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An Organic Intermolecular Dehydrogenative Annulation Reaction

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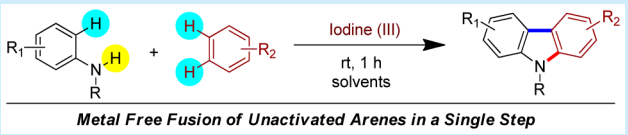
Supporting Information

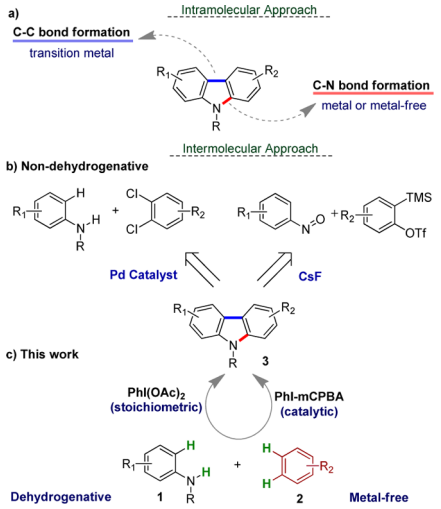
ABSTRACT: The discovery of a direct method for the synthesis of three-ring heterocyclic carbazoles from unactivated arenes and anilides by a metal-free (organic) intermolecular dehydrogenative annulation reaction under ambient laboratory conditions is reported. Iodine(III) was used as the sole reagent either stoichiometrically from inexpensive phenyliodine diacetate or organocatalytically by in situ generation from PhI–*m*CPBA. In a single step, three C(sp^2)–H bonds and one N(sp^3)–H bond are functionalized from two different arenes for tandem C–C and C–N bond formation reactions.



The use of readily available chemicals for atom- and step-economical syntheses of bioactive molecules, pharmaceuticals, and materials is a state-of-the-art practice in organic synthesis.[1] Nitrogen-based heterocycles are considered as highly important among those molecules.[2] Transition-metal catalysis of annulation reactions has emerged as a powerful technique to convert unreactive C–H and N–H bonds into C–C and C–N bonds in heterocycle synthesis.[3] Dehydrogenative coupling reactions between C–H and N–H bonds are more popular than traditional cross-coupling reactions because preactivation of substrates can be avoided.[4] Similarly, metal-free approaches are preferable because any metal impurities may alter the biological activities and physical properties of a compound.[5] For the functionalization of nonreactive C–H bonds, hypervalent iodine(III) reagents are highly advantageous because of their easy accessibility, low toxicity, high reactivity, and environmentally benign nature.[6] Notably, a very limited number of intermolecular annulation reactions[7] for heterocycle synthesis using hypervalent iodine(III) have been documented.[8]

For the synthesis of carbazoles, a majority of the methods are based on an intramolecular approach via formation of one bond (either C–C or C–N) using either transition-metal catalysts or metal-free conditions (Scheme 1a).[9] Contrastingly, examples are rare for the intermolecular approach, which can be more advantageous in terms of step economy and the nonrequirement of preorganization of substrates.[10] To date, the known examples of intermolecular approaches for carbazole synthesis are non-dehydrogenative type, such as (a) the palladium-catalyzed reaction of 2-iodoaniline with arenes reported by Liu and Larock,[11] (b) the coupling reaction between anilines and 1,2-dihaloarene substrates based on palladium catalysis described by Ackermann's group (Scheme 1b),[12] and (c) a reaction of aryne precursors with nitrosoarenes developed by Studer and co-workers (Scheme 1b).[13] However, to the best of our knowledge, there are no reports of a transition-metal-free intermolecular dehydrogenative annulation approach for polycyclic heteroaromatic carbazoles.

Scheme 1. Approaches for Carbazole Synthesis



Herein we report the discovery of a metal-free intermolecular dehydrogenative annulation reaction for N-substituted carbazole synthesis via tandem C–C/C–N bond formation through simultaneous multiple C–H and N–H bond functionalizations (Scheme 1c). Non-prefunctionalized arenes and anilides were used for hypervalent iodine(III)-mediated intermolecular coupling reactions under stoichiometric as well as organocatalytic conditions. The commercially available hypervalent iodine(III) reagent phenyliodine(III) diacetate (PIDA)[14] was used as the sole reagent, and the reactions were completed at room temperature within 1 h in fluorinated solvents under open atmosphere. Similarly, in the organocatalytic method, iodobenzene and *m*-chloroperoxybenzoic acid (*m*CPBA)[15] were used under the same conditions. We anticipated that intermolecular oxidative fusion of multiple rings might lead to a powerful

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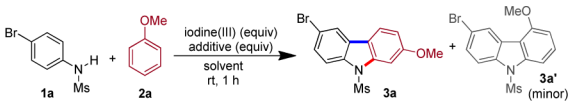
approach for the synthesis of polycyclic heterocycles like carbazoles. Carbazoles are extensively used as pharmaceuticals, photoconducting materials, organic dyes, etc.[16]

We considered *N*-(4-bromophenyl)methanesulfonamide (**1a**) and anisole (**2a**) for optimization of the intermolecular dehydrogenative annulation reaction. For stoichiometric optimization (method A), substrates **1a** and **2a** (3.0 equiv) were treated with 2.5 equiv of PIDA at room temperature in 2,2,2-trifluoroethanol (TFE) (0.2 M), and the desired product, 6-bromo-2-methoxy-9-(methylsulfonyl)carbazole (**3a**), was obtained in 34% yield (Table 1, entry 1). Nevertheless, 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) was found to be most efficient among the solvents examined (Table 1). In addition, we extended our investigation by using different iodine(III) reagents as the oxidant. The stronger oxidant $PhI(OCOCF_3)_2$ (PIFA) could not afford a better yield of **3a** (entry 5), and PhIO was found to be ineffective under the studied conditions (entry 6). Oxidants like $PhI(OCOPh)_2$, HTIB, and $PhI(OPiv)_2$ were also inefficient, providing less promising results than PIDA (entries 7, 8, and 11). A significant increase in yield was observed by diluting the reaction mixture to 0.1 M using HFIP/DCM (1:1) (entry 9). The most appropriate conditions were identified to be treatment of 1 equiv of **1a** and 3.0 equiv of **2a** with 2.5 equiv of $PhI(OAc)_2$ in the presence of 2.5 equiv of the additive K_2CO_3 at 0.1 M in HFIP/DCM (1:1). The desired product **3a** was isolated as the major isomer in 78% yield within 1 h at room temperature under aerobic conditions (entry 10). The formation of trace amounts of the minor isomer, 3-bromo-5-methoxy-9-(methylsulfonyl)-9*H*-carbazole (**3a′**) was also detected. The use of a Lewis acidic additive like $BF_3{\cdot}Et_2O$ or an acidic additive like AcOH did not offer better results (entries 13 and 14). Most of the arenes **2** are volatile in nature, and therefore, the use of ∼3.0 equiv was established as the optimum amount for the reaction. The organocatalytic approach established using various iodoarenes ($4\text{-}NO_2C_6H_4I$, $4\text{-}MeOC_6H_4I$, PhI) and oxidants by in situ generation of iodine(III) reagent (method B; Table S1 in the Supporting Information (SI)). The best conditions were achieved when 20 mol % PhI and 3.0 equiv of the oxidant *m*CPBA were used at room temperature in HFIP/DCM (1:1).

The optimized annulation protocol was subsequently applied to a range of simple arenes and anilides to explore the substrate scope of the multisubstituted carbazole synthesis (Scheme 2).

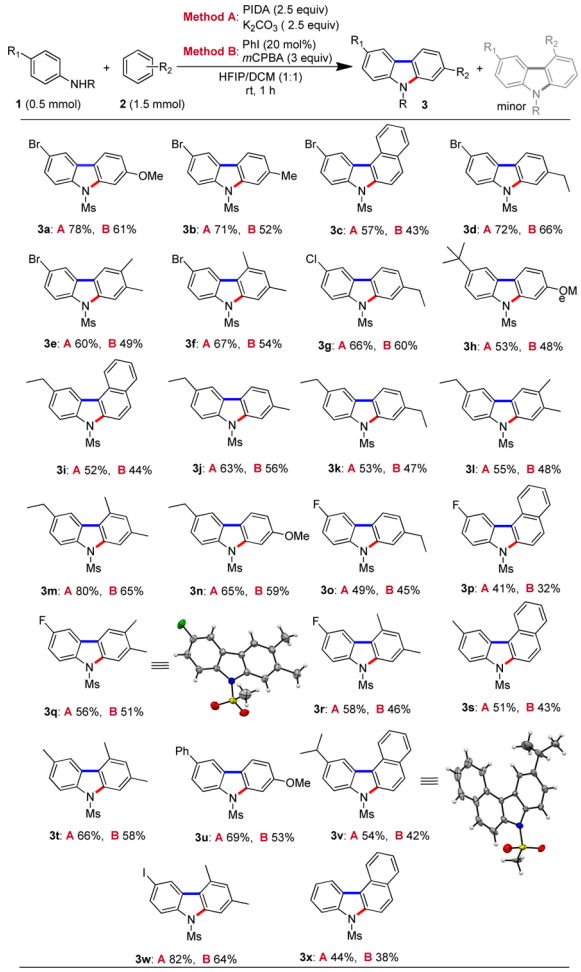
Table 1. Optimization of Method A[a]



entry	iodine(III) (2.5 equiv)	additive (2.5 equiv)	solvent	yield of **3a** (%)[b]
1	PIDA	–	CF_3CH_2OH	34
2	PIDA	–	DCM	10
3	PIDA	–	ACN	0
4	PIDA	–	HFIP	57
5	PIFA	–	HFIP	21
6	PhIO	–	HFIP	<5
7	$PhI(OCOPh)_2$	–	HFIP	44
8	HTIB[c]	–	HFIP	18
9	PIDA	–	HFIP/DCM (1:1)	66
10	PIDA	K_2CO_3	HFIP/DCM (1:1)	78
11	$PhI(OPiv)_2$	K_2CO_3	HFIP/DCM (1:1)	41
12	PIDA	K_2CO_3	HFIP	67
13	PIDA	AcOH	HFIP	35
14	PIDA	$BF_3{\cdot}Et_2O$	HFIP	<5
15[d]	PIDA	K_2CO_3	HFIP/DCM (1:1)	30

[a]Unless otherwise mentioned, 3.0 equiv of **2a** was used. [b]Yields of the isolated major product after column chromatography. [c]HTIB = hydroxy(tosyloxy)iodobenzene. [d]1.1 equiv of **2a** was used.

Scheme 2. Scope of the Intermolecular Annulation Reaction



Carbazoles were isolated in good yields under the standard conditions. A wide array of anilides with different functional groups at the *para* position were compatible here. Electron-withdrawing groups like halogen (**3a**–**g**, **3o**–**r**, **3w**) or phenyl (**3u**) and electron-donating alkyl groups (**3h**–**n**, **3s**, **3t**, **3v**) on the anilide substrate were fair-yielding as well under both stoichiometric and organocatalytic conditions. In general, aryl rings with electron-donating groups like alkyl or alkoxy underwent cyclization more readily on anilide substrates (see the SI). Furthermore, various sulfonyl or carbonyl groups on the N center of the aniline were also found to be efficient in carbazole synthesis (Scheme 3, **3aa**–**ag**). However, aniline substrates containing an electron-donating benzyl group were unsuccessful in providing carbazole (see the SI). Notably, using *para*-unsubstituted acetanilides instead of sulfoanilides (**1x**), we were unsuccessful in achieving product formation, which is in good agreement with a previous report.[17] In all cases, better

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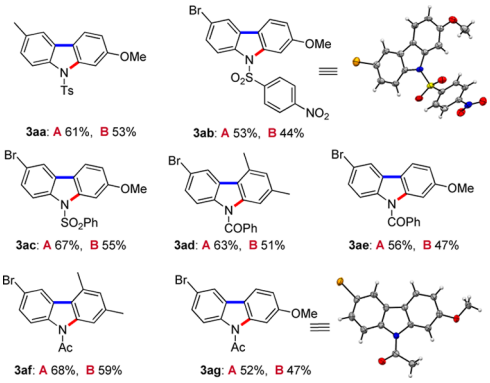
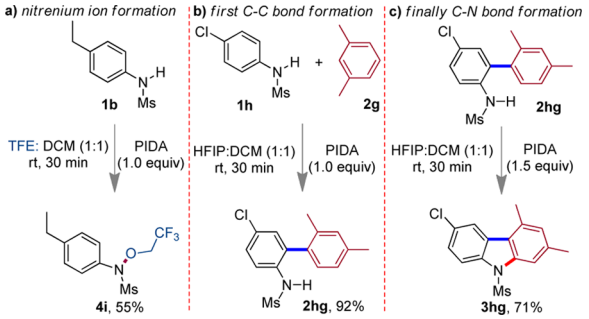
Scheme 3. Scope of N-Substituted Anilines



yields were observed for the stoichiometric pathway than the organocatalytic one.

On the basis of control experiments (Scheme 4) and literature precedents,[18] a plausible mechanism of the intermolecular

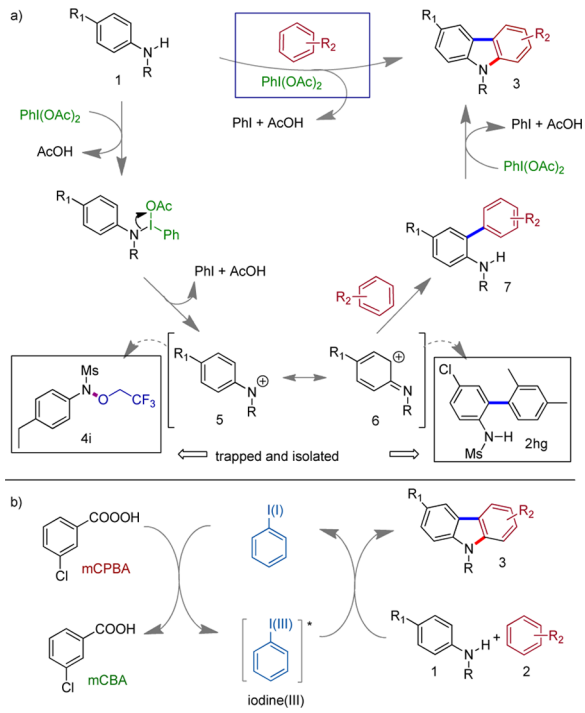
Scheme 4. Control Experiments



dehydrogenative annulation reaction is proposed in Scheme 5. Upon reaction with PIDA, anilide **1** generates nitrenium ion[19] intermediate **5** (Scheme 5). Reaction of sulfoanilide **1i** and 1.0 equiv of PIDA in TFE led to the formation of *N*-(4-ethylphenyl)-*N*-(2,2,2-trifluoroethoxy)methanesulfonamide (**4i**) in 55% yield (Scheme 4a). Formation of the solvent-incorporated product **4i** established the presence of nitrenium ion **5**. Similarly, the existence of nitrenium ion in an iodine(III)-mediated alkoxylation reaction was also reported by Kikugawa et al.[19b] The nitrenium ion intermediate would be expected to get stabilized by charge delocalization to form carbenium ion intermediate **6** (Scheme 5). Nucleophilic attack by the arene could possibly take place on either carbenium ion **6** (C−C bond formation) or nitrenium ion **5** (C−N bond formation). In the reaction of *N*-(4-chlorophenyl)methanesulfonamide (**1h**) with *m*-xylene in the presence of 1.0 equiv of PIDA, the C-arylated product *N*-(5-chloro-2′,4′-dimethyl-[1,1′-biphenyl]-2-yl)methanesulfonamide (**2hg**) was isolated in 92% yield (Scheme 4b). Addition of 1.5 equiv of PIDA to C-arylated product **2hg** afforded 6-chloro-2,4-dimethyl-9-(methylsulfonyl)carbazole (**3hg**) in 71% yield (Scheme 4c).

This observation led to the conclusion that the C−C bond is preferentially formed over the C−N bond during the carbazole ring construction. Hypervalent iodine(III)-mediated selective C-arylation of *para*-substituted *N*-sulfonyl anilides in polar fluorinated solvents was formerly described by Kita[20] and Canesi,[21] where it was anticipated that the σ-donation effect of the sulfonyl group is operative to stabilize the positively charged aromatic ring to form the C−C bond preferentially over the C−

Scheme 5. Plausible Mechanism for the Annulation Reaction in the (a) Stoichiometric and (b) Organocatalytic Approaches



N bond through an ionic pathway. The availability of a free NH group in the C-arylated intermediate opened up an additional opportunity for the intermediate to react further with additional hypervalent iodine(III) reagent. From intermediate **7**, the oxidative C−N bond formation was controlled by attack of the phenyl ring on the nitrenium ion.[9c] The ligand exchange of PIDA with HFIP could not be anticipated.[22] Interestingly, according to Kita's report, the moderate steric size of the Ms group prevented overoxidation of the biaryl product, whereas we could fruitfully overcome that restriction also during the annulation reaction by creating the C−N bond in addition to the C−C bond. The role of the additive K_2CO_3 might be to neutralize the acetic acid released during the reaction.[21] A trace amount of the 4-substituted isomer was also formed through electrophilic substitution of the arene at the sterically less preferable *ortho* position by an electron-donating group.[23] Thus, apart from the major 2-substituted carbazole derivative, a trace amount of the 4-substituted product also formed. Although the minor isomer could not be isolated in pure form, it was detected by NMR spectroscopy as mixture with the major isomer (see the SI for details). Hence, representative yields correspond to the isolated pure major isomers.

In the organocatalytic approach, we believe that iodobenzene is oxidized by *m*CPBA to generate the trivalent organoiodine species, which enables the intermolecular annulation of arenes and anilides to form the final product **3** (Scheme 5b).[9c]

For further synthetic utility, compound **3a** was converted into 6-bromo-2-methoxycarbazole (**4a**) in 93% yield (Scheme 6a) using 3.0 equiv of Cs_2CO_3 in THF/MeOH (1:1).[24] In addition, the synthesis of the carbazole alkaloid (±)-mahanimbicine (Scheme 6b) can possibly be achieved in two steps from 2-methoxy-6-methyl-9-tosylcarbazole (**3aa**).[25] We have synthesized the alkaloid clauszoline-K (**5ah**) from *N*-(*p*-tolyl)-benzenesulfonamide (**1ah**) and anisole (**2a**) (Scheme 6c).[26] Moreover, this method might lead to the easy synthesis of the potent anti-HIV-active drug siamenol in two steps from 2-

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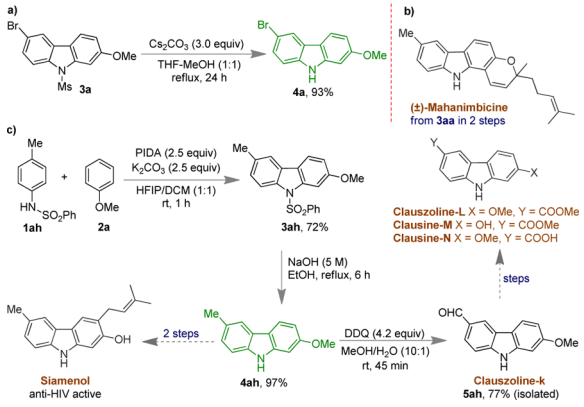
Scheme 6. Postsynthetic Modifications



methoxy-6-methyl-9*H*-carbazole (**4ah**) (Scheme 6c).[27] The alkaloids clauszoline-L, clausine-M, and clausine-N (Scheme 6c) also could be derived from 7-methoxy-9*H*-carbazole-3-carbaldehyde (**5ah**) by applying a literature-known series of transformations.[27]

In summary, we have presented the simplest approach for direct annulation to form carbazoles by fusing two non-prefunctionalized monocyclic arenes via simultaneous functionalization of three C(sp^2)−H bonds and one N(sp^3)−H bond. An iodine(III) reagent was used as the sole reagent, and the reactions were carried out under ambient laboratory conditions. The presented method is a newly discovered intermolecular dehydrogenative annulation (IDA) reaction involving tandem C−C and C−N bond formation. The utility of the synthesized carbazoles for the synthesis of biologically active natural products has also been documented. We foresee that this annulation approach can provide direct access to various polycyclic heteroaromatic compounds and might have a major impact on the synthesis of complex molecules, functionalized materials, and pharmaceuticals.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00562.

Crystallographic data for **3ab** (CIF)
Crystallographic data for **3q** (CIF)
Crystallographic data for **3v** (CIF)
Procedures and additional data (PDF)
Crystallographic data for **3ag** (CIF)

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Notes

The authors declare no competing financial interest.

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