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# Metal-Free *N*-Arylation of Secondary Amides at Room Temperature

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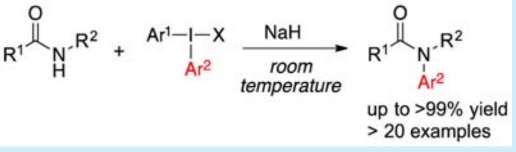
Supporting Information

**ABSTRACT:** The arylation of secondary acyclic amides has been achieved with diaryliodonium salts under mild and metal-free conditions. The methodology has a wide scope, allows synthesis of tertiary amides with highly congested aryl moieties, and avoids the regioselectivity problems observed in reactions with (diacetoxyiodo)benzene.




Aryl amides are found in a range of natural and synthetic products, including peptidomimetics, polymers, and anti-inflammatory compounds.[1] Their importance is illustrated by the immense efforts that have been invested in the development of synthetic routes to such compounds. Metal-catalyzed *N*-arylation of amides has received considerable attention since the pioneering work performed by Goldberg more than a century ago.[2] The transformation has since been improved by the addition of ligands to enable milder reaction conditions.[3] The majority of the protocols are, however, restricted to arylation of cyclic or primary amides. There are only a few metal-catalyzed methods for the intermolecular *N*-arylation of acyclic secondary amides, which are difficult substrates due to steric hindrance. Buchwald and co-workers reported Cu-catalyzed conditions where a number of secondary acyclic amides were arylated,[4] and they subsequently described the Pd-catalyzed synthesis of tertiary acyclic amides employing sophisticated ligands in toluene at 110−130 °C. Aryl groups with *ortho*-substituents or electron-donating groups were unsuitable in this reaction.[5]

Taillefer and co-workers recently developed a Cu-catalyzed protocol for the formation of tertiary acyclic amides. While electron-rich aryl groups could be introduced, *ortho*-substituted aryl moieties were not tolerated.[6] Despite many benefits, metal-catalyzed arylations of amides require ligand addition, high temperature, and long reaction times. Considering the cost of palladium and ligands and the requirement to remove trace amounts of metal residues in biologically interesting targets, development of metal-free methodology is of importance.

Only a handful of metal-free *N*-arylations of amides are known. The use of arynes has been reported,[7] as well as intramolecular arylations under strongly basic conditions and high temperatures.[8] Antonchick and co-workers have recently reported *N*-arylations of acetanilides with simple arenes using (diacetoxyiodo)benzene (DIB) as oxidant.[9] This elegant transformation allows for introduction of sterically demanding aryl groups but requires electron-rich arenes and has inherent regioselectivity issues due to the reaction mechanism.

Diaryliodonium salts are readily available, versatile electrophiles for regiospecific arylation of a variety of nucleophiles.[10] *N*-Arylation with diaryliodonium salts often requires copper catalysis, and metal-catalyzed arylations of lactams and primary amides have indeed been realized.[11] Metal-free *N*-arylation has only been achieved with a limited number of amides[12] and amide derivatives.[13] As a continuation of our long-term interest in metal-free arylation of heteroatom nucleophiles with diaryliodonium salts,[14] we herein report a general protocol for *N*-arylation of secondary acyclic amides that allows introduction of sterically hindered aryl groups under mild conditions.

The phenylation of acetanilide (**1a**) with iodonium salt **2a** to yield tertiary amide **3a** was chosen as model reaction (Table 1).[15] A solvent screening revealed that *o*-xylene and toluene outperformed other common solvents (entries 1−5), and toluene was chosen for further optimizations due to easier handling. Sodium bases were better than potassium bases, and NaH proved to be the best (entries 5−9). Only starting material was recovered with $Et_3N$ (entry 10). The reagent amounts could be lowered from 2 to 1.5 equiv without loss in yield (entries 11 and 12), and the reaction was finished within 2 h by heating to 60 °C (entry 13). The reaction could easily be scaled up to 1 mmol; the base should then be added last to ensure a good yield (entry 14).[15] Finally, the influence of the iodonium anion (X) was investigated, and triflate **2a**, tetrafluoroborate **2b**, and tosylate **2c** all resulted in similar yields, whereas hexafluorophosphate **2d** was inferior (entries 10 and 15−17). Compatibility with the common anions (OTf, OTs, $BF_4$) is important in order to avoid tedious anion exchanges, since different synthetic routes to diaryliodonium salts are employed depending on the structure and electronic properties of the aryl substituents.[16]

The scope of the reaction was first investigated by phenylation of amides **1** with iodonium salt **2a** (Scheme 1). Increased steric hindrance at the α-carbon was well tolerated (**3a−d**), and tertiary cyclohexyl amide **3d** was isolated in 82% yield. The results in parentheses refer to reactions in *o*-xylene with increased reagent amounts and illustrate that the yields can be further improved at the expense of atom efficiency and workup simplicity.

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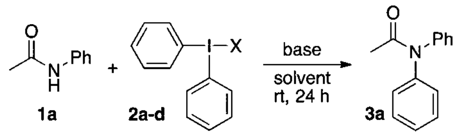
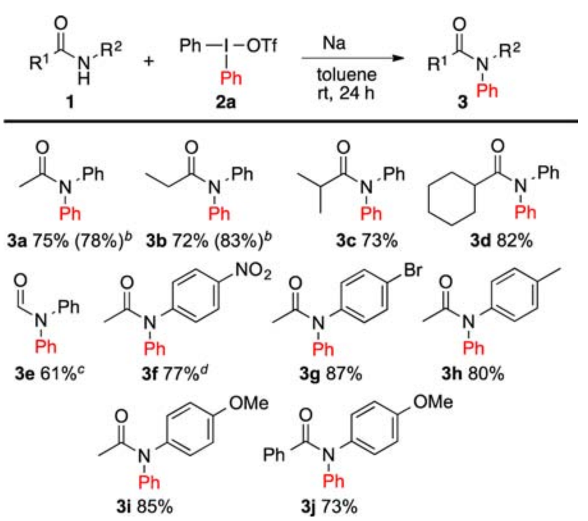
**Table 1. Optimization**[a]




| entry | solvent | base (equiv) | **2** (equiv) | X | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | THF | NaH (2.0) | **2a** (2.0) | OTf | nr |
| 2 | $CH_3CN$ | NaH (2.0) | **2a** (2.0) | OTf | 3 |
| 3 | DMF | NaH (2.0) | **2a** (2.0) | OTf | 11 |
| 4 | *o*-xylene | NaH (2.0) | **2a** (2.0) | OTf | 81 |
| 5 | toluene | NaH (2.0) | **2a** (2.0) | OTf | 76 |
| 6 | toluene | NaOH (2.0) | **2a** (2.0) | OTf | 64 |
| 7 | toluene | *t*-BuONa (2.0) | **2a** (2.0) | OTf | 44 |
| 8 | toluene | *t*-BuOK (2.0) | **2a** (2.0) | OTf | 32 |
| 9 | toluene | $K_3PO_4$ (2.0) | **2a** (2.0) | OTf | 20 |
| 10 | toluene | $Et_3N$ (2.0) | **2a** (2.0) | OTf | 0 |
| 11 | toluene | NaH (1.5) | **2a** (1.5) | OTf | 75[c] |
| 12 | toluene | NaH (1.1) | **2a** (1.1) | OTf | 51[c] |
| 13[d] | toluene | NaH (1.5) | **2a** (1.5) | OTf | 75[c] |
| 14[e] | toluene | NaH (1.5) | **2a** (1.5) | OTf | 70[c] |
| 15 | toluene | NaH (1.5) | **2b** (1.5) | $BF_4$ | 81[c] |
| 16 | toluene | NaH (1.5) | **2c** (1.5) | OTs | 75[c] |
| 17 | toluene | NaH (1.5) | **2d** (1.5) | $PF_6$ | 59[c] |

[a]Conditions: **1a** (0.25 mmol), salt **2**, and base in anhydrous solvent (5 mL). [b]$^1$H NMR yield with 1,3,5-trimethoxybenzene as internal standard. [c]Isolated yield. [d]60 °C, 2 h. [e]1 mmol scale.

**Scheme 1. Amide Scope**[a]



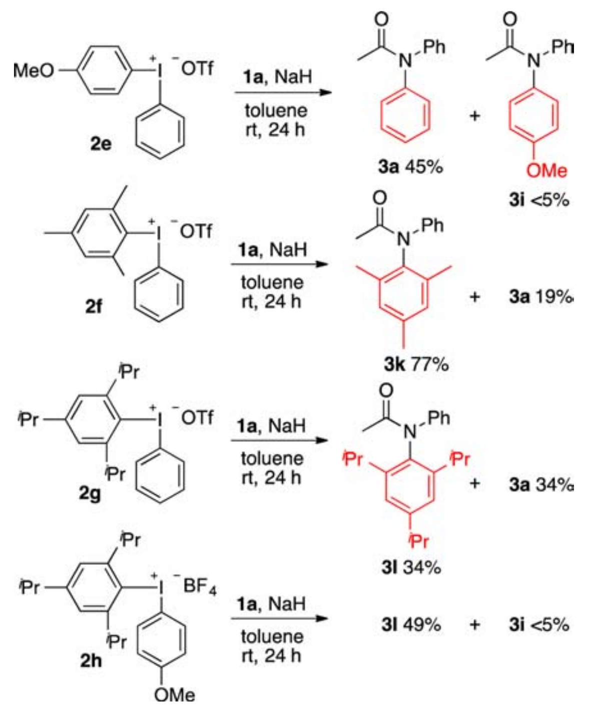

[a]Conditions in Table 1, entry 10. [b]In *o*-xylene with 2 equiv of **2a** and 2 equiv of NaH. [c]60 °C, 3 h. [d]60 °C, 5 h.

Formanilide was less reactive than acetanilide and required heating to 60 °C to give **3e**.[15] Similarly, *p*-nitroacetanilide was almost completely unreactive at room temperature, and mainly starting material was recovered, whereas 77% yield of amide **3f** was obtained at 60 °C. Bromide-substituted acetanilide was easily phenylated to give amide **3g**. The halide is a good handle for further functionalization, and **3g** could be difficult to synthesize under Pd-catalyzed conditions. Amides **3h** and **3i** with electron-donating *N*-substituents were efficiently obtained. Benzamides showed similar reactivity, and **3j** was isolated in good yield despite a difficult purification to remove traces of starting material. This product, and other diarylated benzamides, are interesting targets that display biological activity.[1f] Amides with aliphatic *N*-substituents displayed lower reactivity, and *N*-methylbenzamide was phenylated in poor yield, with unidentified byproducts forming at increased temperature.[15] Arylation of *p*-hydroxyacetanilide under the standard conditions selectively delivered the corresponding diaryl ether in moderate yield.[15]

The reaction was subsequently investigated with a range of diaryliodonium salts, which are easily available via one-pot reactions.[16] Unsymmetric diaryliodonium salts are generally easier to synthesize and can also be more economic in transfer of precious aryl moieties, since only a "dummy" iodoarene is wasted if the arylation proceeds with high chemoselectivity.[10] *Ortho*-substituted aryl groups, such as mesityl or triisopropylphenyl (TRIP), are often used as dummies in metal-catalyzed reactions with diaryliodonium salts.[17] We have recently reported a thorough study on chemoselectivity trends with representative *O*-, *N*-, and *C*-nucleophiles under metal-free conditions.[18] In general, electron-donating aryl moieties are useful dummies, whereas the selectivities with mesityl and TRIP vary with the nucleophile.

To utilize the benefits of unsymmetric diaryliodonium salts in the *N*-arylation of amides, a chemoselectivity study was undertaken with acetanilide (**1a**) and the selected salts **2e–h** (Scheme 2). As expected, the more electron-deficient aryl group

**Scheme 2. Chemoselectivity Trends**




in **2e** was transferred with high selectivity to give **3a**, and the anisyl group can thus be used as a dummy ligand. Metal-catalyzed *N*-arylations of amides are generally sensitive to *ortho*-substituents.[4−6] Hence, we were pleased to see that mesityl salt **2f** transferred the more electron-rich and sterically hindered mesityl group to furnish amide **3k** as the major product, in line with the so-called "*ortho*-effect". This is different from the *N*-arylation of anilines, which is unaffected by *ortho*-substituents.[18] Reactions with the highly congested TRIP salt **2g** were unselective, indicating that the *ortho*-effect can be canceled with too sterically hindered salts. Hence, the more electron-rich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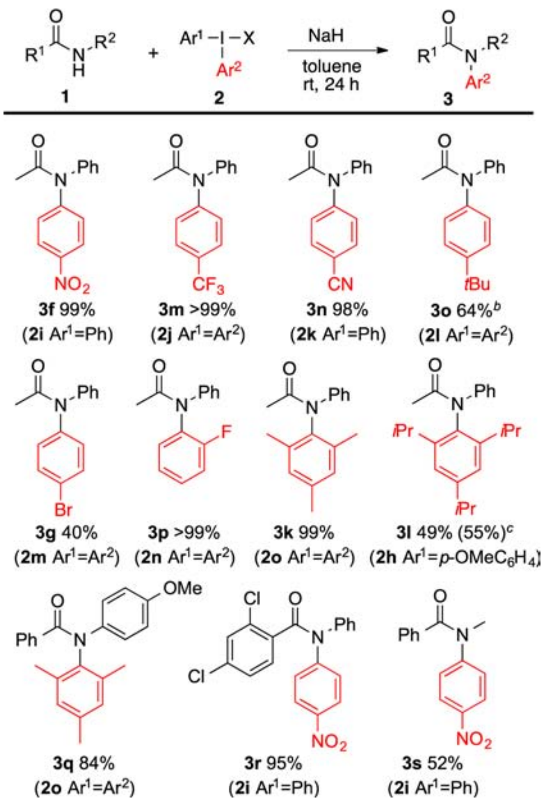
salt **2h** was employed to give the novel and remarkably hindered amide **3l** with high chemoselectivity.

With the chemoselectivity data at hand, the scope with salts **2** and acetanilide (**1a**) was explored (Scheme 3). As expected, complete chemoselectivity was observed with (*p*-nitrophenyl)-phenyliodonium triflate, and amide **3f** was more efficiently obtained in this way (rt vs 60 °C in Scheme 2). Other electron-withdrawing aryl moieties were also transferred in nearly quantitative yields (**3m**,**n**). The *tert*-butyl salt was rather unreactive and required prolonged heating to give **3o**. Electron-rich aryl groups are difficult to transfer to amides with metal-catalyzed methods,[5,6] and arylation of acetanilide with a symmetric *p*-methoxy salt to give amide **3i** mainly resulted in recovered starting material, whereas **3i** easily formed by phenylation of *N*-(4-methoxyphenyl)acetamide (cf. Scheme 1).

**Scheme 3. Diaryliodonium Salt Scope**[a]




[a]Conditions in Table 1, entry 10. [b]60 °C, 24 h. [c]In *o*-xylene.

The use of the bromide-substituted iodonium salt **2m** led to a substantially reduced yield of **3g**, compared to the phenylation of the *p*-bromoanilide yielding **3g** (cf. Scheme 1). This illustrates that high yields of various tertiary amides are obtainable by the proper combination of the two reagents, the secondary acyclic amide and the iodonium salt. *Ortho*-substituents were well tolerated, and fluoro-substituted amide **3p** was formed in quantitative yield. The synthesis of mesityl amide **3k** was further improved by utilization of a symmetric mesityl salt, which delivered **3k** in excellent yield (cf. Scheme 2). The synthesis of TRIP-amide **3l** was slightly more efficient in *o*-xylene, furnishing **3l** in 55% yield. The synthesis of these highly congested products illustrates the utility of the methodology, as metal-catalyzed amide arylations are sensitive to steric hindrance.

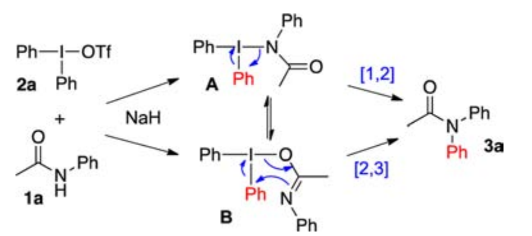
The scope with benzamides was screened next, and the mesityl group was efficiently transferred to furnish the sterically hindered **3q**, carrying three different aryls. Likewise, dichlorobenzamide **3r** was isolated in excellent yield. Finally *N*-methylbenzamide was arylated with nitro salt **2i** to give **3s**, illustrating the increased reactivity of salts with electron-deficient substituents.

It should be emphasized that complete selectivity for *N*-arylation was observed, which is interesting and opposite to previous diaryliodonium arylations of compounds containing amide moieties, such as the *C*-arylation of acetanilide,[19] the *C*-arylation of oxindoles,[20] and the *O*-arylation of pyrimidones.[21]

Metal-free arylations with diaryliodonium salts can either proceed via a SET mechanism[22] or via formation of a T-shaped intermediate, followed by a ligand coupling between the nucleophile and the equatorial aryl moiety.[23] The *N*-arylation of amides proved insensitive to radical traps,[15] which makes a SET mechanism unlikely. An ICP-OES analysis of the crude reaction mixture supports that the transformation is indeed metal-free.[15] Furthermore, amides with electron-donating *N*-substituents reacted faster than those with electron-withdrawing *N*-substituents,[15] which is in agreement with the developing charges in the transition state of the ligand coupling.[23]

Hence, we suggest a mechanism via two possible T-shaped intermediates **A** and **B**, which could be in fast equilibrium with each other (Scheme 4). Intermediate **A** would form product **3a** via a normal ligand coupling, i.e., a [1,2]-rearrangement, whereas intermediate **B** would form **3a** via a [2,3]-rearrangement.

**Scheme 4. Proposed Mechanism**




We have previously reported that the $\alpha$-arylation of enolates preferentially proceeds via a [2,3]-rearrangement of the T-shaped O–I intermediate.[24] The facile formation of highly hindered tertiary amides in this protocol might indicate that intermediate **B** is important in the arylation, and this mechanism will be investigated further.

To conclude, the high reactivity of diaryliodonium salts has been utilized in metal-free arylations yielding tertiary acyclic amides at ambient temperature. Amides with electron-donating groups give the desired product in high yield, whereas electron-withdrawing substituents reduce the reactivity. The trends for the iodonium salts are reversed, and electron-deficient aryl groups are efficiently transferred, while electron-rich aryls result in lower yields. Hence, any type of diaryl amide can be obtained by the appropriate selection of starting materials, and the reaction scope is wide. Furthermore, products with unprecedented steric congestion can be obtained. Contrary to other hypervalent iodine-mediated reactions, this arylation is regiospecific and efficiently transfers aryl groups with electron-withdrawing substituents.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental details and spectral data for novel compounds as well as NMR spectra of all products. The Supporting Information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### Notes

The authors declare no competing financial interest.

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