C–H Functionalization

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Organocatalytic, Oxidative, Intramolecular C–H Bond Amination and Metal-free Cross-Amination of Unactivated Arenes at Ambient Temperature**

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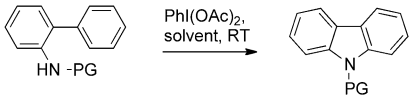
The importance and value of nitrogen-containing compounds stem from their wide occurrence in nature and broad application in chemistry, biology, and material sciences.[1] The development of effective methods for the formation of C–N bonds is an intensively investigated area of great significance.[2] In recent work, researchers have focused on milder versions of the Ullmann reaction and the application of substoichiometric amounts of metals.[3] A breakthrough in this area was the development of the Pd-catalyzed Buchwald–Hartwig amination of aryl halides.[4] In recent reports C–N bonds are formed through direct C–H activation using transition-metal catalysis.[5] However, these reports are limited to intramolecular processes. Very recently, a new metal-free approach has been developed for intramolecular, oxidative C–N bond formation using stoichiometric amounts of a hypervalent iodine(III) compound as the oxidant; in the absence of metal this method had lower efficiency.[6] We herein report our preliminary results on an atom-economical, environmentally friendly organocatalytic method for the preparation of carbazoles through C–N bond formation and the unprecedented first cross-amination of non-prefunctionalized arenes which was performed under metal-free conditions.[7]

We began our studies by testing the conversion of 2-acetaminobiphenyl to *N*-acetylcarbazole using (diacetoxy)iodobenzene as an oxidation reagent at room temperature (Table 1).[8,9] Preliminary attempts led to the formation of the desired acyl carbazole in low yield (Table 1, entry 1). In subsequent solvent screening we found that the yield of direct amination was higher in polar nonnucleophilic solvents, and the best results were obtained in hexafluoro-2-propanol (Table 1, entries 2–6).

We then optimized the protecting groups on 2-aminobiphenyl, along with the concentration of the substrate and the oxidant (Table 1, entries 7–13). Application of unprotected or alkyl-protected 2-aminobiphenyl in the amination under the described reaction conditions was not successful. Besides 2-acetaminobiphenyl, 2-toluenesulfonamide biphenyl also reacts to give the corresponding product in good yield.

Table 1: Optimization of the reaction conditions.[a]



1 **2**

Entry	PG	Solvent	*c* [M]	*t* [h]	Yield [%][b]
1	Ac	CH_2Cl_2	0.10	72	9
2	Ac	MeOH	0.10	72	n.d.
3	Ac	MeCN	0.10	72	9
4	Ac	$MeNO_2$	0.10	72	12
5	Ac	CF_3CH_2OH	0.10	4.5	41
6	Ac	HFIP	0.10	1.25	66
7	H	HFIP	0.15	12	n.d.
8	Bz	HFIP	0.15	3	47
9	Bn	HFIP	0.15	12	n.d.
10	Tos	HFIP	0.15	4	62
11	Tos	HFIP	0.05	12	68
12	**Ac**	**HFIP**	0.05	**12**	**81**
13[c]	Ac	HFIP	0.05	16	19

[a] Conditions: (diacetoxy)iodobenzene (1.1 equiv) in solvent. PG = protecting group, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol. [b] Yield of isolated product after column chromatography; n.d. = not detected. [c] Phenyliodine bis(trifluoroacetate) (1.1 equiv) was used as the oxidant.

The yield of the product could be improved to 81% by dilution of the reaction mixture (Table 1, entry 12). Interestingly, replacement of (diacetoxy)iodobenzene by phenyliodine bis(trifluoroacetate) led to a dramatic drop in yield to 19%. Application of a variety of oxidants based on hypervalent iodine (e.g. Koser's reagent, 2-iodoxybenzoic acid, Dess–Martin periodinane) did not lead to product formation.

After we had optimized the reaction conditions, we focused on the development of organocatalytic conditions.[9,10] Since stoichiometric use of (diacetoxy)iodobenzene results in co-production of an equimolar amount of PhI, a catalytic procedure would be achieved by in situ oxidation of iodo(I)arenes to iodine(III) species. Indeed, use of substoichiometric amounts of PhI in the presence of an oxidant such as *meta*-chloroperbenzoic acid (*m*CPBA) provided the target product in 51% yield (Table 2, entry 1). A similar result was obtained using peracetic acid as an atom-economical and environmentally friendly oxidant (Table 2, entry 2). Many iodine-containing substances were screened in order to improve the yield of the carbazole and to reduce the loading of the catalyst (Table 2, entries 3–11). Besides 4-iodoanisole, substituted iodobenzenes provided access to carbazole **2a** in 41–55% yield at a catalyst loading of 25 mol%. Application of iodoalkane or ionic species was not successful. To our

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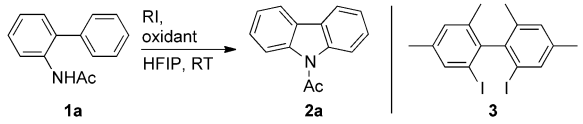
Table 2: Optimization of the organocatalytic reaction conditions.[a]



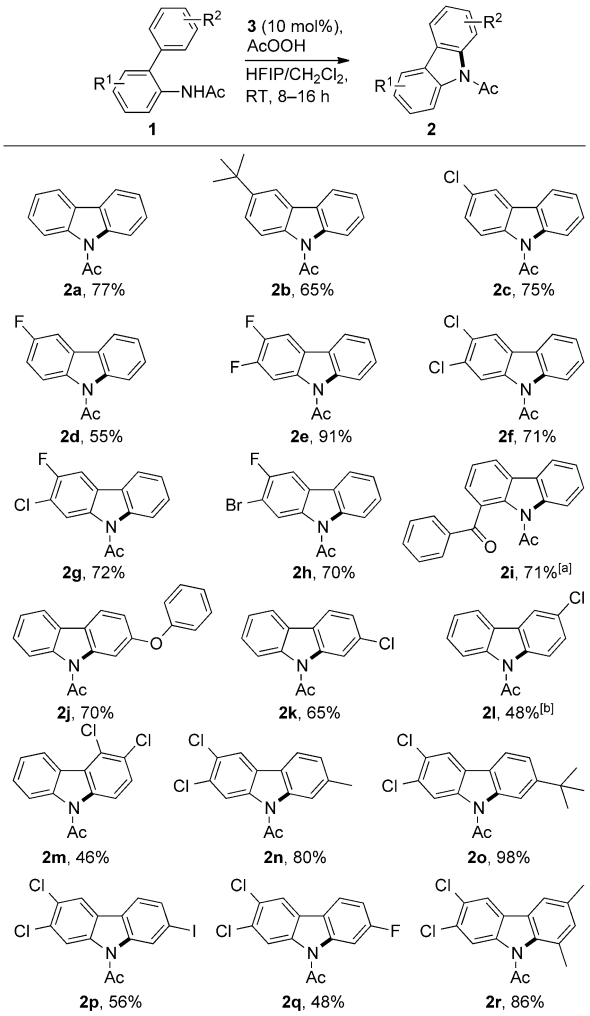
1a **2a** **3**

Entry	RI	RI [mol%]	*t* [h]	Yield [%][b]
1[c]	PhI	25	15	51
2	PhI	25	16	52
3	4-MeC_6H_4I	25	16	55
4	3,5-$Me_2C_6H_3I$	25	16	55
5	4-$MeOC_6H_4I$	25	16	<10
6	4-FC_6H_4I	25	16	48
7	4-IC_6H_4I	25	16	41
8	*n*BuI	25	24	traces
9	nBu_4NI	25	45	<20
10	NIS	25	45	traces
11	**3**	10	8	63
12[d]	**3**	10	8	76
13[d,e]	**3**	**10**	**8**	**77**
14[d,e]	**3**	5	16	71
15[d,e]	**3**	2	30	56

[a] Conditions: RI (2–25 mol%), AcOOH (2.2 equiv), HFIP (0.05 M). NIS = *N*-iodosuccinimide. [b] Yield of isolated product after column chromatography. [c] *m*CPBA (2.2 equiv) was used. [d] Solvent: CH_2Cl_2/HFIP (1:1). [e] AcOOH (2.0 equiv) was used.

delight, we found that 2,2′-diiodo-4,4′,6,6′-tetramethylbiphenyl (**3**), which was obtained in one step by oxidative dimerization[10e,11] of 1-iodo-3,5-dimethylbenzene, catalyzes the intramolecular amination at an even lower catalyst loadings, resulting in a shorter reaction time and a better yield of **2a** (Table 2, entry 11). Furthermore, we could increase the yield of **2a** to 77% by optimization of the solvent and the amount of the oxidation reagent (Table 2, entry 13). A further decrease in the catalyst loading resulted in lower product yields. However, it is impressive that 2 mol% of simple, cheap, and easily accessible organic substance is sufficient to catalyze intramolecular C–H amination at room temperature (Table 2, entry 15). The by-products of the developed methodology are just acetic acid and water. The desired carbazole was not formed in the absence of catalyst.[12]

With the optimized reaction conditions in hand, we then explored the scope and generality of the method. We first examined the effect of substituents in the aniline part of 2-acetaminobiphenyl (Scheme 1, products **2a**–**2i**). In general, we found that the presence of substituents with different electronic and steric properties in various positions did not have an effect on the formation of the carbazole. However, the reaction of 2-acetamino-3-benzoylbiphenyl required higher catalyst loading and additional peracetic acid (Scheme 1, product **2i**). Afterwards, we examined the substituents in the phenyl part of 2-acetaminobiphenyl (Scheme 1, products **2j**–**2r**). To our delight, various groups with different electronic properties are tolerated and the developed methodology could be used to construct unsymmetrically, polysubstituted carbazoles. In the case where two regioisomers could be formed (Scheme 1, product **2l**), one product was obtained with good selectivity.

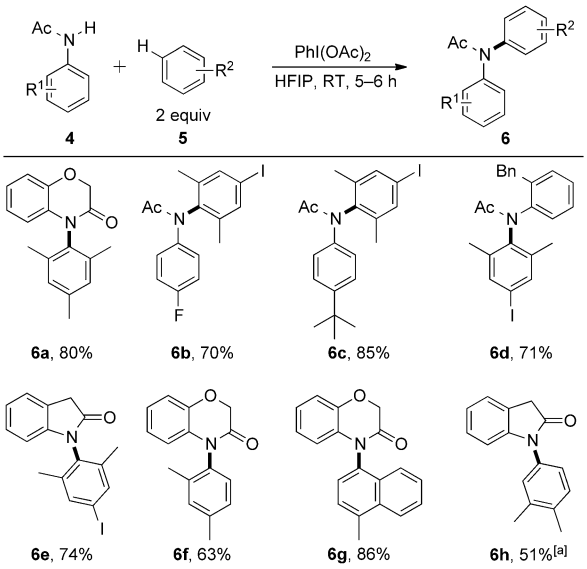


1 **2**

Scheme 1. Scope of organocatalytic C–H bond amination. Conditions: acetaminobiphenyl (**1a**–**1r**), **3** (10 mol%), AcOOH (2.0 equiv), in CH_2Cl_2/HFIP (1:1; 0.05 M). Yields are given for isolated products after column chromatography. Newly formed C–N bonds are shown in bold. [a] Using **3** (20 mol%); additional AcOOH (2.0 equiv) was added after 36 h and the reaction was complete after 40 h. [b] Isomer ratio is 7:1 by ^{1}H NMR analysis; structure and yield given for the isolated major regioisomer.

After the development of intramolecular organocatalytic C–H bond amination, we focused on the intermolecular version of this reaction. Interestingly, intermolecular amination had not been reported previously; the corresponding transition-metal-catalyzed reactions of aniline derivatives with unactivated arenes led to the formation of C–C bonds through C–H activation.

In preliminary experiments we tested metal-free conditions using stoichiometric amounts of hypervalent iodine(III). We were pleased to find that in the test reaction 2*H*-1,4-benzoxazin-3(4*H*)-one reacts smoothly with mesitylene to give the cross-amination product at room temperature (Scheme 2, product **6a**). However, our subsequent attempts to develop organocatalytic transformations using various aryl iodides and oxidation reagents were unsuccessful. Application of 10 mol% of **3** in the presence of AcOOH led to the

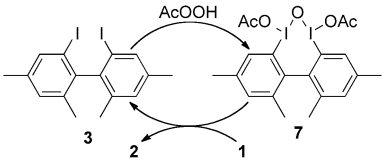


Scheme 2. Scope of metal-free cross-amination. Conditions: acetanilide **4** (1 equiv), arene **5** (2 equiv), (diacetoxy)iodobenzene (1.5 equiv), 0.10 M HFIP. Yields are given for isolated products after column chromatography. Newly formed C–N bonds are shown in bold. [a] 2-Oxindole (10 mmol), *ortho*-xylene (5 equiv) (diacetoxy)iodobenzene (1.5 equiv), HFIP (0.5 M), 1 h.

formation of trace amounts of the product (**6a**) and after 20 h the starting material was recovered in 95% yield. Furthermore, with stoichiometric amounts of aryl iodide **3**, **6a** was obtained in 32% yield and the starting material was isolated in 64% yield. Therefore, we focused on investigating the generality of the discovered metal-free cross-amination using stoichiometric amounts of (diacetoxy)iodobenzene. Once again, numerous aniline derivatives having different electronic and steric properties were tolerated (Scheme 2). Additionally, diverse mono- and polysubstituted unactivated arenes underwent the desired transformation without the use of a large excess. Unfortunately, arenes bearing electron-withdrawing groups were not reactive. Interestingly, product **6f**, from the cross-amination with *meta*-xylene, was formed as single regioisomer.

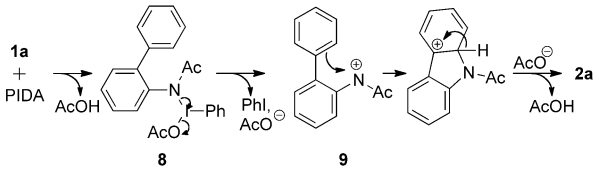
Finally, we performed experiments on a larger scale to demonstrate the practicability of the developed methodology. Applying 5 mmol of **1a** and lowering the organocatalyst loading to 5 mol%, we obtained the desired carbazole (**2a**) in 75% yield. Additionally, 92% of the catalyst (**3**) was recovered from the reaction. Moreover, we performed the cross-amination of 2-oxindole with *ortho*-xylene at high concentrations. The desired product, *N*-aryl-2-oxindole (**6h**), was isolated as a single regioisomer (Scheme 2, product **6h**).

Mechanistically, we assume that aryl iodide **3** is oxidized by peracetic acid to generate the active form of the catalyst, **7**, which facilitates the amination of **1** to give the desired product **2** (Scheme 3). The structure of the μ-oxo-bridged reactive hypervalent iodine(III) species **7** was confirmed in a control experiment (see the Supporting Information). Furthermore product **2a** was obtained from **1a** in 90% yield when a stoichiometric amount of **7** was used (see the Supporting



Scheme 3. Proposed catalytic cycle.

Information). Application of 2,6-di-*tert*-butyl-4-methylphenol as a radical scavenger was unsuccessful because in a control experiment the radical trap reacted with (diacetoxy)iodobenzene. However, we found that *N*-*tert*-butyl-α-phenylnitrone can be used as a radical scavenger in the presence of iodine(III), and it does not affect the formation of the desired intra- and intermolecular products. This finding indicates that radical species do not play a role in the C–H amination. Based on these results, we believe that the reaction proceeds as follows (Scheme 4). Initially (diacetoxy)iodobenzene reacts with the amide to give intermediate **8**, which is then transformed into nitrenium ion **9** through an oxidative process. The nucleophilic arene attacks the electron-deficient nitrenium ion **9** to give the desired product.



Scheme 4. Proposed mechanism of C–H bond amination. PIDA = (diacetoxy)iodobenzene.

In conclusion, we have developed a highly efficient, atom-economical, environmentally friendly organocatalytic method for the preparation of carbazoles through intramolecular C–H amination. Our method can be used to synthesize various carbazoles without any additives such as bases, acids, transition metals, and alkali metals. Since the desired products form smoothly at ambient temperature, the reaction mixture must not be cooled or heated, which would require additional energy. Moreover, the developed methodology has been extended to the unprecedented metal-free cross-amination of nonactivated arenes with various aniline derivatives. Further work is in progress.

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