] but some diamination product formation in cases where such an intermediate is not possible indicates that it is not essential. We have speculated in prior work that PIDA may function by activation of the amine vicariously through iodamine formation or perhaps more directly by associating with the amine to modulate its reactivity as an electrophilic nitrogen source.[9] The latter picture appears to prevail in work using electron-deficient amine sources.[17] The success of NIS in the exploratory work (Table 1) indicates that the role here could be simply the former, as outlined in Figure 2. The importance of a phenol substrate arises in the transition state leading to **35**, and the electron-donating ability could extend further into the subsequent reaction with amine by weakening any degree of benzylic carbon−nitrogen bond formation. Remarkable, however, is the resistance of the phenolic aromatic

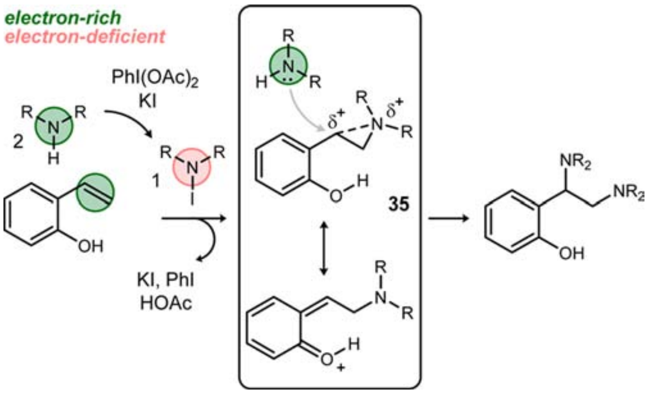


Figure 2. Mechanistic hypothesis for PIDA/KI-mediated intermolecular diamination.

ring, including more electron-rich versions (e.g., **32a**) to both direct aromatic ring oxidation and halogenation.

In summary, we have developed the I(III)/iodide-mediated inter/intermolecular oxidative alkene diamination reaction using *o*- and *p*-hydroxystyrenes with a wide range of commercially available amine sources. The overall transformation provides immediate access to a diverse range of of *vic*-diamines based on commercially available amines. This is accomplished despite the potential for aromatic ring oxidation[10] or halogenation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Complete preparatory and analytical data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01177.

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Notes

The authors declare no competing financial interest.

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