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# Metal-free direct oxidative intermolecular diarylation of anilides at ambient temperature assisted by cascade selective formation of C–C and C–N bonds†

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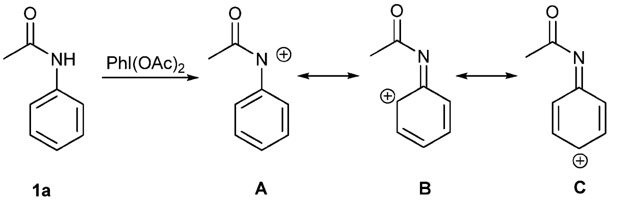
**A new atom-economical process of direct oxidative intermolecular functionalization of aniline derivatives by simple arenes was developed. The products were formed in a highly regioselective manner under metal-free conditions at ambient temperature.**

Carbon–carbon and carbon–heteroatom intermolecular bond formation reactions are easily reasoned from broad applications of these transformations and represent a fundamental and challenging topic in organic chemistry.[1] The development of effective methods for the formation of cross-coupled products is an intensively investigated area of great significance. Direct oxidative cross-coupling between two unfunctionalized compounds through cleavage of C–H bonds represents an environmentally benign and economically attractive synthetic strategy.[2] Recently, hypervalent iodine(III) compounds found application for direct oxidative, metal-free cross-coupling of unfunctionalized arenes in a regioselective manner under environmental friendly reaction conditions.[3] However, these methods are limited to electron rich arenes. The development of new efficient, direct oxidative cross-coupling methods which could provide access to new scaffolds and/or are based on new reaction mechanisms is highly demanded.

During studies on the direct functionalization of unactivated C–H bonds, we developed an intermolecular, metal-free, direct oxidative method of C–N bond formation *via* cross-coupling with non-prefunctionalized arenes.[4,5] The mechanistic studies indicated the formation of a nitrenium ion (**A**) which undergoes an electrophilic aromatic substitution leading to the desired products of the C–H bond amination (Scheme 1).[4] Based on this study, we considered possibilities for stabilization of the cation (**A**) by charge delocalization to a carbenium ion (**C**) *via* an ion (**B**). Ion **C** can be trapped by non-prefunctionalized arenes leading to biphen-4-yl acetamides *via* formation of a new C–C bond in *para*-position to the acetamide group under metal-free conditions.[6,7] We herein report our results on an atom-economical, regioselective, environmentally benign method of diarylation of derivatives of aniline with non-prefunctionalized arenes *via* cascade formation of C–C and C–N bonds at ambient temperature under metal-free reaction conditions.



**Scheme 1** Resonance structures of the aryl nitrenium ion.

To test our hypothesis, we employed derivatives of aniline and mesitylene (**2a**) in the presence of PhI(OAc)$_2$ in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) (Table 1, entries 1–6).[8] To our delight, we observed formation of product **3** of the diarylation. The best result was obtained using *N*-phenylacetamide which resulted in a yield of 63% for the product of the cascade formation of C–C and C–N bonds (Table 1, entry 5). It is notable that the diarylation could be carried out without usage of a large excess of arenes at ambient temperature. Interestingly, the formation of typical by-products of transition-metal-catalyzed reactions such as homodimers was not observed in any reaction. Furthermore, all transformations resulted in regioselective C–C bond formation and products of *ortho*-arylation of aniline derivatives were not detected in the reaction mixtures.[6,7] Only a trace amount of the mono-*N*-arylated product with mesitylene (**2a**) was detected. However, decrease in the loading of mesitylene led to increase of the mono-*N*-arylated product. Additionally, an *N*-iodophenylation product of **1e** was detected as a result of *mono*-arylation with iodobenzene.[6a] Afterwards, various solvents were tested in order to improve the yield of the product (Table 1, entries 7–12). However, only in 2,2,2-trifluoroethanol (TFE) the desired product was obtained in moderate yield. Other sources of hypervalent iodine(III) oxidants were tested. Besides *para*-tolyliodonium diacetate which gave a little increase in the yield of the diarylated product (Table 1, entry 13), the application of different oxidants was unsuccessful (Table 1, entries 14–16). Importantly, the usage of *para*-tolyliodonium diacetate instead of PhI(OAc)$_2$ as the oxidation reagent prevents formation of the product of the *N*-iodophenylation.

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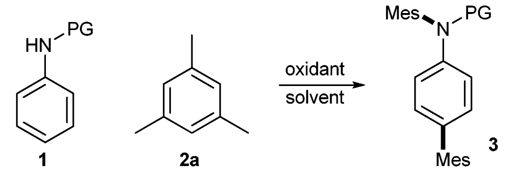
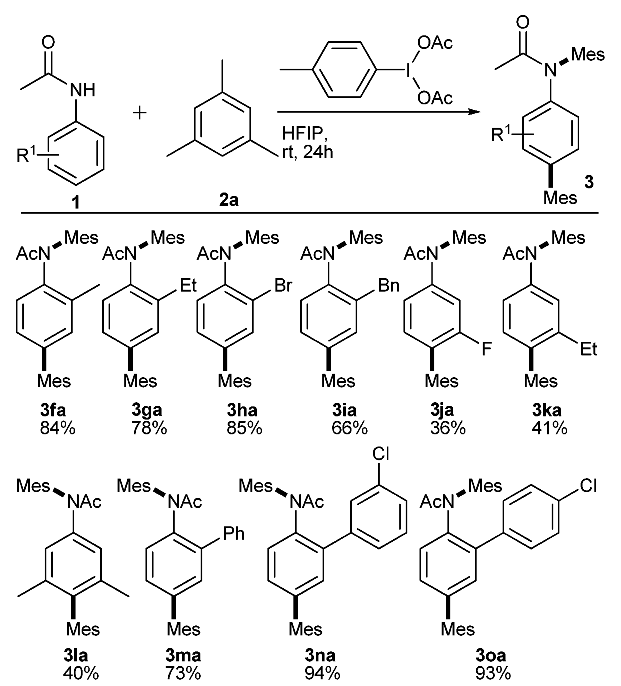
**Table 1** Screening of reaction conditions[a]



| Entry | PG | Solvent | Oxidant | Time/h | Yield[b] [%] |
|---|---|---|---|---|---|
| 1 | H (**1a**) | HFIP | $PhI(OAc)_2$ | 40 | < 5 (**3aa**) |
| 2 | Bz (**1b**) | HFIP | $PhI(OAc)_2$ | 29 | 38 (**3ba**) |
| 3 | *p*-Tos (**1c**) | HFIP | $PhI(OAc)_2$ | 20 | 36 (**3ca**) |
| 4 | $CF_3CO$ (**1d**) | HFIP | $PhI(OAc)_2$ | 29 | 24 (**3da**) |
| 5 | Ac (**1e**) | HFIP | $PhI(OAc)_2$ | 16 | 63 (**3ea**) |
| 6 | $Me_3CCO$ | HFIP | $PhI(OAc)_2$ | 48 | < 5 |
| 7 | Ac (**1e**) | TFE | $PhI(OAc)_2$ | 16 | 40 (**3ea**) |
| 8 | Ac (**1e**) | $MeNO_2$ | $PhI(OAc)_2$ | 20 | 4 (**3ea**) |
| 9 | Ac (**1e**) | MeOH | $PhI(OAc)_2$ | 16 | < 5 |
| 10 | Ac (**1e**) | $CH_2Cl_2$ | $PhI(OAc)_2$ | 16 | < 5 |
| 11 | Ac (**1e**) | DMF | $PhI(OAc)_2$ | 16 | < 5 |
| 12 | Ac (**1e**) | none | $PhI(OAc)_2$ | 16 | < 5 |
| 13 | Ac (**1e**) | HFIP | $4\text{-}MeC_6H_4I(OAc)_2$ | 23 | 65 (**3ea**) |
| 14 | Ac (**1e**) | HFIP | $PhI(OCOCF_3)_2$ | 16 | < 5 |
| 15 | Ac (**1e**) | HFIP | PhI(OH)OTos | 16 | < 5 |
| 16 | Ac (**1e**) | HFIP | $Ph_2IOTf$ | 16 | < 5 |
| 17[c] | Ac (**1e**) | HFIP | $4\text{-}MeC_6H_4I(OAc)_2$ | 21 | 60 (**3ea**) |
| 18[d] | Ac (**1e**) | HFIP | $4\text{-}MeC_6H_4I(OAc)_2$ | 21 | 62 (**3ea**) |
| 19[e] | Ac (**1e**) | HFIP | $4\text{-}MeC_6H_4I(OAc)_2$ | 21 | 68 (**3ea**) |
| 20[e,f] | Ac (**1e**) | HFIP | $4\text{-}MeC_6H_4I(OAc)_2$ | 21 | 68 (**3ea**) |

[a] Conditions: derivative of aniline **1** (0.1 mmol, 1 equiv.), **2a** (0.3 mmol), oxidant (0.22 mmol, 2.2 equiv.) in solvent (0.1 M). [b] Isolated yields after column chromatography. [c] 10 equiv. of **2a**. [d] 0.03 M solution. [e] 0.2 M solution. [f] Using 3 equiv. of $4\text{-}MeC_6H_4I(OAc)_2$. PG = protection group.

**Table 2** Cascade diarylation of acetanildes with mesitylene[a]



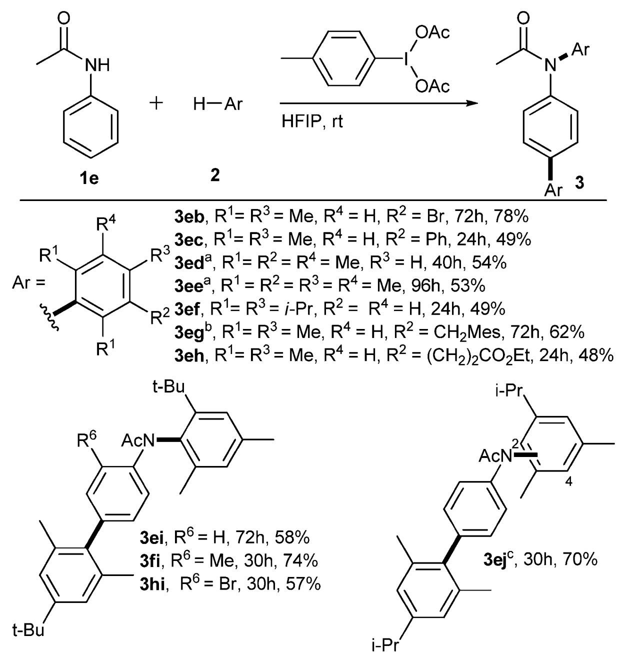
[a] Reaction conditions: aniline derivative **1** (0.2 mmol, 1 equiv.), **2a** (0.6 mmol), $4\text{-}MeC_6H_4I(OAc)_2$ (0.44 mmol) in HFIP (0.2 M).

The yield of **3ea** slightly depended on the concentration of the reaction mixture (Table 1, entries 17–20). However, increase of the yield of the mono-*N*-arylated product was detected. The best yield of 68% for cascade formation of C–C and C–N bonds was obtained using a 0.2 M solution of **1e**.

With optimized conditions in hand, we focused on the exploration of the scope and generality of the method. We first examined the effect of substitutions in the aniline derivatives (Table 2). In general, we found that the presence of a substituent with different electronic and steric properties in the *ortho*-position did not have any negative effects on the formation of the desired products (Table 2, products **3fa–3ia**). Unfortunately, when using cyclic aniline derivatives such as 2*H*-1,4-benzoxazin-3(4*H*)-one and 2-oxindole, formation of mono-*N*-arylation products was observed and the desired products of diarylation were obtained in yields of < 10% under optimized conditions. Afterwards, we examined substitutions in the *meta*-position (Table 2, products **3ja–3la**). Unfortunately, the products of cascade diarylation were obtained only in moderate yields. Gratifyingly, the developed method allows the formation of the sterically congested product **3la** bearing four methyl groups around the newly formed C–C bond which is challenging for metal catalyzed reactions. As expected, the *para*-substituted derivatives led to the selective formation of the mono-*N*-arylation product under identical reaction conditions (see ESI†). Afterwards, we drew our attention to 2-acetaminobiphenyls which under similar reaction conditions in the absence of the non-prefunctionalized arene undergo an intramolecular amination to carbazoles. To our delight, we found that the developed method allows suppression of the formation of intramolecular reaction products and led to the selective formation of C–C and C–N bonds in 73–94% yield (Table 2, products **3ma–3oa**).

Subsequently, a variety of non-prefunctionalized arenes were tested in the developed intermolecular cascade process. We were pleased to find out that different electron rich benzene derivatives undergo the oxidative cascade diarylation process giving products in moderate to good yields (Table 3). The application of complex or sterically congested derivatives is tolerated. However, our attempts to employ two structurally different non-prefunctionalized arenes in diarylation led to the formation of an inseparable mixture of products. Furthermore, a difference in behaviour of carbenium and nitrenium ions was found in diarylation with 1-*tert*-butyl-3,5-dimethylbenzene (**2i**) (Table 3, products **3ei**, **3fi**, **3hi**). The nitrenium ion is attacked by the most nucleophilic and sterically congested position of **2i**, while the carbenium ion is attacked by the less nucleophilic and less sterically bulky position of **2i**. This result is exceedingly significant due to the achievement of highly chemoselective new bond formation. A mixture of regioisomers was obtained when a *tert*-butyl group was changed to *iso*-propyl (Table 3, product **3ej**). The application of less nucleophilic arenes such as *ortho*- or *para*-xylene resulted in the selective formation of mono-*N*-arylation products. Furthermore, the products of arylation were not detected if benzene or its electron poor derivatives were employed. In general, the obtained *N*-arylbiphenyl-4-amines (**3**) represent a key scaffold of numerous biological probes and electroluminescent

**Table 3** Cascade diarylation of *N*-phenylacetamides with non-prefunctionalized arenes



Reaction conditions: aniline derivative **1** (0.2 mmol, 1 equiv.), arene (1.0 mmol), 4-$MeC_6H_4I(OAc)_2$ (0.54 mmol) in HFIP (0.2 M). [a] Using arene (2.0 mmol), 4-$MeC_6H_4I(OAc)_2$ (0.8 mmol). [b] In the mixture DCM/HFIP (1/1) 0.1 M. [c] Regioisomer ratio is 1 : 1.2.

materials and can be aminated under metal free conditions (see ESI†, Scheme S1).

Mechanistically, we assume that the oxidation of *N*-phenylacetamides (**1**) led to the formation of the nitrenium ion (**A**) which is stabilized by charge delocalization to the carbenium ion (**C**) (see ESI†, Scheme S2). Both ions **A** and **C** may react with nucleophilic arenes giving products of arylation. The electron-deficient ion **C** is attacked by the nucleophilic arene giving *N*-(biphenyl-4-yl)acetamides (**4**), while arylation of intermediate (**A**) leads to formation of a mono-*N*-arylation product (**5**). We assume that under optimized reaction conditions, the extensively charge delocalized intermediate **C** is preferred although this depends on the structure of derivatives **1**. Product **4** is oxidized by the second equivalent of iodine(III) reagent to give nitrenium ion (**D**), which is involved in the electrophilic aromatic substitution with the arene to yield product **3**. We found that in the presence of radical scavenger, the yield of product **3** was not decreased. This finding indicates that radical species do not take part in the diarylation process. In a control experiment, anilide (**5**) did not lead to product **3** under identical oxidative reaction conditions. Furthermore, application of *para*-substituted aniline derivatives led to mono-*N*-arylation products. This result indicates that the developed process is implemented *via* a conserved reaction sequence where the first step is the formation of the C–C bond and the second step is *N*-arylation.

In conclusion, we developed a new highly efficient atom-economical, cascade, oxidative intermolecular process of introduction of two aryl groups in aniline derivatives. The desired products were formed in a highly regioselective manner under metal-free conditions at ambient temperature. The developed transformation was realized by using a single environmental friendly reagent—*para*-tolyliodonium diacetate.

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