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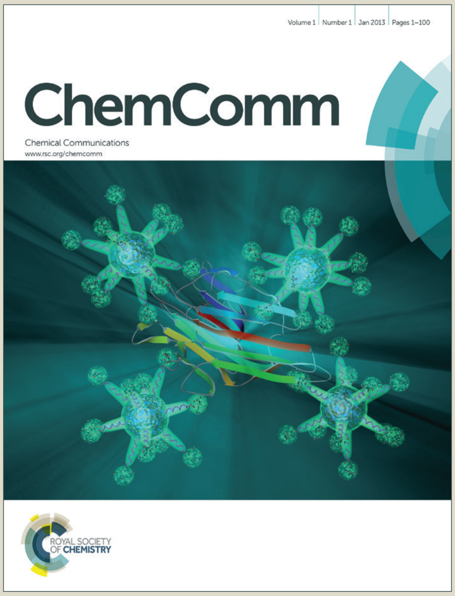

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Nitrogen-Centered Radical-Mediated C–H Imidation of Arenes and Heteroarenes via Visible Light Induced Photocatalysis†

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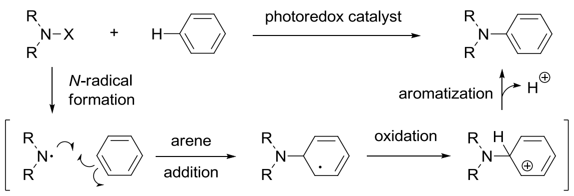
The C–H imidation of arenes and heteroarenes has been achieved via visible light induced photocatalysis. In the presence of an iridium(III) photoredox catalyst, the reaction of aromatic substrates with *N*-chlorophthalimide furnishes the *N*-aryl products at room temperature through a nitrogen-centered radical mediated aromatic substitution.

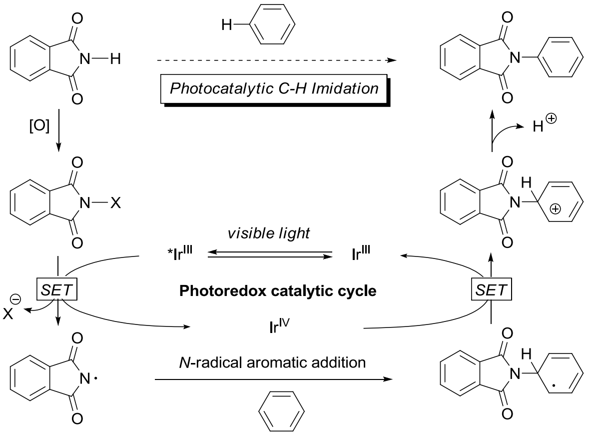
The direct C–H amination of arenes is a valuable transformation, as the aromatic amine moiety prevalent in pharmaceuticals, agrochemicals and organic materials can be constructed from aryl substrates without prefunctionalization.[1] Not surprisingly, formation of *N*-aryl bonds via selective C–H functionalization has been a subject of intense investigations, largely making use of transition metal mediated catalysis. Particularly notable are the advances in the protocols enabling *N*-aryl bond formation in intermolecular settings.[2] Mechanistically, these processes rely on metalation of the arene followed by conversion of the aryl-metal σ bond to a C–N bond. The amination using this strategy is highly efficient with substrates possessing directing groups that can facilitate the metalation step. Without such directing groups, however, the use of large quantities of arene substrates is typically required in order for the reaction to proceed under catalysis.[3] Distinct from these approaches is the amination exploiting the arene π system, instead of targeting the aryl-metal σ complex as a key intermediate. Based on this mechanistic modality, intermolecular oxidative amination has been achieved that gives *N*-aryl compounds from non-prefunctionalized arenes,[4] thus obviating the harsh reaction conditions of nitration and the subsequent reduction step as required in the early aniline synthesis en route from nitroarenes. These metal-free protocols, though performed with a large excess of arene substrates and expensive oxidants, have provided important examples of the direct formation of aryl C–N bonds via tandem C–H and N–H functionalization. While the nitrogen intermediate involved in these reactions remains to be established, an intriguing effect of a palladium catalyst on the regioselectivity of the oxidative imidation[5] and a related process utilizing a bimetallic catalyst system with an elaborate scaffold have been reported to achieve an expanded substrate scope.[6]

Given the feasibility of arene C–H amination by engaging oxidatively generated nitrogen species, most likely electrophilic in nature, with the arene π system, a general strategy could be formulated for *N*-aryl bond formation using a nitrogen-centered radical (*N*-radical) intermediate.[7] More specifically, *N*-radicals derived from N–X bonds may be rendered amenable to undergo arene addition and lead in turn to C–H amination (Scheme 1).[8,9] However, except for a few limiting cases, intermolecular amination of this type is complicated by hydrogen abstraction, rearrangement and redox processes of *N*-radicals.[10] In addition, competing formation of aryl C–X bonds may arise when the *N*-radical intermediate is produced via homolysis of N–X bonds.[8c,10d,e] In connection with our studies on the reductive transformations of organohalides via visible light induced photocatalysis,[11] we questioned whether the efficiency and mildness noted in the *C*-radical mediated reductive reactions could be translated to redox-neutral, *N*-radical mediated arene amination processes.[12] Taking guidance from the findings of electrochemical studies, we anticipated that reductive scission of the N–X bond might be controlled to generate $R_2N\bullet$ and X^- rather than R_2N^- and $X\bullet$ by tuning the X group.[13] Furthermore, it was envisioned that facile oxidation of the *C*-radical emanated from the *N*-radical arene addition could bring about efficient aromatic substitution while suppressing potentially intervening radical chain processes.[10e,14] Reported here is a visible light photocatalytic method for C–H imidation of arenes that can be performed in preparative scales with commercially available, inexpensive reagents under mild and operationally simple conditions.



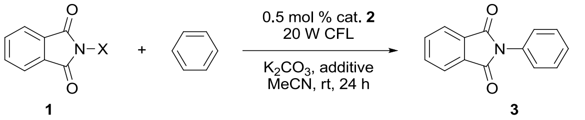
Scheme 1 Nitrogen radical mediated C–H amination or arenes.

Our approach to C–H amination was examined based upon the strategy depicted in Scheme 2, in which the iridium complex was envisioned to facilitate the *N*-radical mediated aromatic substitution process through a photoredox catalytic mechanism. The catalytic cycle begins with irradiation of Ir^{III} that would generate photoexcited $^*Ir^{III}$ capable of undergoing oxidation or reduction. With a substrate containing a reduction susceptible N–X bond, the single electron transfer (SET) from $^*Ir^{III}$ to the substrate could induce reductive fragmentation of the N–X bond to form the requisite *N*-radical intermediate. Subsequent to arene addition, the resulting *C*-radical undergoes an electron-recycling SET with Ir^{IV} to regenerate photocatalyst Ir^{III} while entering on a carbocation (Wheland intermediate) pathway en route to aromatization. Thus, the overall scheme harnesses the energy of visible light for metathesis of N–X and C–H bonds into C–N and H–X bonds. In implementing the plan, the phthalimidyl system was chosen for several reasons. First, phthalimide derivatives to be probed for *N*-radical generation are commercially available or easily prepared often via a one-pot procedure.[15] The nitrogen flanked by two carbonyl groups lacks α-amino hydrogen, thus devoid of potentially problematic β-elimiation of the N–X bond and disproportionation of the *N*-radical species.[16] The ring opening process associated with cyclic imidyl radicals is less prone in the phthalimidyl framework.[10b-g] Finally, phthalimidation would constitute effective amination since a phthalimido group could not only be readily converted to an amino group via straightforward deprotection but also avoid the issue of polyamination.

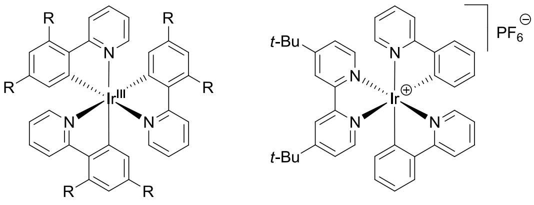


Scheme 2 Proposed approach for *N*-radical mediated C–H imidation.

Table 1 Photocatalytic imidation of benzene with phthalimide derivatives[a]



Entry	X	Cat.	Additive	Yield[b] (%)
1	OAc, **1a**	**2a**	-	NR
2	OMs, **1b**	**2a**	-	20
3	OTs, **1c**	**2a**	-	22
4	OTf, **1d**	**2a**	-	13
5	I, **1e**	**2a**	-	0
6	Br, **1f**	**2a**	-	4
7	Cl, **1g**	**2a**	-	43
8	Cl, **1g**	**2b**	-	55
9	Cl, **1g**	**2c**	-	24
10	Cl, **1g**	**2b**	CH_3CO_2H	65
11	Cl, **1g**	**2b**	*t*-BuCO_2H	46
12	Cl, **1g**	**2b**	CF_3CO_2H	36
13	Cl, **1g**	**2b**	CH_3CO_2H	52
14	H, **1h**	**2b**	*t*-BuOCl/*t*-BuOH	50
15	H, **1h**	**2b**	aq. NaOCl/*t*-BuOH/AcOH	47



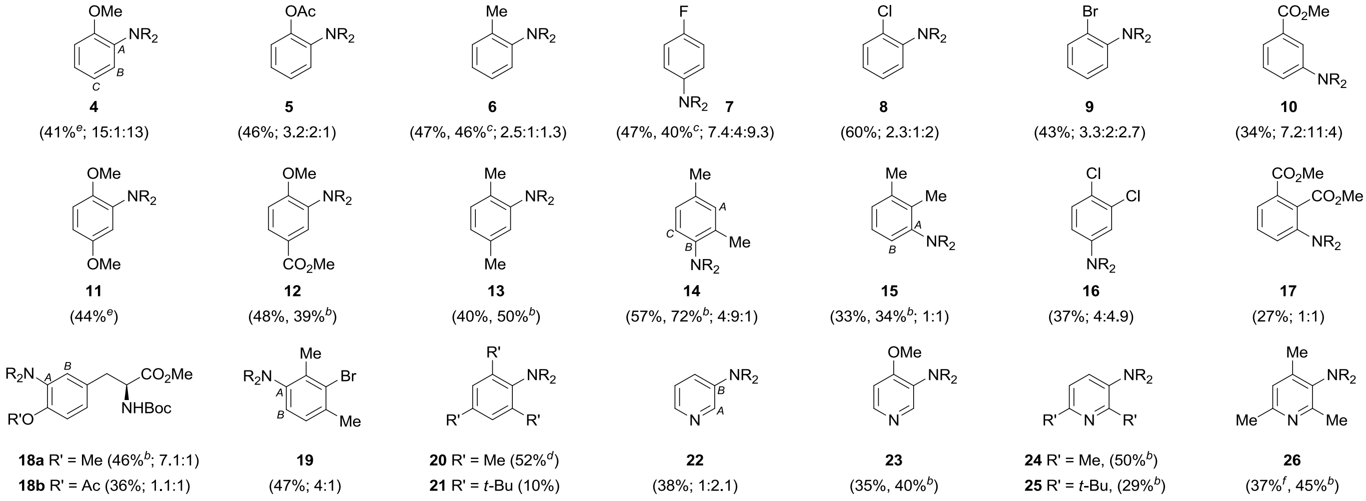
2a R = H, *fac*-Ir(ppy)$_3$
2b R = F, *fac*-Ir(dFppy)$_3$
2c [Ir(ppy)$_2$(dtbbpy)]PF$_6$

[a] *Reaction conditions (unless otherwise specified)*: N–X reagent (0.5 mmol), benzene (1.0 mmol, 2 equiv), catalyst (0.5 mol %), K_2CO_3 (1.5 mmol), MeCN (5.0 mL). [b] Yield determined by ^{1}H NMR analysis. [c] For entries 13–15, N–X reagent (1.0 mmol, 2 equiv) and benzene (0.5 mmol) were used.

Our initial investigations were focused on the identification of a suitable N–X bond capable of engaging in arene C–H imidation (Table 1). We first examined a series of phthalimide derivatives **1** possessing differential *N*-substituents in their reaction with benzene (2 equiv) at room temperature in the presence of K_2CO_3 (3 equiv) and 0.5 mol % *fac*-Ir(ppy)$_3$ (**2a**) using a 20 W household fluorescent light bulb as the source of visible light. Whereas *N*-acetoxy substrate **1a** did not react at all under these conditions (entry 1), the reactions of *N*-sulfonyloxy derivatives **1b**–**d** produced the desired *N*-phenylphthalimide (**3**) in 13–22% yield along with largely unreacted starting materials (entries 2–4). In light of low conversion, further screening experiments were performed with more reactive *N*-halogenated phthalimides. When *N*-iodo and *N*-bromophthalimides (**1e** and **1f**) were used, rapid reactions took place, where reduction to phthalimide (**1h**, >80%) was a dominant pathway (entries 5 and 6). In contrast, *N*-phenyl product **3** was generated in 43% yield from the reaction of *N*-chlorophthalimide (**1g**) (entry 7). These results are in congruence with previous observations in related studies, indicating that dissociative one-electron reduction leading to formation of an *N*-radical and expulsion of a halide ion is more efficient with N–Cl bonds than with N–Br or N–I bonds.[17] Given the interconnection of the catalyst redox with both *N*-radical generation and *C*-radical removal (two SET processes in Scheme 2), we turned our attention to examining the photocatalyst (entries 7–9). A brief survey revealed that catalyst **2b** with a more strongly oxidizing potential ($E_{1/2}$ $[Ir^{IV}/Ir^{III}]$ = +1.23 V vs SCE),[18] relative to catalyst **2a** ($E_{1/2}$ $[Ir^{IV}/Ir^{III}]$ = +0.77 V vs SCE),[18] indeed proved more effective, giving rise to **3** in 55% yield (entries 7 and 8). Interestingly, however, cationic complex **2c** also possessing a higher oxidizing potential ($E_{1/2}$ $[Ir^{IV}/Ir^{III}]$ = +1.17 V vs SCE)[11a,19] displayed poor performance (entry 9). Additional improvement came from running the reaction in the presence of acetic acid (20 mol %), which increased the yield of **3** to 65% (entries 10-12).[20] It was found that the optimized conditions were applicable to a reaction employing benzene as the limiting agent, where imidation product **3** was obtained in 52% yield (entry 13). Finally, the C–H imidation was successfully carried out directly starting from phthalimide (**1h**) through a one-pot *N*-chlorination/C–H imidation procedure (entries 14 and 15).

With the standard conditions, the scope of the reaction was examined with an assortment of substrates possessing varied electronic and steric properties. As summarized in Table 2, a wide range of arenes with mono- (**4**–**10**), di- (**11**–**18**) and tri- (**19**–**21**) substitution as well as pyridines (**22**–**26**) participated

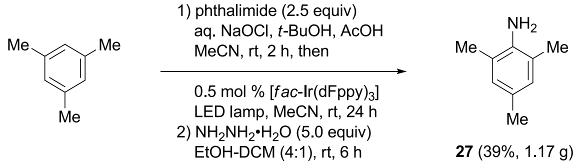
Table 2 Substrate scope of iridium-catalysed C–H imidation of arenes and heteroarenes[a]



4 (41%[e]; 15:1:13)
5 (46%; 3.2:2:1)
6 (47%, 46%[c]; 2.5:1:1.3)
7 (47%, 40%[c]; 7.4:4:9.3)
8 (60%; 2.3:1:2)
9 (43%; 3.3:2:2.7)
10 (34%; 7.2:11:4)
11 (44%[e])
12 (48%, 39%[b])
13 (40%, 50%[b])
14 (57%, 72%[b]; 4:9:1)
15 (33%, 34%[b]; 1:1)
16 (37%; 4:4.9)
17 (27%; 1:1)
18a R' = Me (46%[b]; 7.1:1)
18b R' = Ac (36%; 1.1:1)
19 (47%; 4:1)
20 R' = Me (52%[d])
21 R' = *t*-Bu (10%)
22 (38%; 1:2.1)
23 (35%, 40%[b])
24 R' = Me, (50%[b])
25 R' = *t*-Bu, (29%[b])
26 (37%[f], 45%[b])

[a] *Reaction conditions (unless otherwise specified)*: *N*-chlorophthalimide (**1g**, 0.5 mmol), arene (1.0 mmol), catalyst **2b** (0.5 mol %), AcOH (20 mol %), K_2CO_3 (1.5 mmol), MeCN (5 mL, 0.1 M), 20W CFL, room temperature, 24 h. Isolated yield. [b] **1g** (1.0 mmol) and arene (0.5 mmol) were used. [c] Phthalimide (1.0 mmol), *t*-BuOCl (1.0 mmol), *t*-BuOH (1.0 mmol), then arene (0.5 mmol). [d] Phthalimide (1.25 mmol), NaOCl(aq.) (1.0 mmol), AcOH (1.0 mmol), *t*-BuOH (1.0 mmol), then arene (0.5 mmol). [e] Along with **4** and **11**, *ipso*-substitution products were formed in 4% and 10% yield, respectively. [f] A 20 mmol scale reaction.

well in this C–H imidation process. The observed pattern of regioselectivity was similar to that of electrophilic aromatic substitution reactions, as expected for a reaction mediated by a radical intermediate.[21] However, the reaction proceeded well with both electron-rich and electron-poor arenes,[22] including substrates (e.g. **17**) that would not exhibit comparable reactivity in classical electrophilic aromatic substitution processes.[23] A variety of functional groups such as halides, esters, ethers and carbamates were tolerated in this reaction, as exemplified well by the formation of L-tyrosine derivatives **18**. In line with the findings in the initial studies, the products arising from multiple imidation were not detected or produced only in small amounts (<5%). Neither did benzylic C–H bonds interfere with the reaction.[24] It was also noteworthy that the process could be conducted employing either the imidating reagent (**1g** or **1h**) or arene substrate as a limiting agent, providing similar results. Although the reactions carried out in inert atmosphere gave more consistent results, rigorous removal of air and moisture was unnecessary, as manifested by the comparable yields of **6** and **7** obtained through the one-pot chlorination/imidation procedure starting with phthalimide (**1h**). The process, however, was ineffective with highly electron-rich 1,3,5-trimethoxybenzene, which underwent chlorination,[25] and was often accompanied by *ipso*-phthalimidation when certain methoxyarenes (e.g. **4** and **11**) were employed, thus posing a limitation.



27 (39%, 1.17 g)

Scheme 3 Gram scale one-pot C–H amination of mesitylene.

In order to demonstrate the practicality of the reaction, a one-pot *N*-chlorination/C–H imidation/deprotection sequence was applied to mesitylene (Scheme 3). After in situ preparation of *N*-chlorophthalimide from phthalimide, a gram scale imidation was uneventfully performed under the standard conditions. In this preparative scale experiment, it was found that the reaction rate could be significantly accelerated, while maintaining a low catalyst loading, by simply increasing the intensity of light.[26] Upon completion of the imidation step, hydrazinolysis of the resulting phthalimido product **20** afforded aminomesitylene (**27**) in 39% overall yield. This result serves to illustrate the potential utility of the process as an efficient C–H amination method.

Conclusions

In summary, we report a mild and convenient photocatalytic method for C–H imidation of arenes. The process allows for formation of *N*-aryl bonds by introducing a phthalimido group to unfunctionalized arenes via a nitrogen radical mediated aromatic substitution mechanism, accomplishing a Minisci-type C–H functionalization. An important feature of this imidation is mild generation of the phthalimidyl radical intermediate from *N*-chlorophthalimide at room temperature via reductive scission of the N–Cl bond using a visible light photoredox catalyst. The present imidation method is operationally simple and can be conducted on gram scale using only inexpensive, commercially available reagents with very low catalyst loading. It is expected that this unique method representing an alternative mode of arene C–H activation will be of broad utility in the preparation of aromatic amines.

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† Electronic Supplementary Information (ESI) available: Details of experimental procedures and accompanying spectroscopic data. See DOI: 10.1039/c000000x/

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