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Metal-Free *C*-Arylation of Nitro Compounds with Diaryliodonium Salts

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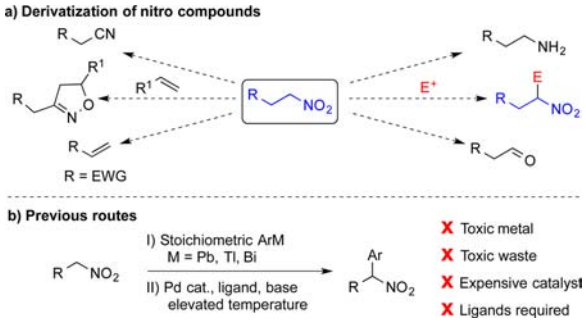
Supporting Information

ABSTRACT: An efficient, mild, and metal-free arylation of nitroalkanes with diaryliodonium salts has been developed, giving easy access to tertiary nitro compounds. The reaction proceeds in high yields without the need for excess reagents and can be extended to α-arylation of nitroesters. Nitroalkanes were selectively *C*-arylated in the presence of other easily arylated functional groups, such as phenols and aliphatic alcohols.

Carbon−carbon bond formation belongs to the fundamental transformations in synthetic organic chemistry, and efficient methods to achieve C−C bonds are of high importance. Synthetic strategies toward complex molecules often rely on functional groups that are compatible with a range of conditions. Such groups can hence be introduced at an early stage and later on be selectively transformed into other interesting functional groups. Nitroalkanes fulfill these criteria and are often key intermediates in total synthesis,[1] due to the plethora of derivatization possibilities (Scheme 1a).[2]

Scheme 1



The acidity of nitroalkanes parallels that of stabilized carbonyl compounds, and they are easily functionalized with electrophiles under basic conditions.[2,3] While α-arylation of carbonyl compounds has been studied extensively,[4] the arylation of nitroalkanes remains largely unexplored. Stoichiometric use of heavy metal reagents based on lead[5] or thallium[6] generates toxic waste, while reactions with triphenylbismuth reagents[7] have poor atom efficiency. Furthermore, the above reagents have only been demonstrated with a limited substrate scope (Scheme 1b). Palladium-catalyzed methodology has mainly focused on arylation of nitromethane and primary nitroalkanes and requires excess substrate, elevated temperature, and expensive ligands (Scheme 1b).[8]

Hypervalent iodine(III) compounds have recently been demonstrated as efficient reagents for a wide range of transformations.[9] Diaryliodonium salts are nontoxic, bench-stable, and readily available electrophilic arylating reagents useful in a range of transformations.[10] Although diaryliodonium salts have been applied in α-arylation of carbonyl compounds, the scope remains moderate especially for acyclic systems.[11] The arylation of preformed alkali nitronates with diaryliodonium salts was reported in the 1960s with a very limited substrate scope.[12]

Our research group has focused on the synthesis and applications of diaryliodonium salts in metal-free arylations of oxygen and nitrogen nucleophiles.[13] Motivated by the ubiquitous nature of the nitro functional group, we envisioned the use of diaryliodonium salts in *C*-arylation of nitro compounds under mild and metal-free conditions. We focused on the arylation of secondary nitroalkanes, as tertiary nitro compounds are difficult to access with conventional methods and can be converted to highly useful α-tertiary amines.[14] The α-arylation of nitroesters was also targeted, and herein we present our preliminary results.

The arylation of nitrocyclopentane was optimized at room temperature, revealing that potassium *tert*-butoxide in 1,2-dimethoxyethane (DME) as solvent was most efficient.[15] An excess of diaryliodonium salt or nitroalkane was not needed, and the reaction proceeded with high efficiency using diaryliodonium salts with OTf, BF_4, or PF_6 as counterions, while OTs gave a slightly lower yield.[15] The high counterion tolerance was pleasing, as this facilitates the synthesis of the iodonium salts.[16]

The optimized conditions were then applied in the arylation of nitroalkanes **1** with various diaryliodonium salts **2** (Scheme 2). Nitrocyclopentane was smoothly phenylated (**3a**), as well as arylated with electron-deficient aryl groups to provide products

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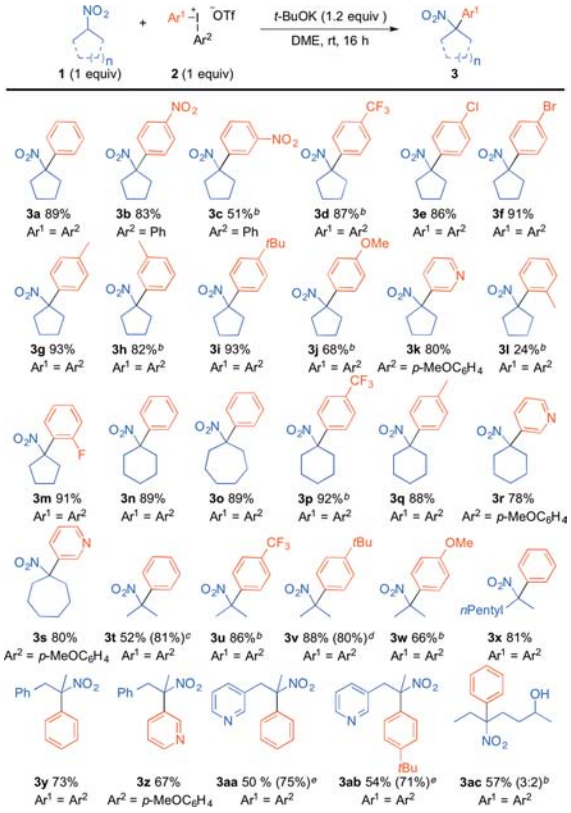
Scheme 2. *C*-Arylation of Nitroalkanes[a]



[a]Reaction conditions: **1** (0.2−0.5 mmol) and *t*-BuOK were stirred in anhydrous DME (1−2 mL) for 10 min at rt before addition of **2** and anhydrous DME (0.5−1 mL). [b]BF_4 as counterion [c]^{1}H NMR yield with 1,4-dimethoxybenzene as internal standard. [d]5 mmol scale. [e]Based on recovered **1**.

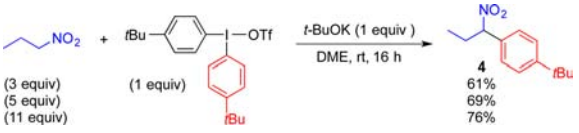
3b−d. Importantly, halide-substituted diaryliodonium salts easily underwent the reaction, delivering the products **3e,f** in high yields. Halide substituents can be used for further transformations, and such products can be difficult to access via metal-catalyzed arylations.

Electron-donating groups on the diaryliodonium salts were well tolerated, yielding **3g−j**. Anisyl-substituted product **3j** could be obtained despite its instability.[5b,15] To our delight, transfer of a pyridyl group could be accomplished to furnish **3k** in high yield. This is important, as pyridyl moieties are omnipresent in biologically interesting molecules.[17] Steric hindrance in the *ortho*-position of the aryl group hampered the reaction, and dimesityliodonium triflate gave only traces of product. While an *ortho*-tolyl group could only be transferred to reach product **3l** with difficulty, the corresponding *ortho*-fluoride substituted product **3m** was obtained in excellent yield. Nitroalkanes with varying ring sizes were compatible with this transformation, and both the six- and seven-membered phenylated products **3n,o** were isolated in comparable yields to **3a**. Various diaryliodonium salts were applied to these nitroalkanes, delivering products **3p−s** in high yield, including pyridyl-substituted products **3r** and **3s**.

The scope could be extended to also include C−C bond formation with acyclic nitroalkanes. These compounds underwent the arylation smoothly with both electron-withdrawing and -donating diaryliodonium salts, delivering products **3t−ac** in good to excellent yields. Phenylation of 2-nitropropane furnished the product **3t** in high yield, but the volatility of **3t** lowered the isolated yield. The synthesis of **3v** could easily be scaled up, with efficient recovery of the resulting iodoarene.[15] Nitroalkanes with longer carbon chains were employed to provide products **3x−3ac**. Importantly, acyclic products containing a pyridyl moiety could be obtained both by arylation with a pyridyl moiety (**3z**) and by arylation of a pyridyl-substituted nitroalkane (**3aa** and **3ab**). Selective *C*-arylation was observed with 5-nitro-2-heptanol to reach **3ac** (*vide infra*).

Pd-catalyzed arylations of nitromethane and primary nitroalkanes use 2−10 equiv of nitroalkane.[8a−d] Under our optimized conditions, the arylation of 1-nitropropane resulted in a mixture of mono- and diarylated products. To our delight, monoarylation proceeded well in the presence of excess nitropropane, delivering compound **4** in up to 76% yield (Scheme 3).

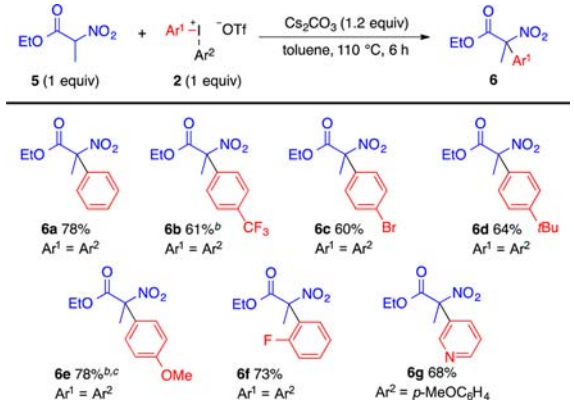
Scheme 3. Monoarylation of 1-Nitropropane



α,α-Disubstituted *α*-amino acids are important structural motifs present in many natural products and antibiotics,[18] and the *α*-arylation of *α*-amino acid derivatives introduces new structural motifs that can affect the binding mode to proteins and receptors.[19] We envisioned a complementary method to access such compounds via *α*-arylation of nitroesters,[8e] the products of which are easily reduced to the corresponding *α*-amino acids.[19a,b]

Upon arylation of 2-nitroester **5** under the optimized conditions, only trace amounts of product **6** was obtained with recovery of starting material **5** (Scheme 4). Reoptimization of the reaction with this less reactive nucleophile revealed that *α*-arylated product **6a** could be obtained in good yield with cesium carbonate in toluene at reflux.[15] Upon exploring the scope of the

Scheme 4. *α*-Arylation of Nitroesters[a]



[a]Reaction conditions: **5** (0.2 mmol) and Cs_2CO_3 were stirred in anhydrous toluene (1 mL) for 10 min at rt before addition of **2** and anhydrous toluene (0.5 mL). The resulting mixture was stirred for 1 h at rt followed by 6 h at 110 °C. [b]BF_4 as counterion. [c]Reaction time 16 h.

reaction, electronically and sterically different iodonium salts were employed under the optimized reaction conditions, affording *α*-arylated nitroesters **6**. Again, electron-withdrawing as well as electron-donating aryl groups could be transferred (**6b−f**). The synthesis of *α*-anisyl nitroester **6e** was accomplished in good yield upon prolonged reaction time. Also this arylation

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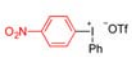
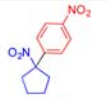
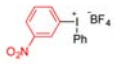
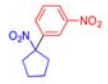
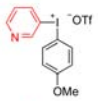
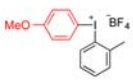
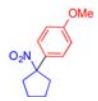
proved sensitive to *ortho*-substituents on the aryl group, and reaction with dimesityliodonium triflate only afforded trace amounts of product. Pleasingly, transfer of an *ortho*-fluorophenyl group to nitroester **6f** was achieved in 73% yield, and a pyridyl moiety was easily incorporated to reach product **6g**.

The use of unsymmetric diaryliodonium salts ($Ar^1 \neq Ar^2$) is desirable, due to their straightforward synthesis and the possibility to use an inexpensive aryl iodide as a "dummy" ligand. High chemoselectivity, i.e. selective transfer of Ar^1 over Ar^2, is necessary to ensure high yields of the desired products and to avoid isolation problems. We have recently reported a detailed study on chemoselectivity trends for arylations of *N*-, *O*-, and *C*-centered nucleophiles under metal-free conditions.[20] Based on those results, electron-rich or *ortho*-substituted aryl moieties could be good dummy groups for the *C*-arylation of nitroalkanes.

As expected, the more electron-deficient aryl group was transferred to nitrocyclopentane, delivering products **3b** and **3c** with moderate to excellent selectively (Table 1, entries 1−2).

Table 1. Chemoselectivity Trends

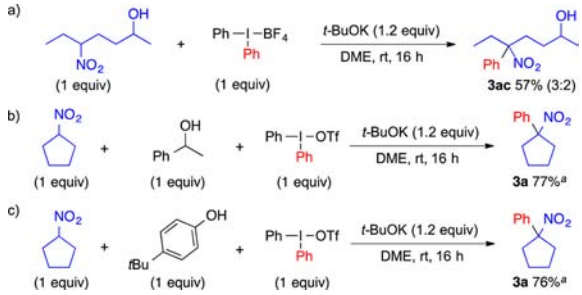
entry	salt **2**	^{1}H-NMR ratio[b]	major product **3** or **6**	yield (%)[c]
1		>20:1	 **3b**	83
2		4.5:1	 **3c**	51
3		9:1	 **6g**	68
4		6:1	 **3a**	78[d]
5		>20:1	 **6a**	75
6		3.3:1	 **3j**	51[e]

[a]Conditions according to Schemes 2, 4. [b]Ratio of arylated products (Ar^1 vs Ar^2) in the crude reaction mixture. [c]Isolated yield of major product. [d]Isolated as a mixture. [e]^{1}H NMR yield with internal standard.

The anisyl moiety proved to be a good dummy ligand for chemoselective transfer of a pyridyl group (**6g**, entry 3). The observed sensitivity to *ortho*-substituents could be exploited with aryl(mesityl)iodonium salts, selectively providing products **3a** and **6a** (entries 4,5). This dummy group could also be employed in transfer of other aryl groups.[15] This chemoselectivity is opposite to the commonly encountered "*ortho*-effect"[21] and has been termed an "*anti-ortho* effect".[20] We subsequently set out to compare the electronic and steric effects using an anisyl(*o*-tolyl)iodonium salt, which resulted in preferential transfer of the more electron-rich aryl group to give **3j** (entry 6). This is a unique example of the "*anti-ortho* effect" overriding the electronic effect in a metal-free arylation with diaryliodonium salts.[22,23]

Competition experiments were performed to investigate the compatibility of the reaction with other functional groups. As mentioned above, selective *C*-arylation to **3ac** was observed with 5-nitro-2-heptanol (Scheme 5a), despite the known reactivity of

Scheme 5. Competition Experiments



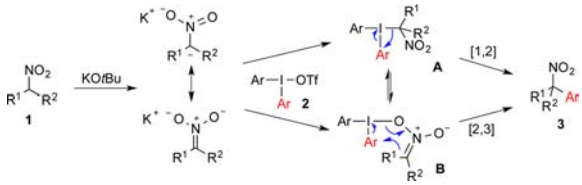
[a]^{1}H NMR yield with internal standard.

aliphatic alcohols at room temperature.[13c] The addition of a benzylic alcohol to the reaction was well tolerated, delivering product **3a** in good yield (Scheme 5b).[13d]

To our delight, even a phenol remained untouched under the reaction conditions (Scheme 5c), although phenols are excellent substrates in arylations with diaryliodonium salts.[13e] In all cases, no *O*-arylation byproducts were detected. These features allow for late stage *C*-arylation of relevant nitro compounds.

Arylations with diaryliodonium salts under metal-free conditions can either proceed via an SET mechanism[24] or by formation of a T-shaped intermediate followed by ligand coupling between the nucleophile and the equatorial aryl ligand.[20,25] The arylation of nitroalkanes proved to be insensitive to the radical trap 1,1-diphenylethylene (DPE), and an aryne intermediate seems unlikely, as regioisomeric mixtures of products were not observed.[15] We therefore propose a ligand-coupling mechanism similar to that proposed for α-arylation of carbonyl compounds.[25c] Scheme 6 depicts product formation via

Scheme 6. Proposed Mechanism



two different T-shaped intermediates that could be in fast equilibrium, with product formation to **3** either by normal ligand coupling (**A**) or via a [2,3]-rearrangement (**B**).

In conclusion, we have demonstrated an efficient, straightforward, and metal-free approach for the *C*-arylation of nitroalkanes and nitroesters. The reaction entails equimolar amounts of reagents, gives high yields, and can be easily up-scaled with recovery of the formed iodoarene. Electron-rich and -deficient iodonium salts are equally compatible, and the reaction proceeds smoothly with cyclic as well as acyclic nitroalkanes. The arylations can be chemoselectively performed using either an anisyl or a mesityl dummy group and provides a strong "*anti-ortho* effect" that overrides the electronic preference.

The functional group tolerance toward aliphatic alcohols and phenols is excellent, despite the well-known, high reactivity of alcohols with diaryliodonium salts under mild conditions. The

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reaction is proposed to proceed by a ligand-coupling pathway via two possible intermediates.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental details and spectral data for novel compounds; NMR spectra of all products (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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