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C–H Amination

Towards Uniform Iodine Catalysis: Intramolecular C–H Amination of Arenes under Visible Light

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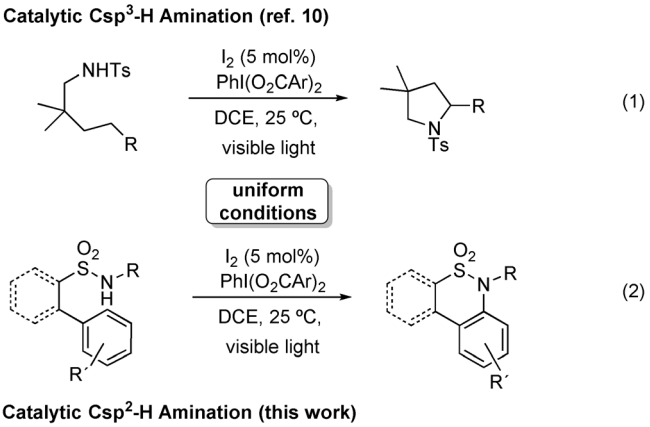
Abstract: A photochemical catalytic amination of arenes is presented. The reaction proceeds under benign iodine catalysis in the presence of visible light as the initiator and provides access to a range of differently substituted arylamines. A total of 29 examples demonstrate the broad applicability of this mild oxidation method. The scope of the reaction could further be expanded to silyl-tethered derivatives, which undergo intramolecular amination upon formation of seven-membered heterocycles. Cleavage of the silicon tether provides access to the corresponding 3-substituted anilines.

Approaches toward the direct C–H amination of arenes are of significant interest because they provide a straightforward and economic access to anilines and higher-functionalized aryl amine derivatives.[1] Entities of this type are present in a large number of functional molecules of pharmaceutical and biological interest.[1,2] Common approaches toward C–H amination rely on the use of transition-metal catalysts and an impressive body of recent work has demonstrated the usefulness of palladium, rhodium, iridium, and other metals for the aforementioned transformation.[3]

High oxidation state iodine reagents have been identified as useful alternatives to common transition metals.[4] Their particular appeal stems from their broad scope in general oxidation chemistry combined with the fact that their use is not hampered by the occurrence of residual metal contamination. Consequently, iodine(III)-mediated and catalyzed amination of aromatic C–H bonds has recently been explored.[5–7] In another area of iodine(III)-mediated reactions, several reports on the combined use of stoichiometric amounts of molecular iodine in combination with excess equivalents of compounds of the general structure $ArI(O_2CR)_2$ have become available for intramolecular C–H amination reactions. Such reactions have previously been addressed under conditions of overstoichiometric reagent combinations, which in several cases led to undesired side-product formation upon overoxidation.[8] One may anticipate that catalysis should avoid such problems because it can operate under more defined oxidation conditions. Despite the general interest in the field, reliable iodine catalyses remain largely unexplored for the intramolecular oxidative synthesis of aniline derivatives.[5,9]

We recently reported on the iodine-catalyzed Hofmann–Löffler reaction, which includes the visible-light-induced amination of a sp^3-hybridized carbon as the key step (Scheme 1, [Eq. (1)]).[10] Within this context, we became interested in the application of this amination concept[11] for the related light-induced functionalization of arenes (Scheme 1, [Eq. (2)]).[12] Usually, conditions for either alkyl or aryl C–H amination are not transferable from one case to the other because the operating reaction mechanisms are profoundly different in nature. From this perspective, the exploration of nitrogen radical intermediates from iodine catalysis could result in a useful uniform reactivity comprising both cases.



Scheme 1. Uniform reaction conditions for light-initiated iodine-catalyzed alkyl and aryl amination (Equations (1) and (2), respectively). Ar = 3-Cl-C_6H_4, DCE = 1,2-dichloroethane.

We here report that this assumption indeed leads to a feasible approach toward a new direct catalytic arene amination using visible-light initiation.[13] The reaction was initially developed for biaryl derivatives, and was explored for the phenyl derivative **1a** (Scheme 2). Suitable conditions were obtained already at the outset of a short screening and consist of the application of comparable catalysis from alkyl amination. A cata-

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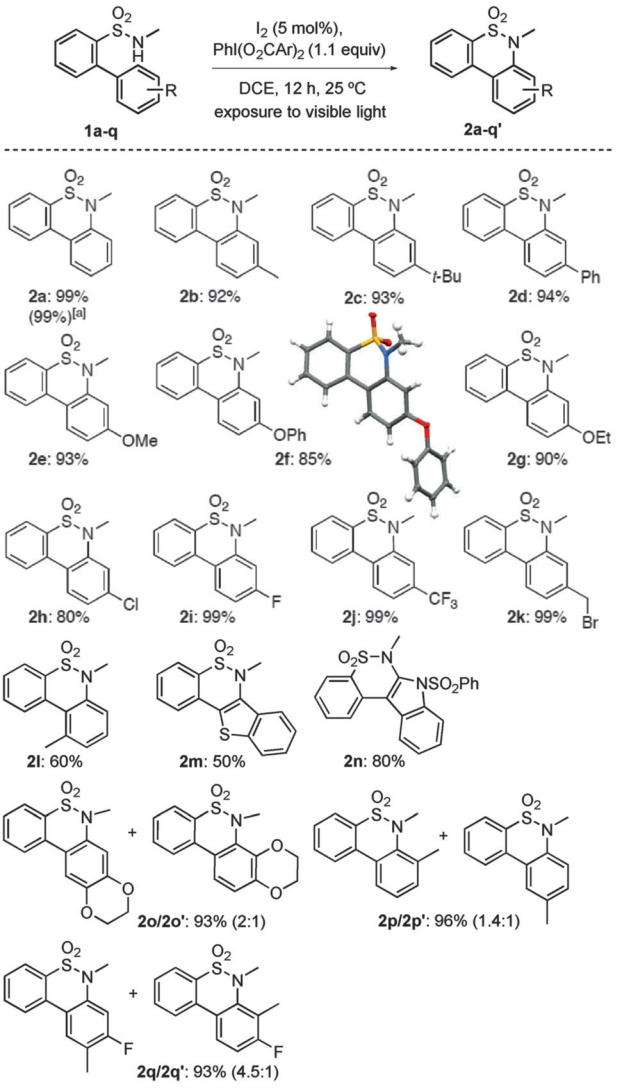
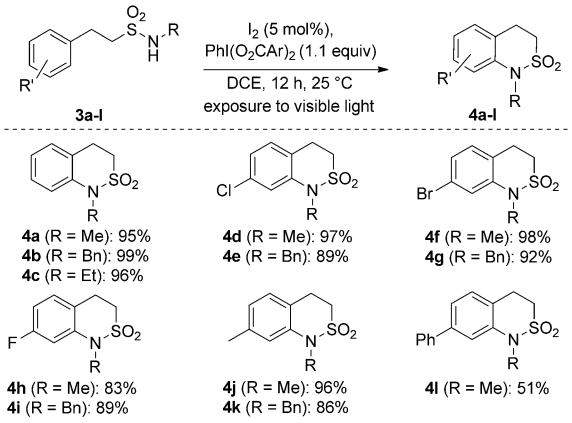


Scheme 2. Scope of intramolecular C–H amination of biaryls. Yields refer to isolated yields after purification. [a] Reaction at 4.1 mmol scale.

lyst loading of 5 mol% elemental iodine was optimum, in combination with a hypervalent iodine reagent as terminal oxidant.[14] The formation of **2a** proceeds in quantitative yield and can be carried out conveniently at 4.1 mmol scale (1.06 g). The reaction is general for a series of these derivatives and proceeds in high yields and with complete selectivity. For example, *para*-substituted arenes of different electronic parameters were all tolerated in the amination (compounds **2b–k**, 80–99%). The constitution of the products was unambiguously assured from X-ray analysis of the 4-phenoxy derivative **2f**.[15]

1,2,3-Trisubstituted compound **2l** demonstrates the compatibility of an *ortho*-disubstituted arene, and the successful aminations of **1m** and **1n** expand the scope to heteroarenes such as benzothiophene and indole. Higher-substituted arenes also undergo the intramolecular amination, although they form regioisomeric mixtures (products **2o/2o'** to **2q/2q'**, 1.4:1 to 4.5:1 regioisomeric ratio).

A rigid preorganization of the coupling entities within a biaryl scaffold is not a requirement as related alkyl-connectivity also led to a protocol with related efficiency (Scheme 3). Representative substrates **3a–l** include common arene substitution patterns and were investigated for different *N*-alkyl sulfonamides. As in the case of related biaryl derivatives **2**, the formation of compounds **4** proceeds in high isolated yields (51–99%) and with complete selectivity.

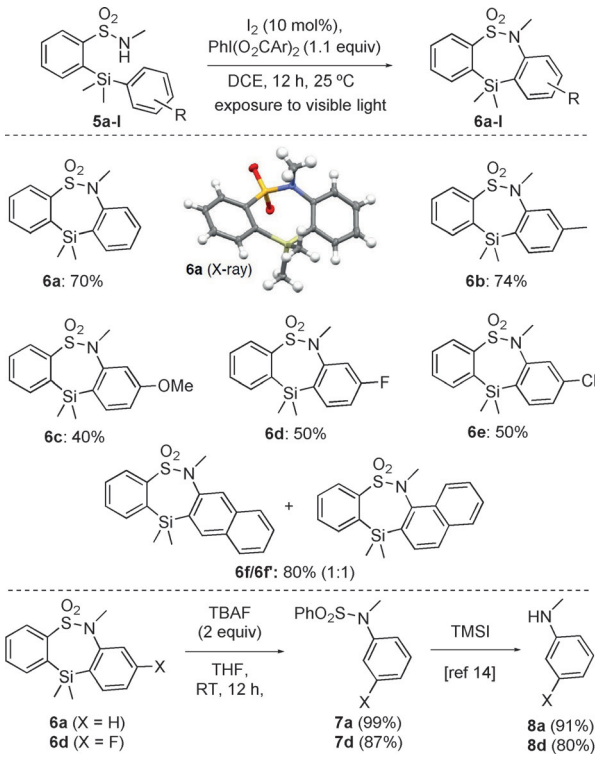


Scheme 3. Scope of intramolecular C–H amination of ethylenylarenes. Yields refer to isolated yields after purification.

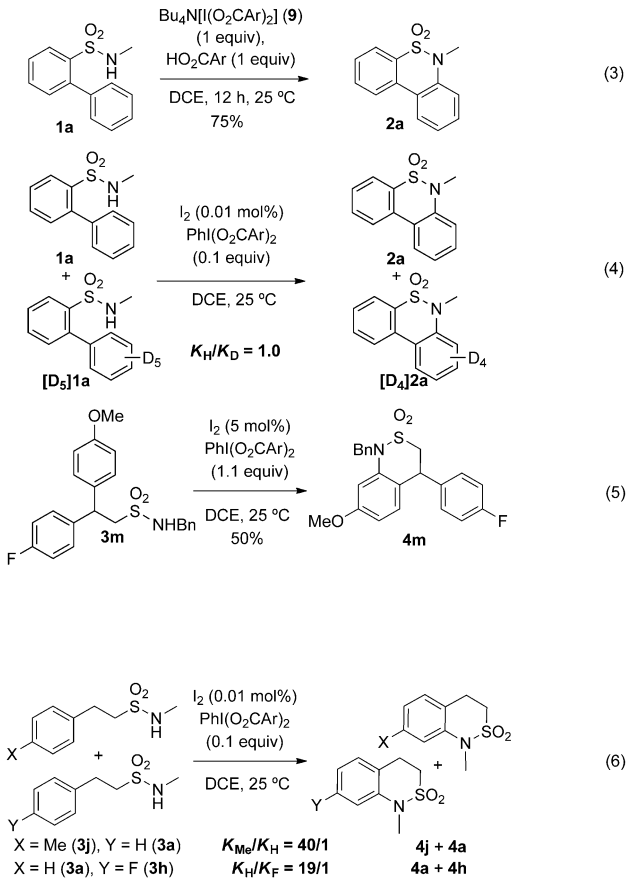
Deprotection of these heterocycles is readily accomplished through hydrogenolysis of the benzyl derivatives, as demonstrated for the representative case of product **4b** (H_2, Pd/C, EtOH, 91%).[14]

The reaction scope could be extended to silicon-tethered arenes **5**.[16] The subsequent intramolecular C–H amination proceeds upon seven-membered ring formation. It requires a slightly higher catalyst loading of 10 mol%, but proceeds with the expected complete selectivity in favor of C–H amination (Scheme 4). For the parent derivative **6a**, the product constitution was secured from X-ray analysis.[15] Arenes **5b–e** with electronically different substitution undergo the C–H amination within this protocol (40–78% yield), and a 2-naphthalene derivative **5f** forms the two regioisomeric amination products **6f/f'** in combined 80% yield. Advantageously, as demonstrated for products **6a,d**, the silyl tether can be removed upon mild exposure to tetrabutylammonium fluoride to give the phenylsulfonyl-substituted anilines **7a,d** quantitatively. Conversion of these compounds into the free anilines **8a,d** is possible following a modified literature procedure.[17] This sequence starting from **5** thus provides access to the corresponding 3-substituted anilines with complete selectivity. Such a substitution pattern would be synthetically difficult via a direct C–H amination or would not be accessible from standard electrophilic aromatic substitution.

Control experiments demonstrate that no conversion is obtained either in the absence of molecular iodine or in the dark lab.[12] The reaction appears to involve the expected N–I bond as in the related catalytic alkane Csp^3-amination.[10] The isolated tetrabutylammonium iodinane **9**[10] was employed to demonstrate the nature of an electrophilic iodine(I) catalyst state at the outset of the reaction. In line with this anticipation, reagent **9** promoted clean aryl amination with standard com-



Scheme 4. Scope of intramolecular C–H amination using a silyl tether. Yields refer to isolated yields after purification.



Scheme 5. Control experiments.

pound **1a** upon acid activation[18] (Scheme 5, [Eq. (3)]). A competition experiment between **1a** and its pentadeuterated derivative [D_5]**1a** revealed no difference regarding the individual rates (kinetic isotope effect $k_H/k_D = 1$, see Scheme 5, [Eq. (4)]). Finally, an internal electronic competition experiment with precursor **3m** showed exclusive amination at the more electron-rich anisole ring forming **4m** in 50% yield (Scheme 5, [Eq. (5)], 99% based on recovered starting material). A related outcome was observed for two intermolecular competition experiments between **3a** and **3j**, and **3a** and **3h**, respectively. In both cases, a significant preference for amination of the more electron-rich arene was encountered, favoring formation of **4j** over **4a**, and **4a** over **4h**, respectively (Scheme 5, [Eq. (6)]).

The reaction starts from the established I(O_2CAr) catalyst **10** that promotes *N*-iodination of the sulfonamide starting materials to intermediate **A** (Figure 1, the structure of **3** is shown ar-

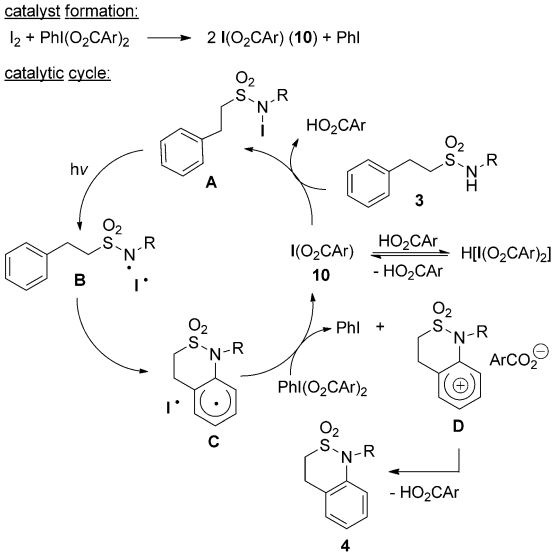


Figure 1. Mechanistic context.

bitrarily). As demonstrated by the control experiment using the isolated reagent **9**, a potential alternative pathway proceeding via aryl radical cations generated from the hypervalent iodine reagent itself can be ruled out.[19] Photolytically assisted homolysis of the N–I bond in **A** provides access to *N*-centered radical **B**. This electrophilic nitrogen radical directly adds to the aromatic ring to generate a delocalized cyclohexadienyl radical **C**. Subsequent oxidation by the terminal hypervalent iodine leads to the cationic intermediate **D** and directly regenerates the iodine(I) catalyst **10**. Although less probable, oxidation may occur already at stage **B** to generate a positively charged nitrogen atom, which engages in electrophilic aromatic substitution[20] toward **D**. Both of the two potential C–N bond formation events should be influenced by the electronic situation of the arene as corroborated by the control experiments from Equations (5) and (6). From **D**, the reaction terminates by final proton loss upon re-aromatization to the C–N coupling product **4**. This final step is rapid as demonstrated by the kinetic isotope experiment from Equation (4).

In summary, we have developed an iodine catalysis protocol that provides conditions for a mild and selective intramolecular aryl amination reaction. This chemistry demonstrates that photochemical iodine catalysis can provide general oxidative amination conditions for the cases of aliphatic and aromatic hydrocarbons alike. This broad scope is unprecedented in the area and should stimulate the development of additional reactivity.

Acknowledgements

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Keywords: amination · arenes · catalysis · iodine · visible light

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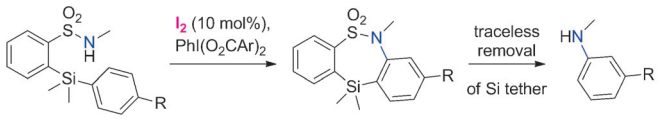

Iodine catalysis aminates arenes! Iodine in catalyst loadings of 5–10 mol% provides access to intramolecular Csp^2–N bond formation. Sulfonamides are employed as nitrogen sources, leading to excellent yields. In some cases, introduction of a traceless linker provides ready access to aniline derivatives.

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