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Direct *meta*-C–H Perfluoroalkenylation of Arenes Enabled by a Cleavable Pyrimidine-Based Template

Massimo Brochetta,[a,b] † Tania Borsari,[a] † Sukdev Bag,[c] Sadhan Jana,[c] Siddhartha Maiti,[d] Alessio Porta,[a] Daniel B. Werz,*[b] Giuseppe Zanoni,*[a] and Debabrata Maiti*[a,c]

Abstract: The development of efficient and mild methods for the synthesis of organofluorine compounds is of foremost interest in various fields of chemistry. A direct pyrimidine-based selective *meta*-C–H perfluoroalkenylation of arenes involving several commercially available perfluoroolefins is described. The synthetic versatility of the protocol is demonstrated by an extensive substrate scope including different benzylsulfonyl, alkylarene and phenylacetic acid scaffolds. The generality of this methodology including Ibuprofen *meta*-C–H perfluoroalkenylation, facile cleavage of the directing group and gram-scale reactions are presented.

Fluorine-containing compounds are known to play a pivotal role in pharmaceutical/medicinal chemistry, but also in agrochemical and material sciences. Fluorine and in particular the incorporation of C–F bonds into organic molecules strongly influence their properties such as thermal stability, high chemical inertness and solubility in organic solvents.[1] Bioavailability and metabolic stability are commonly increased by substitution with fluorine atoms.[2] Alkenes and aromatic moieties bearing perfluorinated tails are widely used as a stable isosteric and isoelectronic mimics of the amide bond, and bioisosteres in structure/activity relationship studies.[3] Although of great importance, the synthesis of perfluoroalkenylated arenes through the incorporation of fluoroalkyl chains has remained an outstanding challenge. Few strategies for the preparation of these structural motifs, such as the classical cross-coupling reaction have been shown to be effective.[4],[5] The existing methods usually require prefunctionalization of substrates or employment of non-readily available starting materials, and these methods often suffer from low regio- or stereoselectivity and poor functional group tolerance due to the employment of sensitive reagents.[6] Therefore, new synthetic strategies featuring high efficiency and mild conditions are highly desirable.

Over the past decades, transition metal catalyzed C–H bond functionalization has been established as an effective strategy in late-stage functionalization of pharmaceuticals and bioactive molecules.[7] In order to achieve site-selective C–H bond functionalization at a desired position, directing group (DG) approaches[8] have been employed extensively for the *ortho*-C–H bond,[9] while distal *meta*- and *para*-C–H bonds have been much less addressed. In the past few years, *meta*-selective C–H functionalizations of arenes have been accomplished by exploiting the inherent steric and electronic properties of substrates, or by designing suitable templates.[10] In this context, direct C–H perfluoroalkenylation of arenes is an important route in terms of both atom and step economy. Very recently, Loh, Wang, and Ackermann elegantly reported *ortho*-C–H fluoroalkenylation of arenes *via* C–F bond activation.[11] Intriguingly, the *meta*-functionalization of arenes using sterically demanding electrophilic perfluoroalkenes remains a difficult task, owing to the formation of highly strained macrocyclic transition states (TSs). Despite its potential application, the distal *meta*-C–H perfluoroalkenylation has not been reported yet. Focusing on this scarcity, and our continuous effort to reaching out to the distal *meta*-C–H bond, we envisioned to develop a Pd-catalyzed *meta*-C–H perfluoroalkenylation of arenes utilizing readily available fluorinated partners (Figure 1).

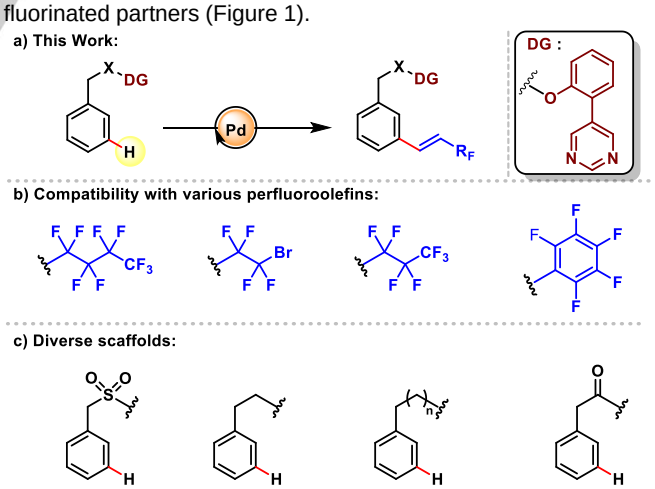

Figure 1. a) DG-assisted *meta*-C–H perfluoroalkenylation; b) Selected perfluoroolefins; c) Variation of the scaffold to be *meta*-C–H activated

We focused our initial efforts on the pyrimidine-based template which has recently been used for different *meta*-selective C–H functionalizations.[12-13] We initiated our investigations on a model substrate **1a** (X = *m*-Me) with the benzylsulfonyl unit and perfluorohexene as coupling partners. The reaction was carried

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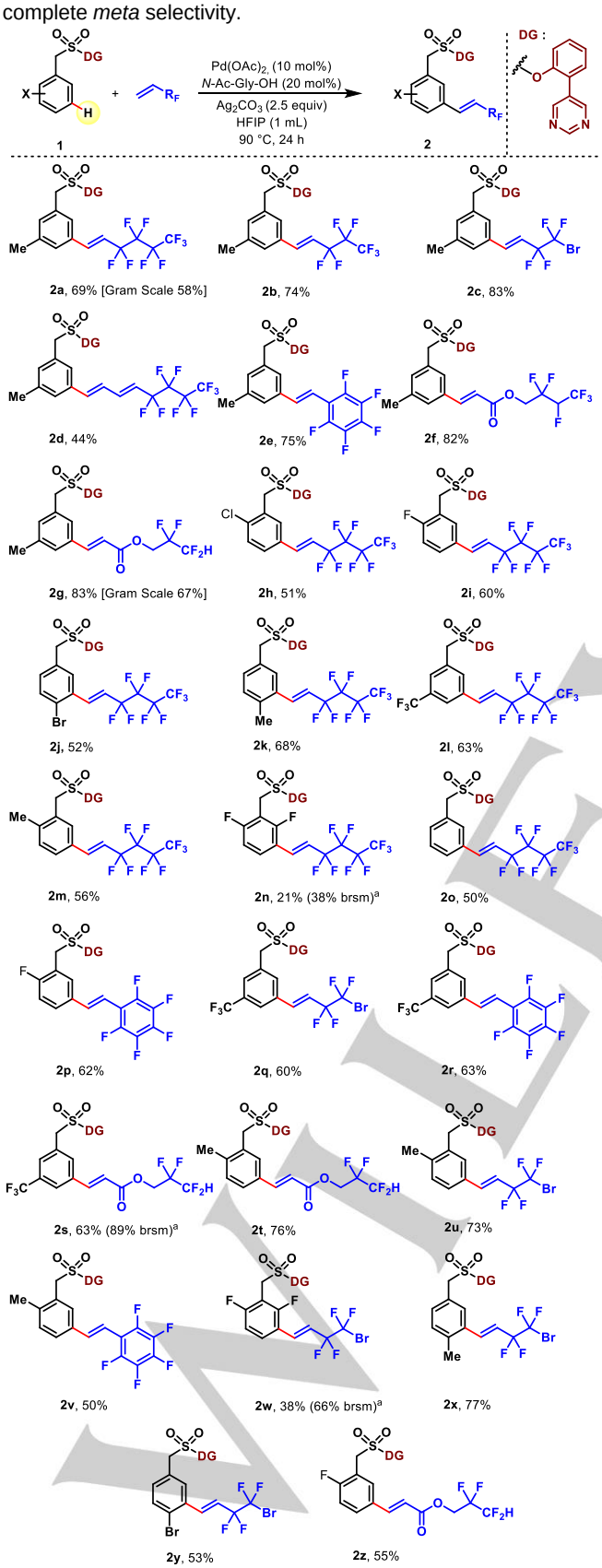
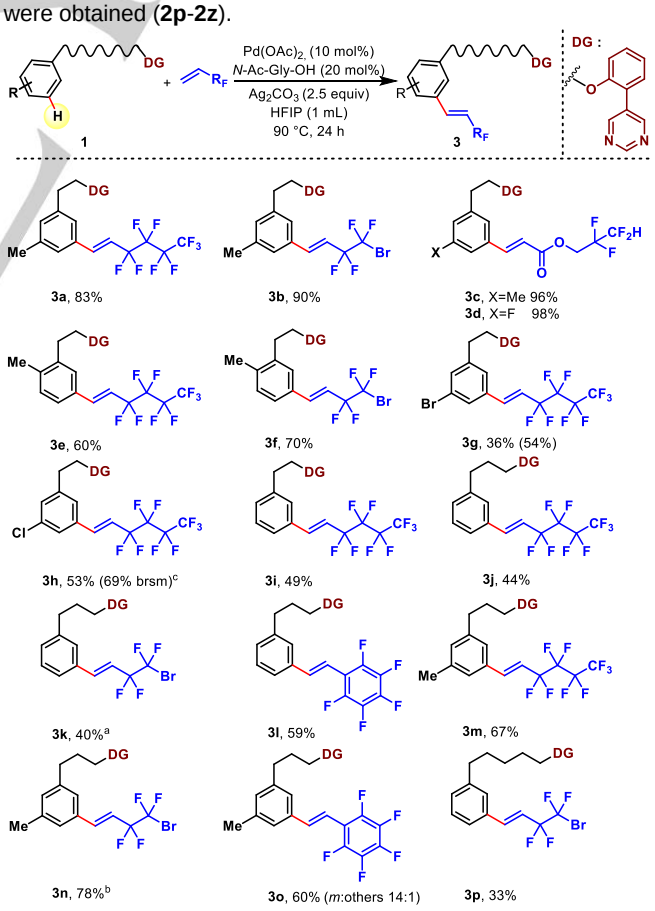
out in dichloroethane using $Pd(OAc)_2$ (10 mol%) as catalyst, mono-protected amino acid (MPAA) *N*-Ac-Gly-OH (20 mol%) as ligand, and AgOAc as oxidant at 90 °C. The desired perfluoroalkenylated product was obtained in 45% yield with complete *meta* selectivity.



Scheme 1. The *meta*-perfluoroalkenylation of benzylsulfonyl scaffolds. [a] brsm (based on recover starting material)

Encouraged by this result, we started the optimization of the reaction conditions.[14] Oxidant Ag_2CO_3 (2.5 equiv) proved to be the most effective and provided *meta*-perfluoroalkylated product **2a** in 59% yield. While testing various solvents, an increase of the yield to 69% was achieved by using hexafluoroisopropanol (HFIP). Subsequently, the scope of this transformation was examined under these optimized conditions. First, we evaluated several perfluorinated olefins. Terminal alkenes with different lengths were found to be suitable reaction partners leading to the perfluoroalkenylated products **2a-2c** in 69-83% yield. Interestingly, heptafluoro-5,5-bis(trifluoromethyl)-1,3-octadiene has been incorporated at the *meta*-position in synthetically useful yields (**2d**, **2e**, **2f**, and **2g**). The presence of a bromine atom in product **2c** might be effective for a late stage functionalization.[15] Two different gram-scale reactions using **1a** were carried out. While a slightly higher reaction temperature was required to achieve the desired conversion, products **2a** and **2g**, respectively, were isolated in 58% and 67% yields. Next, we tested different substituted benzylsulfonyl esters with perfluorohexene (Scheme 1). It was observed that the trifluoromethyl group at *meta*-position did not affect the reaction protocol (**2l**). In contrast, bulkier substituents at the *ortho* (**2h**, **2i**, **2m** and **2n**) or *para* (**2j** and **2k**) positions resulted in a slight decrease of the yield, probably because of steric repulsions affecting the metalacycle formation and/or due to ineffective olefin insertion. Nevertheless, this drawback was partially overcome by changing the perfluorinated olefin partner as shown in Scheme 1; moderate to good yields were obtained (**2p**-**2z**).



Scheme 2. Scope of the *meta*-perfluoroalkenylation with respect to the linker length; [a]reaction was carried out at 70°C; [b] 3 equiv. of olefin were used.[c] brsm

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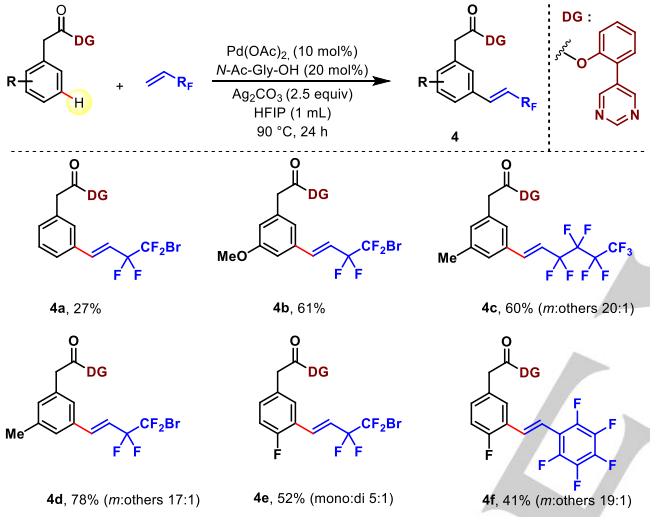
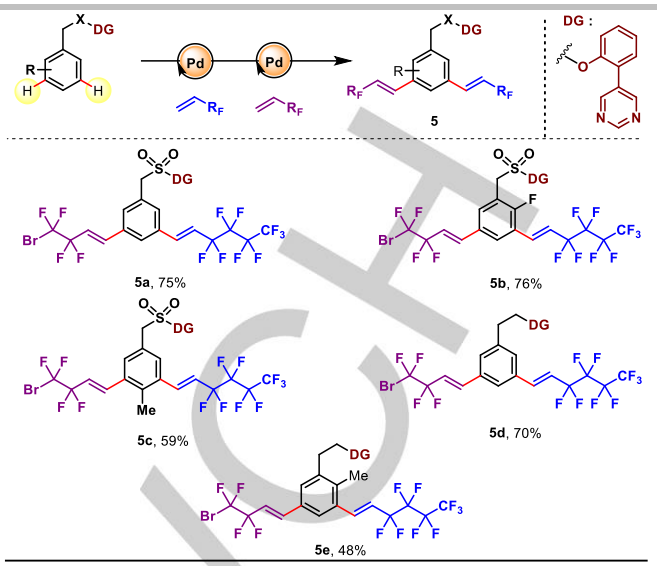
To demonstrate the generality of our developed protocol, we expanded our study to other linkers (Scheme 2). Interestingly, a substrate with ethano tether (instead of CH_2SO_2) furnished a higher yield of the respective product **3a** than in the analogous reaction to **2a**. The perfluoroalkenylation reaction was found to be feasible with a wide range of substituted ethyl arenes and perfluorinated olefins affording compounds **3a-3i** in yields up to 98%. Additionally, we extended the linker length to propyl and pentyl tethers affording different *meta*-perfluorinated products **3j-3p** in moderate to good yields (Scheme 2).

Furthermore, we investigated whether this *meta*-C–H activation process is also possible when phenylacetic acid derivatives are employed. Since phenylacetic acid is an important motif in drugs (*i.e.* -profen type drugs), we subjected the respective esters to our catalytic protocol (Scheme 3). Fortunately, the reaction did not afford any transesterification product. Thus, six different phenylacetic acid esters were transformed into products **4a-4f** including derivatives with methyl, methoxy and fluorine substitution at the arene.



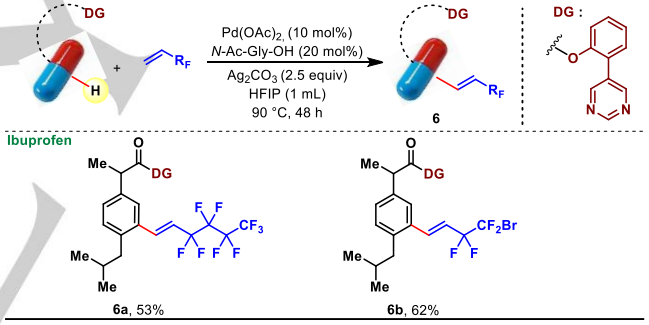
Scheme 3. *Meta*-perfluoroalkenylation of phenylacetic acids

To obtain sequential perfluoroolefination in a position-selective manner, mono-perfluoroalkenylated products were utilized. With the prefunctionalized mono-olefinated products (Scheme 1, **2o** and Scheme 2, **3i**), various fluoro-olefins were incorporated at the remaining *meta*-position in an exclusive manner with preparatively useful yields under the present reaction conditions (**5a**-**5e**; Scheme 4).



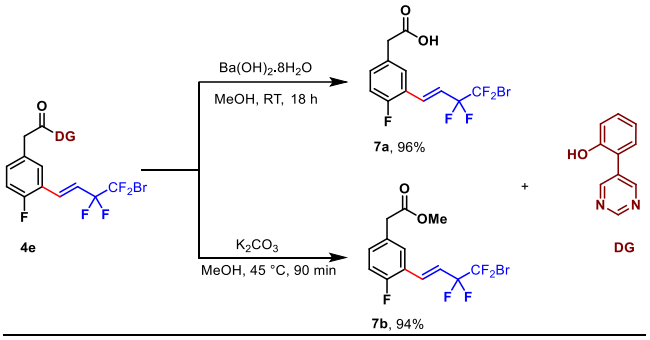
Scheme 4. Iterative *meta*-bisperfluoroalkenylation of benzylsulfonyl and ethylbenzene scaffolds.

To showcase that this transformation can also be used for the derivatisation of pharmaceuticals, Ibuprofen (**1e**) was attached to the pyrimidine-based directing group and submitted to the perfluoroalkenylation protocol. The presence of the benzylic substituent (Me) and the bulky group (^{i}Pr) were not found to be a hindrance for the catalytic cycle; reactions proceeded smoothly leading to **6a** and **6b** (Scheme 5).



Scheme 5. *Meta*-perfluoroalkenylation of Ibuprofen

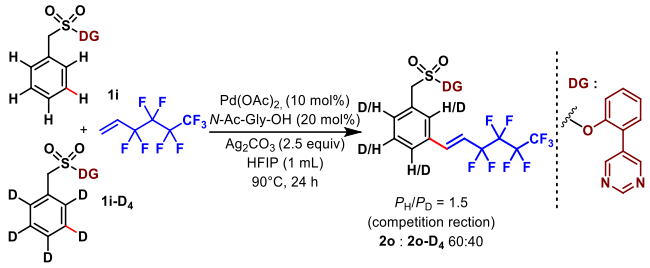
Finally, the template could be removed in a traceless fashion as depicted in Scheme 6 affording the free acid **7a** in 96% yield or the transesterificated product **7b**.



Scheme 6. Traceless deprotection of the pyrimidine-based DG

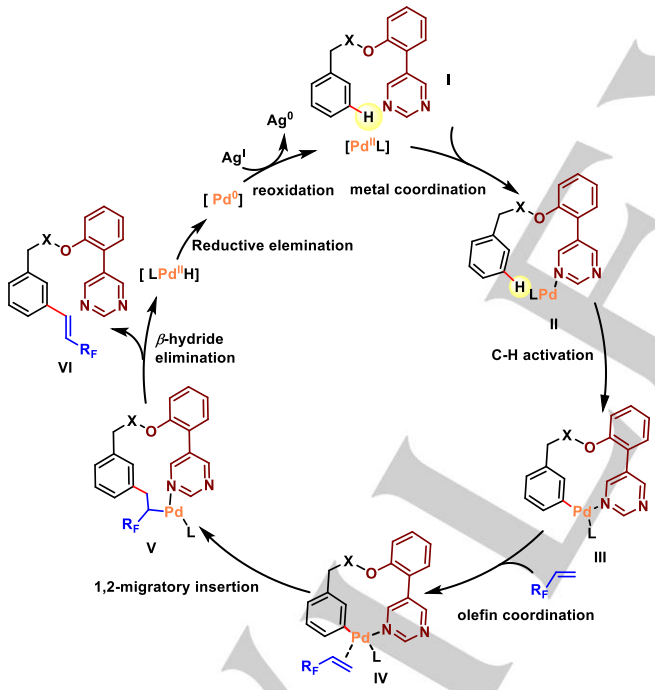
To get insights into the reaction mechanism, a kinetic study was conducted. A competition experiment between **1i** and the deuterated analog **1i-D$_5$** resulted in a P_H/P_D value of 1.5, which indicates that the C–H activation step is not the rate-determining step (Scheme 7).[12] An ESI-HRMS analysis of the reaction

without olefin suggested the formation of a palladacycle (intermediate **III**, Scheme 8).[15]



Scheme 7. Competition reaction between a non-deuterated and a deuterated scaffold

On the basis of these results and previous literature reports, a plausible catalytic cycle is depicted in Scheme 8. The pyrimidine-based DG coordinates the mono-protected amino acid (MPAA)-ligated palladium catalyst (intermediate **II**) and activates the *meta*-C–H bond (probably through a concerted metalation/deprotonation step) affording the macrocyclic intermediate **III**. The olefin binding to the cyclopalladated compound is followed by 1,2-migratory insertion that leads to intermediate **V**. *β*-Hydride elimination provides the desired perfluoroalkenylated product **VI** and [LPd^{II}H]. The latter is reoxidized by stoichiometric silver(I) and is able to start a new catalytic cycle (Scheme 8).



Scheme 8. Proposed catalytic cycle for the *meta*-perfluoroalkenylation

In conclusion, we reported the first palladium-catalyzed highly selective *meta*-C(sp^2)–H perfluoroalkenylation of arenes. The choice of a pyrimidine-based directing group is found to be crucial, giving a high degree of compatibility with perfluoroolefins of different nature. The synthetic versatility of the protocol was demonstrated by a broad substrate scope including different benzylsulfonyl, alkylaryl and phenylacetic acid scaffolds. Ibuprofen C–H perfluoroalkenylation, facile cleavage of the DG and gram-scale reactions demonstrate the practical value of this procedure.

Acknowledgements

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Keywords: C–H activation • *meta*-selectivity • fluorinated compounds • palladium catalysis • iterative functionalization

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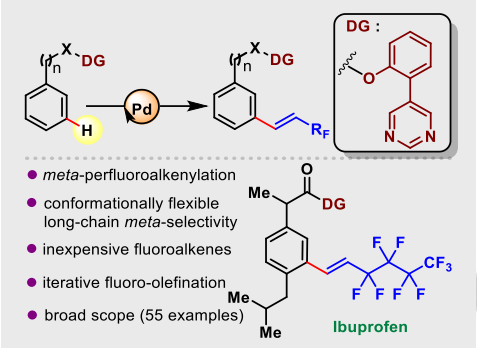
Palladium (II)-catalyzed *meta*-selective C–H perfluoroalkenylation of arenes utilizing readily available fluorinated olefins is described. The practicability of this transformation has been demonstrated by selective perfluoro-olefination of the pharmaceutical Ibuprofen.



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