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Hypervalent-Iodine(III)-Mediated Tandem Oxidative Dearomatization/Aziridination of Phenolic Amines: Synthesis of Functionalized Unactivated Aziridines

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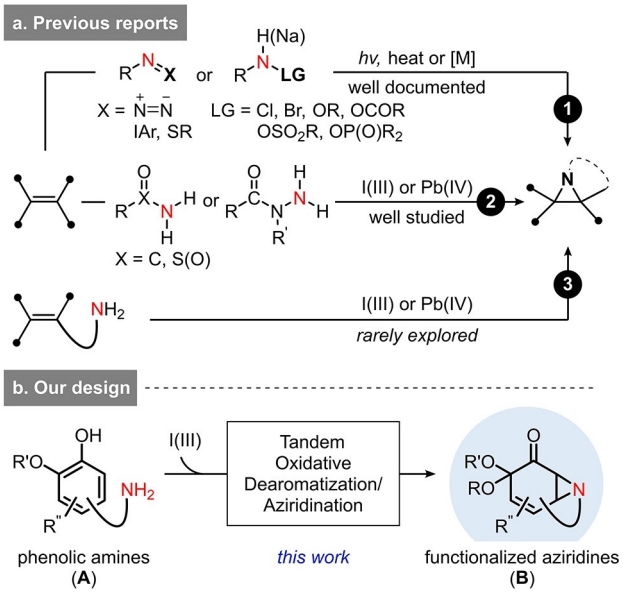
Abstract: A new hypervalent-iodine(III)-mediated tandem reaction involving oxidative dearomatization and *in situ* aziridination of phenolic amines is described, providing a mild and effective method for the assembly of structurally interesting and synthetically useful aziridines. Importantly, the densely functionalized aziridines resulting from this unprecedented tandem reaction offer a platform for expeditious access to architecturally diverse aza-heterocycles through transformations initiated by selective ring-opening of aziridines.

Aziridines are a class of nitrogen-functionalized heterocyclic compounds consisting of strained three-membered ring system in organic chemistry.[1] Chemically, the aziridine units not only widely exist in many natural products and drugs (e.g., azinomycin A, miraziridine A, and FR-900482),[1b] but also constitute versatile building blocks for synthesizing a variety of bioactive compounds (e.g., β-lactams, pyrrolizidines, and tetrahydropyridines).[2] Due to the diverse reactivity arising from the intrinsic strain of aziridine moieties, the development of aziridination methodologies has received considerable attentions in the synthetic community.[1,2] As was known, "C2+N1" addition[1,3] employing alkenes and nitrogen sources represents one of the most general approaches toward the construction of aziridines. Among previous reports, several types of nitrogen-based 1,1-dipole synthon equivalents such as azides,[4] iminoiodinanes,[5] sulfilimines,[6] haloamine-T[7] and hydroxylamine derivatives[8] (route 1, Scheme 1a) have been extensively used in the chemistry of aziridination. Alternative methods resulting from *in situ* formation of nitrenoids or nitrenoid-type species by using electronically deficient amine derivatives (e.g., carbamates,[9] sulfonamides,[10] and hydrazides;[11] route 2, Scheme 1a) in the presence of oxidants (e.g., iodine(III) and lead (IV)) have also provided access to the aziridines. Despite much progress in the synthesis of aziridines, the direct aziridination of alkenes through *in situ* oxidation of aliphatic primary amines has rarely been explored from a methodologic point of view (route 3, Scheme 1a).[12] Combining this with the challenge of straightforward azridination using primary amines as well as the significant impact of oxidative phenol dearomatization to the organic synthesis,[13] we recently have designed a new tandem oxidative dearomatization/aziridination reaction of phenolic amines **A** in the presence of hypervalent-iodine(III) (Scheme 1b), thus providing an effective method for the expeditious construction of unactivated polycyclic aziridines **B** highly functionalized with an olefinic moiety and an *ortho*-diketone monoketal unit. Herein, we report our results.



Scheme 1. Previous methods for the synthesis of aziridines and our design.

The model reaction using the phenolic amine **1a** (Table 1), which was readily derived from isovanillin, was initially investigated in the presence of iodobenzene diacetate as oxidant and MeOH as solvent at 0 °C. Along with the quick disappearance of **1a**, the title reaction involving the oxidation of phenol moiety and amino group led to the formation of the structurally

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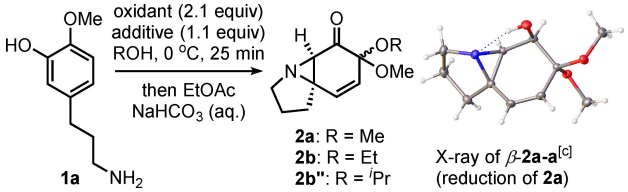
Table 1. The optimization of reaction conditions.[a,b]



Entry	Oxidant	R	Additive	Product	Yield
1	$PhI(OAc)_2$	Me	–	**2a**	32%
2[d]	$PhI(OAc)_2$	Me	Na_2CO_3	**2a**	–[e]
3[d]	$PhI(OAc)_2$	Me	$NaHCO_3$	**2a**	8%[e]
4	$PhI(OAc)_2$	Me	HOAc	**2a**	63%
5	$PhI(OAc)_2$	Me	CF_3CO_2H	**2a**	71%
6	$PhI(OAc)_2$	Me	$4\text{-}MeC_6H_4SO_3H\cdot H_2O$	**2a**	73%
7	$PhI(OAc)_2$	Me	Me_3SiCl/MeOH	**2a**	70%
8	PhIO	Me	$4\text{-}MeC_6H_4SO_3H\cdot H_2O$	**2a**	55%
9	$PhI(CF_3CO_2)_2$	Me	$4\text{-}MeC_6H_4SO_3H\cdot H_2O$	**2a**	67%
10	DMP	Me	$4\text{-}MeC_6H_4SO_3H\cdot H_2O$	**2a**	–[f]
11	IBX	Me	$4\text{-}MeC_6H_4SO_3H\cdot H_2O$	**2a**	–[f]
12	$PhI(OAc)_2$	Et	$4\text{-}MeC_6H_4SO_3H\cdot H_2O$	**2b**	56% (1:1 *dr*)
13	$PhI(OAc)_2$	^{i}Pr	$4\text{-}MeC_6H_4SO_3H\cdot H_2O$	**2b"**	–[f]

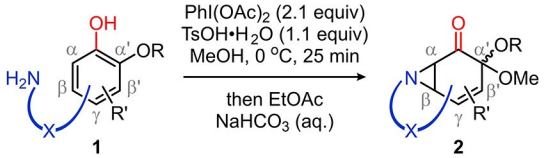
[a] Unless otherwise noted, the reaction was performed with **1a** (0.2 mmol) in the presence of additive (0.22 mmol) and $PhI(OAc)_2$ (0.42 mmol) in MeOH (2.0 mL) at 0 °C. After 25 min, the reaction mixture was diluted with EtOAc (2.0 mL) and quenched with saturated aqueous solution of $NaHCO_3$, and then stirred for 10 min. [b] Yield of isolated product. [c] The stereochemistry of β-**2a-a** as major product was determined by X-ray crystallographic analysis [d] Diluted with EtOAc (2.0 mL) and extracted directly. [e] The starting material disappeared completely, and several unidentified by-products were observed. [f] No desired product was isolated from the complex reaction mixture. DMP=Dess-Martin periodinane, IBX = *o*-iodoxybenzoic acid.

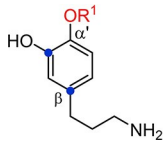
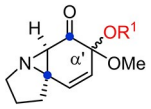
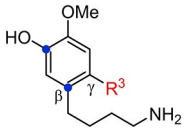
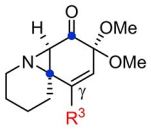
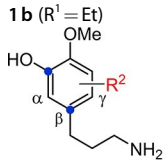
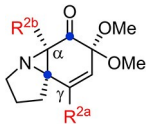
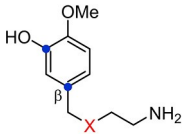
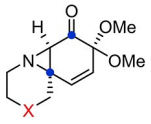
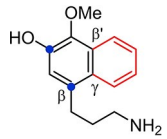
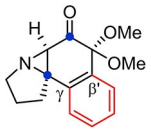
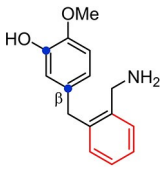
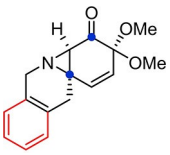
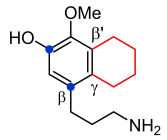
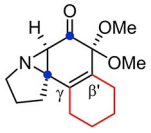
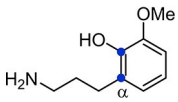
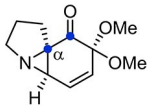
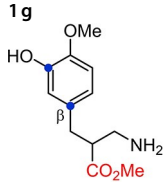
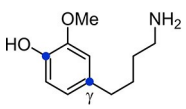
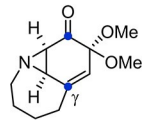
interesting 5,3,6-tricyclic aziridine **2a**, but in a low yield of 32% (entry 1), and its relative configuration was unambiguously determined by X-ray crystallographic analysis of β-**2a-a** resulting from the diastereoselective reduction of **2a**.[14] Considering the chemoselectivity between the phenol motif and the amino unit in model substrate **1a**, some additives were introduced to probe the potential influence of the pH value of reaction system (entries 2–7). Inorganic bases (e.g., Na_2CO_3, and $NaHCO_3$), which could neutralize the HOAc generated *in situ* from the oxidation mediated by $PhI(OAc)_2$, gave a complicated reaction mixture (entries 2 and 3), showing the fact that the acidic medium might be important to the oxidative dearomatization and aziridination. In contrast to the results using basic additives (entries 2 and 3), the employment of a stoichiometric amount of HOAc as acidic additive afforded an improved reaction yield of 63% (entry 4). Pleasingly, the increased acidity of organic additives (CF_3CO_2H, and $TsOH\cdot H_2O$) could give a positive contribution to the reaction yield (entries 5 and 6), in which employing *p*-toluenesulfonic acid as additive obtained the optimal yield of 73% (entry 6). Notably, using the stronger inorganic acid HCl *in situ* formed from TMSCl and MeOH could not further improve the reaction efficiency and only resulted in an analogous yield of 70% (entry 7).

Based on the current optimization of additives (entries 2–7, Table 1), a series of hypervalent iodine reagents were evaluated in the presence of $TsOH\cdot H_2O$ as additive and MeOH as solvent at 0 °C (entries 8–11). Among these oxidants, iodine(III) reagents (PhIO, and $PhI(CF_3CO_2)_2$) were compatible with the current transformation, but the decreased yields of desired aziridine **2a** were obtained (55% and 67%, entries 8 and 9). In contrast to these results, iodine(V) reagents having stronger oxidation ability (Dess-Martin periodinane, and *o*-iodoxybenzoic acid) led to unidentified complex mixture (entries 10 and 11). Following the screening mentioned above, the solvent acting as nucleophile in this oxidative dearomatization was also probed (entries 12 and 13). In addition to MeOH as solvent (entry 6), EtOH was suitable for this model reaction to deliver the aziridine **2b** albeit in a decreased yield of 56% (entry 12). But the bulkier *i*PrOH failed to the formation of the desired aziridine **2b''** (entry 13), demonstrating the unfavorable steric influence of nucleophilic entity in this dearomative transformation.

With the optimized conditions in hand, as shown in Table 2, the substrate scope of tandem oxidative dearomatization/aziridination reaction was investigated. According to the topological connection of the phenol unit and the amino-containing substituent in **1**, a series of *meta*-phenolic amines (**1a**–**1m**) having primary amino pendant group at β position of phenolic core were firstly considered. Compared with the result using model substrate **1a** (R^1 = Me, entry 1), phenolic amine **1b** bearing a slight increased bulkiness of α'-ethoxy group (R^1 = Et, entry 3) yielded the aziridine **2b** with 1:1 *dr*, but in a somewhat decreased yield of 62%. When substrates with γ-substituent group, **1c** (R^2 = γ-prenyl, entry 4) and **1d** (R^2 = γ-Br, entry 5), were subjected to the standard conditions, the expected functionalized aziridines **2c** and **2d** could be obtained in 48% and 67% yields, respectively. In contrast to the case using **1d** with γ-bromo group (R^2 = γ-Br, entry 5), the employment of **1e** with α-bromo group (R^2 = α-Br, entry 6) could not deliver the desired product **2e**, mostly due to the instability of the bromo aziridine **2e**, which was chemically confirmed by the formation of unexpected tetrahydroquinoline **2e-a**[15] through *in situ* one-pot reduction of **2e** and its subsequent elimination and

Table 2. The generality for tandem oxidative dearomatization/aziridination reaction.[a,b]



Entry	Substrate	Product	Yield	Entry	Substrate	Product	Yield
							
1	**1a** (R^1 = Me)	**2a**	73%	10	**1i** (R^3 = H)	**2i**	69%
2		**2a** (gram scale)	69%	11	**1j** (R^3 = Br)	**2j**	55%
3	**1b** (R^1 = Et)	**2b**	62% (1:1 *dr*)				
							
4	**1c** (R^2 = γ-prenyl)	**2c** (R^{2a} = prenyl), R^{2b} = H)	48%	12	**1k** (X=O)	**2k**	52%
5	**1d** (R^2 = γ-Br)	**2d** (R^{2a} = Br, R^{2b} = H)	67%	13	**1l** (X=NTs)	**2l**	58%
6	**1e** (R^2 = α-Br)	**2e** (R^{2a} = H, R^{2b} = Br)	[c]				
							
7	**1f**	**2f**	45%	14	**1m**	**2m**	51%
							
8	**1g**	**2g**	42%	15	**1n**	**2n**	39%
							
9	**1h**	**2h**	65% (1:1 *dr*)	16	**1o**	**2o**	77%

[a] Unless otherwise noted, the reaction was performed with **1** (0.2 mmol) in the presence of additive (0.22 mmol) and $PhI(OAc)_2$ (0.42 mmol) in MeOH (2.0 mL) at 0 °C. After 25 min, the reaction mixture was diluted with EtOAc (2.0 mL) and quenched with saturated aqueous solution of $NaHCO_3$ (2.0 mL), and then stirred for 10 min. [b] Yield of isolated product. [c] For details, see ref. [15].

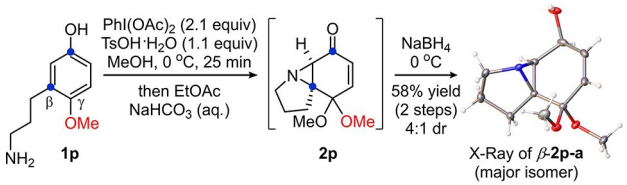
aromatization. Two examples employing phenolic amines **1f** and **1g** with β′,γ-disubstituted subunit smoothly afforded the architecturally interesting 5,3,6,6-tetracyclic aziridines **2f** (entry 7) and **2g** (entry 8) in 45% and 42% yield, respectively.

Following the structural evaluation of substituents at α, γ, α′, β′-position of phenol unit in **1a**–**1g**, the influence of amino-containing pendant group at β position of phenolic core was probed subsequently. The phenolic amine **1h** (entry 9, Table 2) having a remote ester group substituted on the propylamino side chain was suitable to this cascade transformation to provide the corresponding 5,3,6-tricyclic product **2h** in 1:1 *dr* and 65% yield, wherein the potentially competitive lactonization of the ester group was not observed during this oxidative reaction involving subsequent aziridination. Upon treatment of *meta*-phenolic amines (**1i** and **1j**) bearing the butylamino substituent with identical conditions, the synthetically interesting 6,3,6-tricyclic aziridines **2i** and **2j** could be accessed in 69% and 55% yields (entries 10 and 11), respectively. While using the substrates (**1k** and **1l**) with oxygen and nitrogen-containing amino side chains, the 6,3,6-tricyclic aziridines **2k** bearing the morpholine moiety and **2l** bearing the piperazine motif could be analogously achieved in moderate yields of 52% and 58% (entries 12 and 13), respectively. Meanwhile, the substrate **1m** containing the benzylamine subunit was also tested for this reaction, and the 6,6,3,6-tetracyclic aziridine **2m** comprising the

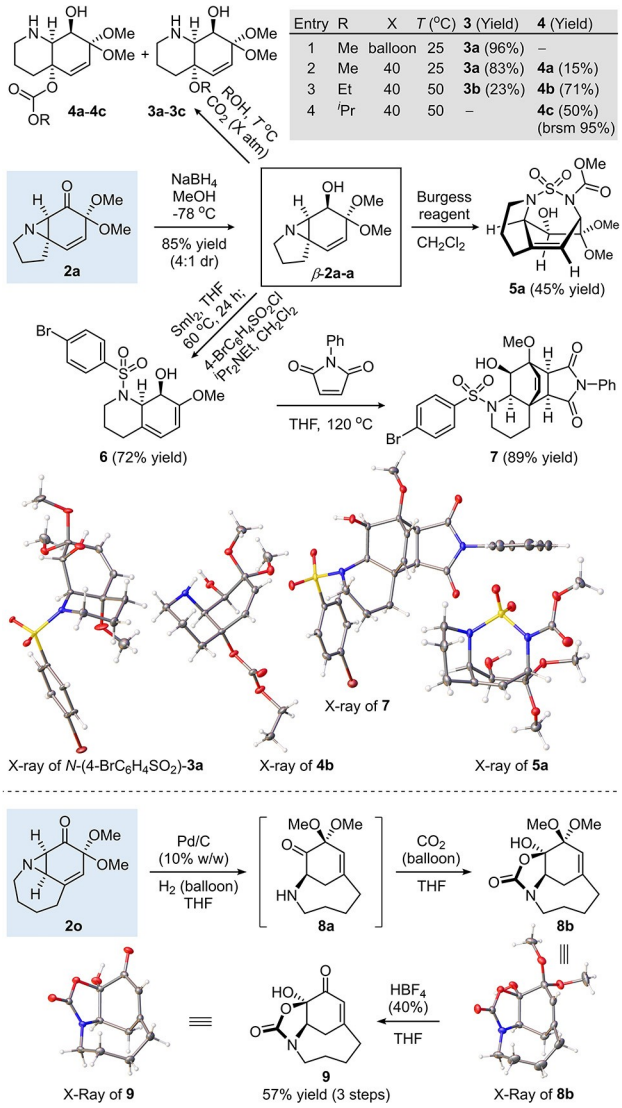
tetrahydroisoquinoline moiety was readily afforded in 51% yield (entry 14).

In addition to the cases employing *meta*-phenolic amines (**1a**–**1m**), *ortho*-phenolic amine **1n** with primary amino pendant group at α position of phenolic core (entry 15, Table 2) was subjected to present tandem oxidative dearomatization/aziridination reaction, and pleasingly the structurally rigid 5,3,6-tricyclic aziridine **2n** was delivered, albeit in 39% yield. Moreover, one example using *para*-phenolic amine **1o** with primary amino pendant substituent at γ position of phenolic core (entry 16) was also conducted, and interestingly this case led to the formation of structurally unique 7,3,6-tricyclic aziridine **2o** bearing a bridgehead double bond in good yield of 77%. To explore the synthetic utility of this protocol, a gram-scale reaction of **1a** was performed by using finely ground $PhI(OAc)_2$ to afford tricyclic aziridine **2a** with analogous efficiency in 69% yield (entry 2). In an attempt to increase the structural diversity of functionalized aziridines, as shown in Scheme 2, tandem oxidative aziridination involving *p*-quinone monoketal intermediate was investigated,[16] and the reaction of *meta*-phenolic amine **1p** having γ-methoxy instead of α′-methoxy in **1a** under the standard conditions resulted in the formation of sterically congested, chemically unstable homoallylic aziridine **2p**, which was reduced *in situ* to give the hydroxy-aziridine **2p-a** in 58% yield and 4:1 *dr*. Structurally, the stereochemistry of β-**2p-a** as major isomer was clearly assigned by X-ray crystallographic analysis.[14]

Chemically inspired by the synthetic importance of vinyl aziridine substructure[1b] embedded in the products resulting from tandem oxidative dearomatization/aziridination, as shown in Scheme 3, several transformations initiated by S_N2 and S_N2' ring opening were explored. Upon the reduction of **2a** with $NaBH_4$ at −78 °C, the chromatographically separable hydroxy-aziridine β-**2a-a** as major isomer could be obtained in 68% yield, and its stereochemistry was characterized by X-ray crystallographic analysis.[14] The regioselective S_N2 ring opening of aziridine β-**2a-a** was achieved by using MeOH as nucleophile at room temperature under a balloon pressure of CO_2,[17] giving the functionalized octahydroquinoline **3a** in 96% yield (entry 1, Scheme 3), which could not be accessed by the related control experiment (MeOH, 25 °C) in the absence of CO_2.[18] To explore the possibility of insertion mediated by CO_2, the increased pressure of CO_2 (40 atm) was introduced to the ring opening of β-**2a-a** in MeOH at 25 °C, and pleasingly the formation of CO_2 insertion carbonate **4a** (15% yield) as minor product accompanied by the major **3a** (83% yield) was observed (entry 2, Scheme 3). While the sterically increased EtOH (entry 3,



Scheme 2. Tandem oxidative aziridination involving *p*-quinone monoketal.



Scheme 3. Synthetic transformations starting from **2a** and **2o**.

Scheme 3) was subsequently examined under 40 atm of CO_2 at 50 °C, the CO_2 insertion carbonate **4b** (71% yield) as major product followed the formation of minor **3b** (23% yield) could be afforded in this case, showing unfavorable effect of the steric hindrance of alcoholic nucleophile to the direct competitive S_N2 ring opening of alcohols. Significantly, using the bulkier *i*PrOH (entry 4, Scheme 3) led to the predominant formation of the allylic carbonate **4c** having the octahydroquinoline framework in 50% yield (95% yield based on the recovery of starting material).

Interestingly, the aziridine β-**2a-a** was subjected to the classic elimination conditions using Burgess reagent,[19] and a cage-like polycyclic sulfamide **5a** was obtained in 45% yield via a transannular (5 + 2) annulation involving S_N2' ring opening of vinyl aziridine, to some extent demonstrating the unique reactivity of tricyclic vinyl aziridine β-**2a-a** and the first example of (5 + 2) annulation between vinyl aziridine and Burgess reagent. Besides, SmI_2-mediated SET reduction of β-**2a-a**

followed by *N*-sulfamidation delivered the densely functionalized bicyclic diene **6** in 72% yield, which could not be accessed efficiently by other known methods. Upon treatment of diene **6** with *N*-Ph maleimide at 120 °C, structurally complicated tetracyclic (4 + 2) cycloadduct **7** could be constructed via *endo*-selectivity in 89% yield. Moreover, an additional example using 7,3,6-tricyclic aziridine **2o** bearing the bridgehead double-bond was also carried out for its synthetic transformation. Under hydrogenation conditions (Pd/C, H_2 (balloon), THF, 25 °C), a chemoselective allylic cleavage of vinyl aziridine **2o** gave α-amino ketone **8a** having an azabicyclo[5.3.1]undecane skeleton through S_N2-type reductive ring-opening. Importantly, the unexpected lability of **8a** during its chromatographic purification and recrystallization disclosed an interesting observation that α-amino ketone unit in **8a** could partially undergo an insertion reaction with CO_2 in air, affording the tricyclic 2-oxazolidone-hemiketal **8b**.[20] Based on this serendipitous result, a combined protocol involving hydrogenation (Pd/C, H_2, THF), carbamation (CO_2, THF), and deketalization (HBF_4, THF) was then adopted to directly access to 5,6,8-tricyclic **9** bearing a unique bridgehead double bond in 57% yield in one pot. Notably, all relative configurations of *N*-(4-$BrC_6H_4SO_2$)-**3a**, **4b**, **5a**, **7**, **8b**, and **9** resulting from the above transformations have been confirmed by X-ray crystallographic analyses.[14]

In conclusion, an unprecedented hypervalent iodine(III)-mediated tandem oxidative dearomatization/aziridination reaction of phenolic amines has been developed for the first time, providing a new method for the effective synthesis of structurally diverse functionalized unactivated aziridines. Based on this cascade methodology, several protocols initiated by regioselective ring opening of vinyl aziridines have been representatively shown to efficiently lead to synthetically versatile nitrogen-containing heterocycles; the related transformations, particularly involving the incorporation of CO_2 and Burgess reagent, have been exploited for their synthetic potential. The present tandem reaction consisting of the oxidative dearomatization of phenols and the aziridination of aliphatic primary amines not only enriches the synthetic chemistry of functionalized aziridines, but also expands synthetic application of the hypervalent iodine chemistry.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Aziridines · cascade reactions · dearomatization · iodine · oxidation

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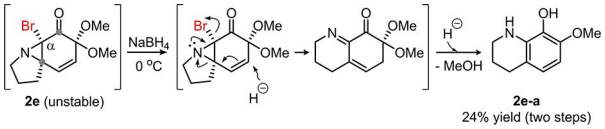

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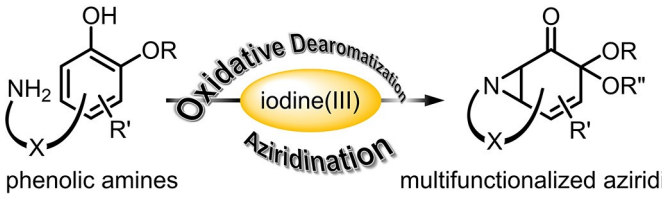

An unprecedented tandem reaction (oxidative dearomatization/aziridination) of phenolic amines in the presence of hypervalent-iodine(III) reagent is described. This cascade reaction shows a chemical unification of the oxidative reactivity of phenol and aliphatic primary amine in the chemistry of dearomatization and aziridination, thus providing a new method for the synthesis of unactivated aziridines with dense functionalization.

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