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Highly Site-Selective Formation of Perfluoroalkylated Anilids via a Protecting Strategy by Molybdenum Hexacarbonyl Catalyst

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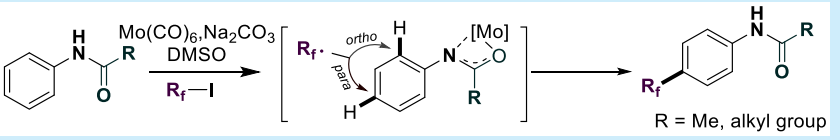
Supporting Information

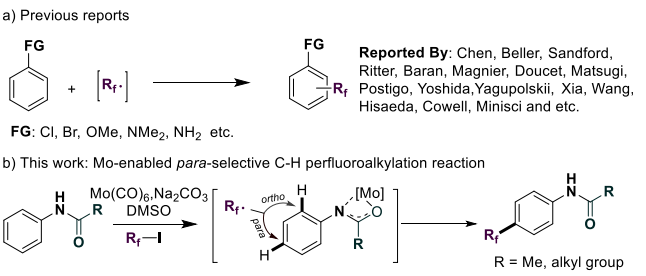


ABSTRACT: Introducing a perfluoroalkyl group on the aromatic ring with high site selectivity remains a challenging area in organofluorine chemistry. We herein report a highly para-selective C−H perfluoroalkylation of aniline substrates using the molybdenum hexacarbonyl catalyst. Various substituted anilids derived from anilids were well-tolerated, affording the corresponding products in moderate to good yields. Preliminary mechanism studies and density functional theory calculations revealed the coordination of Mo catalyst with amides as the key factor to realize para selectivity.

Perfluoroalkyl groups substituted on aromatic rings typically modify the physical and biological properties of organic molecules significantly.[1] Thus, it is highly important to introduce perfluoroalkyl groups into bioactive organic molecules later in the reaction.[2] In the past several decades, thermal,[3] electrophilic,[4] and photochemical[5] reactions have been extensively explored for C−H perfluoroalkylation. However, high site-selective introduction of perfluoroalkyl groups on the multsubstituted benzene ring still remains rare.[6] Hence, the development of a method to address the site selectivity issue would be a milestone in C−H aromatic perfluoroalkylation reactions. Herein, we report the first example of the highly para-selective perfluoroalkylation of acetyl-protected anilids with molybdenum hexacarbonyl ($Mo(CO)_6$) as the catalyst. Various meta- and ortho-substituted acetyl-protected anilids were well-tolerated, leading to the corresponding products in moderate to good yields. More importantly, the perfluoroalkylated Vorinostat, Leflunomide, Teriflunomide, and Prilocaine could be easily obtained through this new method. A density functional theory (DFT) calculation revealed the coordination of $Mo(CO)_6$ with amides as the key factor to realize the para selectivity.

The aniline backbone can usually be found in various natural and medicinally relevant compounds, which can be used to treat diseases such as rheumatism, lymphoma, multiple sclerosis, and others. Since the pioneering work of Zhou and Huang on free perfluoroalkyl radical aromatic substitution reactions,[7] various approaches to realize the C−H perfluoroalkylation of anilids have been regularly investigated (Scheme 1a). Recently, our group demonstrated site-selective C−H difluoromethylation at the meta or para position by adjusting the coordination ability of the directing group[8] or the steric effect of the catalyst.[9] Here, we proposed that the site-selective perfluoroalkylation of aniline could be realized via the transformation into a suitable anilide (Scheme 1b). This formation of the anilide not only reduces the reactivity of aniline but also provides a coordination center for transition metals. Meanwhile, this transform can activate the amide-linked aromatic ring and provide a bulk condition at another position, which would result in a highly para-selective product. More importantly, the anilide is the key structure of various bioactive compounds, which can provide a direct approach to the functionalization of drugs.

Scheme 1. C−H Perfluoroalkylation of Aromatic Compounds



With these conditions in mind, acetanilide was selected to assess whether the site-selective C−H perfluoroalkylation could be achieved with this protecting strategy. Acetanilide (**1a**) was treated with perfluorobutyl iodide (**2a**) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $AgSbF_6$ (10 mol %), and Na_2CO_3 (2 equiv) in dimethyl sulfoxide (DMSO) at 120 °C for 24 h. The *para*-perfluoroalkylated product **3a** was obtained in 15% yield, along with trace amount *ortho*-perfluoroalkylated product **3a′**. Several other catalyst systems

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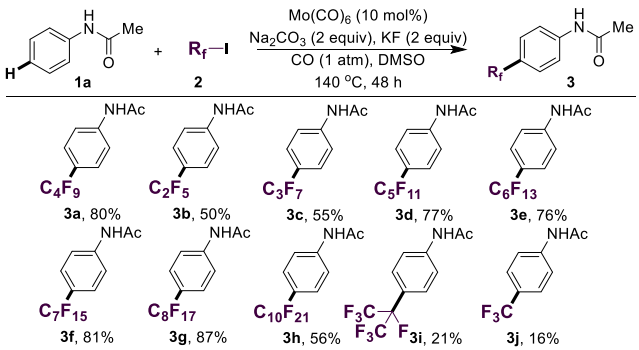
including $[Rh(COD)Cl]_2$ (COD = 1,5-Cyclooctadiene), $Ru_3(CO)_{12}$, and $Fe(acac)_2$ (acac = acetylacetone)were screened. The $Ru_3(CO)_{12}$ catalyst provided the product **3a** in 19% yield, along with a trace amount of *ortho*-perfluoroalkylated product (**3a**/**3a′** > 20:1). Further screening of the catalysts indicated $Mo(CO)_6$ as the best catalyst for this para-selective perfluoromethylation reaction, generating product **3a** in 26% yield (**3a**/**3a′** > 20:1). Next, several ligands and additives were investigated (see Supporting Information). The results showed that, when the reaction was performed under a carbon monoxide atmosphere, an improved yield of **3a** (43%) was obtained. It may be because carbon monoxide can stabilize $Mo(CO)_6$.[10] Interestingly, potassium fluoride also displayed a good promoting effect in combination with carbon monoxide for this transformation, leading to the product **3a** in 68% yield. Although the role of potassium fluoride is unclear, excess amounts fluorine anions may stabilize the perfluoroalkyl radical.[11] Finally, when the reaction was performed at 140 °C for 48 h, the highly para-selective product **3a** could be obtained at 80% yield, while the side product only formed in trace amounts.

With optimal reactions known, a variety of perfluoroiodides were subjected to the standard reaction conditions (Scheme 2). The low-boiling iodopentafluoroethane and heptafluoropropyl iodide both performed well, leading to the highly para-selective perfluoroalkyated products **3b** and **3c** in good yields, along with recovery of the starting material. The perfluoroalkyl iodides ($C_5F_{11}I$, $C_6F_{13}I$, $C_7F_{15}I$, $C_8F_{17}I$, and $C_{10}F_{21}I$) were all compatible, leading to the corresponding products in satisfactory yields (**3d**–**3h**; 56%–87%). When heptafluoroisopropyl iodide was employed as the coupling partner, the corresponding perfluoroalkylated product **3i** was only isolated at 21% yield, indicating that the steric effect greatly affects this transformation. Impressively, trifluoromethyl iodide was also shown to be a suitable substrate, leading to the trifluoromethylated product **3j** at acceptable yields. It may be that the low boiling point of trifluoromethyl iodide resulted in low conversion.

The scope of anilids was next evaluated, and the results are listed in Scheme 3. To facilitate the separation of products, a longer-chain perfluoroalkyl iodide **2g** ($C_8F_{17}I$) was employed. Various functional groups such as OMe, Me, MeS, OBn, CF_3CH_2O, Et, *i*-Pr, *t*-Bu, Ph, Cl, Br, and NO_2 were all well-tolerated and provided highly para-selective perfluoroalkylated products in moderate to good yields (**4a**–**4s**; 26%–88%). The meta-substituted anilids performed well under the standard reaction conditions, leading to *para*-perfluoroalkylated products in moderate to good yields (**4a**–**4d**). Dihydro-2-quinolone is another effective substrate, providing the perfluoroalkylated product **4e** in 61% yield. The 2,5-disubstituted anilids proceeded well and provided products in good yields (**4f** and **4g**). All of the ortho-substituted substrates reacted well, yielding the products in yields of 41%–80% (**4h**–**4s**). Interestingly, the perfluoroalkylation selectively occurred at the amide-linked aromatic ring and not the free phenyl ring (**4i** and **4p**). These results indicated that the Mo coordinated with amide might provide an activated aromatic ring, which preferentially traps the free radical of the perfluoroalkyl group compared to the inactive phenyl rings. The pivaloyl- and benzoyl-protected anilids were compatible in this newly developed method, generating the corresponding products in acceptable yields (**4t** and **4u**). However, the benzyloxycarbonyl (Cbz)- and *tert*-butyloxycarbonyl (Boc)-protected aniline only lead to a complicated reaction, yielding trace amount products, respectively. It might be these carbamates are unstable under the standard reaction condition.

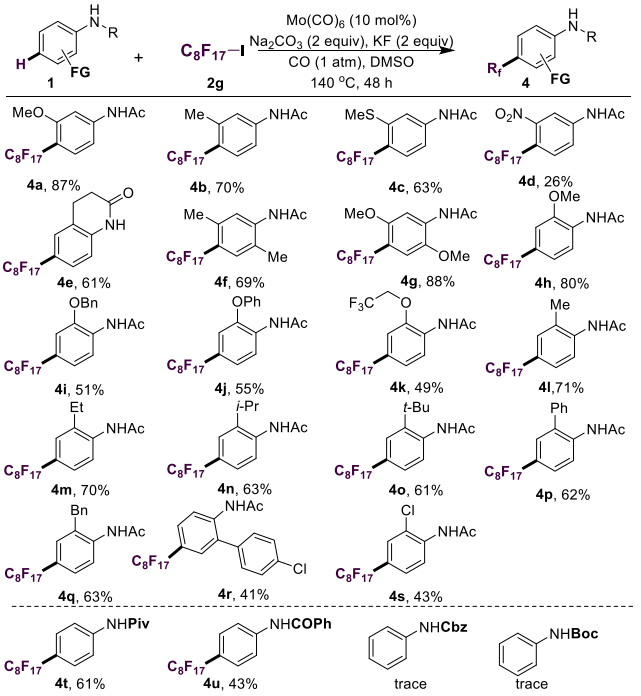
Since the introduction of a perfluoroalkyl group into a drug may modify its solubility, bioavailability, and metabolic stability, functionalization of known drugs is important. To our great delight, a variety of perfluoroalkyl groups can be selectively installed on the key precursor of Vorinostat (Scheme 4, **6a**–**6e**),[12] which is used for the treatment of cutaneous-T-cell-lymphoma. The perfluoroalkylated Vorinostat could be easily obtained in good yields by treating **6e** with NH_2OH. The perfluoroalkylated key precursor of Prilocaine (**7b**) was obtained in acceptable yields under the optimized reaction conditions. Next, a gram-scale reaction was performed with substrate **1a**, leading to the compound **3a** in good yield (Scheme 5). The acetyl protecting group could be removed,

Scheme 2. Scope of Perfluoroalkyl Iodides[a]



[a]Reaction performed at a 0.2 mmol scale with **2** (3 equiv) in a sealed tube; yields of isolated products.

Scheme 3. Scope of Anilids[a]



[a]Reaction performed at a 0.2 mmol scale with **2** (3 equiv) in a sealed tube; yields of isolated products.

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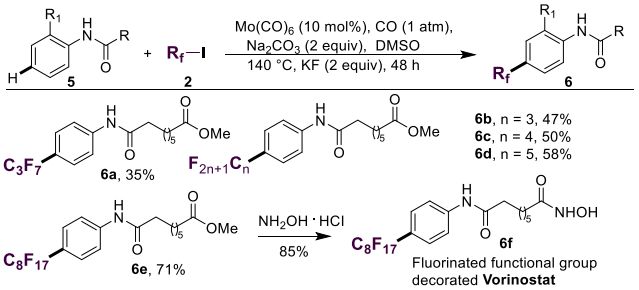
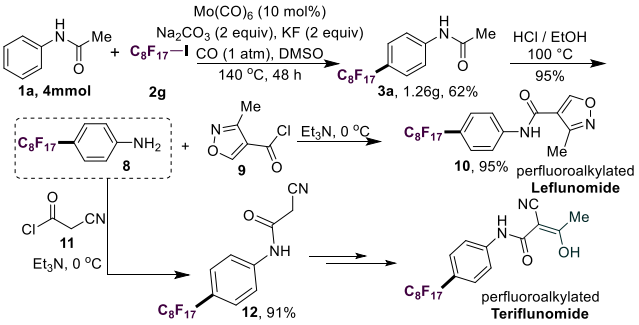
Scheme 4. Functionalization of Bioactive Compounds



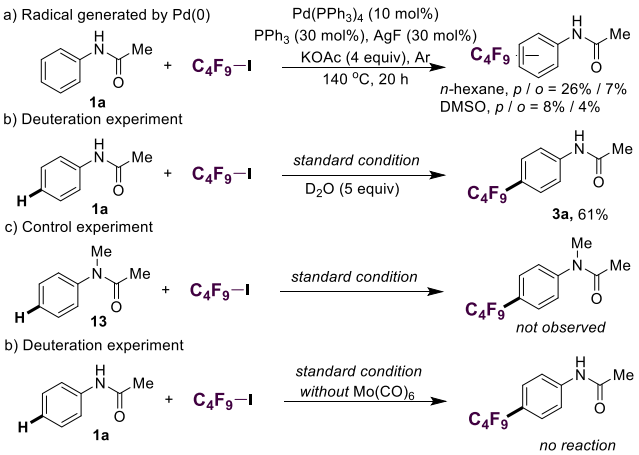
Scheme 5. Synthesis of Perfluoroalkylated Drugs



providing the perfluoroalkylated **8** in excellent yield, which could then be easily transformed into the perfluoroalkylated Teriflunomide (**10**) and Leflunomide (**12**). These results highlighted the synthetic importance of this new method, which might facilitate new developments in medicinal chemistry.

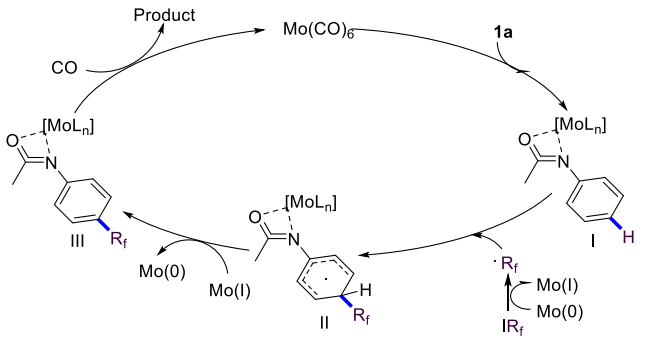
Several parallel experiments were performed to understand the reaction pathway of this Mo-catalyzed para-selective C−H perfluoroalkylation reaction (Scheme 6). First, the radical

Scheme 6. Preliminary Mechanism Studies



scavengers including 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) and butylated hydroxytoluene (BHT) were added to the reaction mixture, and the results showed that the reaction was completely inhibited when 3 equiv of radical scavengers was used, implying the reaction undergoes a free-radical pathway (see Supporting Information).[13] Second, the perfluoroalkyl radical can be generated with palladium(0), which was reported by Chen and co-workers.[14] When the substrate **1a** was directly treated with perfluoroalkyl radical, a mixture of para- and ortho-perfluoroalkylated products **3a** and **3a′** were obtained without site selectivity (Scheme 6a).[7] Third, when the D_2O was added to the reaction as the additive under the standard reaction conditions, **3a** was isolated in 61% yield (Scheme 6b). However, there is no D/H scrambling occurred on the aromatic ring of **3a**. Finally, *N*-methyl-*N*-phenylacetamide could not yield any perfluoroalkylated products, and the starting material was completely recovered (Scheme 6c). Furthermore, control experiments revealed that $Mo(CO)_6$ is essential for this transformation (Scheme 6d). Altogether, these results indicated that the Mo complex should coordinate with amide in the anilide, thereby activating the aromatic ring linked to the amide group without forming a five-membered transition metacycle. Although it is hard to clarify the valence variation during the catalytic cycle at this stage, based on the previous report and the experimental result, it is rationally considered that a perfluoroalkyl radical was generated via a single-electron transfer (SET) by the oxidation of $Mo(CO)_6$ with perfluoroalkyl iodide.[15] The Mo(I) cation complex could act as a Lewis acid to combine with the amide to generate complex I, which would then activate the amide-linked aromatic ring.[16] The free perfluoroalkyl radical could react with complex I to afford the complex II, followed by aromatization to provide **3a** (Scheme 7).

Scheme 7. Plausible Catalytic Cycle



Computational studies were performed to understand the regioselectivity of this para-selective perfluoroalkylation.[17] Three possible attacking sites leading to ortho, meta, and para adducts were considered, and the optimized transition states were denoted as **TS1-o**, **TS1-m**, and **TS1-p**, respectively. The predicted energy barriers of the radical addition step were 15.2, 16.6, and 13.9 kcal/mol for ortho, meta, and para adducts, respectively, demonstrating that the radical attack at the para position has the lowest energy barrier. In addition, the formation of the para adduct was slightly thermodynamically stable by 1.5 kcal/mol, while the formation of the ortho adduct was thermo-neutral. Thus, for the radical attack step, the addition of perfluoroalkyl radical to the para position was favorable both kinetically and thermodynamically among the three possible sites. Moreover, the ionization energy (IE) of the formed radical adduct was calculated to qualitatively characterize the subsequent oxidation step via SET. The calculated IE of the para, ortho, and meta adduct was 88.4, 92.9, and 117.8 kcal/mol, respectively (Figure 1). Computational results indicate that the para adduct has the lowest IE, which is 4.5 kcal/mol lower than that of the ortho adduct, suggesting that the formed para adduct could be more ready to be oxidized via SET process than the ortho adduct. Thus, the computational studies demonstrate that not only is the para

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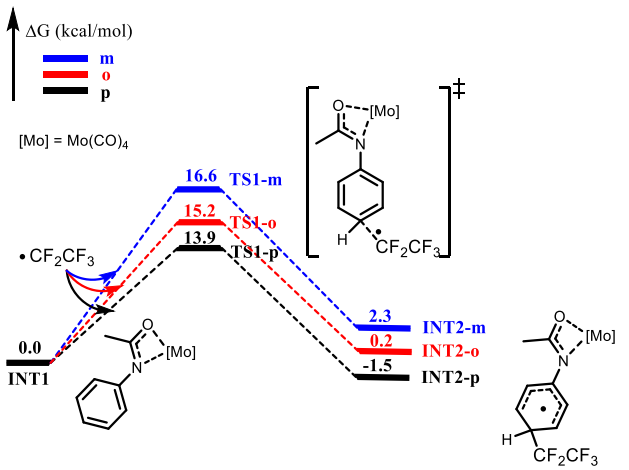

Figure 1. Energy profiles for the radical addition to the aryl moiety.

position preferred by the radical addition but also the formed radical para adduct is more ready to undergo oxidation by one electron transfer, which is consistent with the experimental results.

In conclusion, we have developed an efficient and practical molybdenum hexacarbonyl-catalyzed para-selective perfluoroalkylation of anilids via a protecting strategy. Various meta- and ortho-substituted anilids were well-tolerated, leading to the corresponding products in moderate to good yields. The perfluoroalkylated Vorinostat, Leflunomide, Teriflunomide, and Prilocaine could be easily obtained using our new method. Preliminary mechanism studies and DFT calculations revealed the coordination of the Mo catalyst with amides is the key factor to realize para selectivity. Further studies of the site-selective C−H perfluoroalkylation of other aromatic compounds with molybdenum hexacarbonyl as the catalyst are in progress in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02362.

Experimental procedures and ^{1}H and ^{13}C NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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