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Meta-Selective Arene C−H Bond Olefination of Arylacetic Acid Using a Nitrile-Based Directing Group

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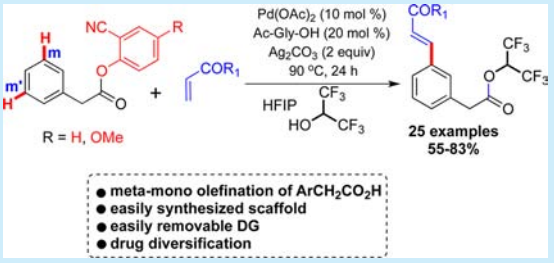
Supporting Information

ABSTRACT: A nitrile-based template attached with a phenylacetic acid framework promoted *meta*-selective C−H bond olefination. This palladium-catalyzed protocol is applicable to a wide range of substituted phenylacetic acids and tolerates a variety of functional groups. The versatility of this operationally simple method has been demonstrated through drug diversification.

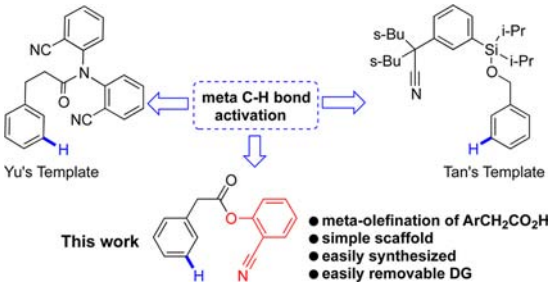


Functionalization of C−H bonds provides a sustainable and efficient protocol to synthesize various organic molecules from simple hydrocarbon derivatives.[1] Different strategies for arene C−H bond functionalization have been developed over the past decade.[2] Selectivity and improved reactivity in metal-catalyzed C−H activation have been achieved with the aid of a variety of directing groups (DGs).[3] In most of the cases, C−H activation occurs in an *ortho*-selective fashion by means of chelation assistance in directing functionality on aromatic rings. Compared to *ortho*-functionalization, development of selective *meta*-functionalization of an arene C−H bond is still in its infancy.[4,5] Pioneering studies by Yu and subsequently by Tan elegantly devised Pd-catalyzed oxidative *meta*-selective functionalization using a DG appended to benzylic alcohol,[5a,c,f] phenol,[5b] arylamine,[5d,g] and hydrocinnamic acid[5a,e] moieties. In these cases, nitrile-containing templates direct the activation of remote *meta*-C−H bonds (≥10 bonds away) of a tethered arene through the cyclophane-like pretransition state (*vide infra*).[5]

Herein, we disclose a phenylacetic acid derived scaffold that can be applied to the position-selective remote *meta*-C−H alkenylation reaction (Scheme 1). The major advantages of the present methodology are as follows (Figure 1): (i) position-selective *meta*-olefination of pharmaceutically relevant phenylacetic acid derivatives; (ii) easy installation (and removal) of the DG; (iii) exclusive formation of a *meta*-selective mono-olefinated product. Notably, an *ortho*-C−H alkenylation reaction using phenylacetic acid has been reporetd in 2010 by Yu et al.[2e]

As part of our ongoing studies toward developing practical C−H functionalization reactions, our laboratory has focused on discovering reactivity with broadly useful and widely available substrates.[6] In our first attempt at position-selective *meta*-C−H activation, we employed 2-hydroxybenzonitrile as the DG—a

Scheme 1. Nitrile-Based Directing Groups



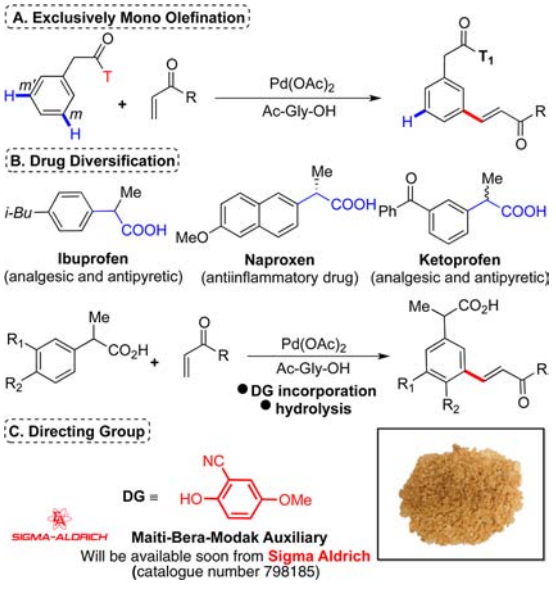


Figure 1. (A) Schematic depiction of *meta*-mono-olefination approach. (B) Pharmaceutically relevant phenylacetic acids. Directed *meta*-olefination of commercial nonsteroidal anti-inflammatory drugs (NSAIDs). (C) Directing group.

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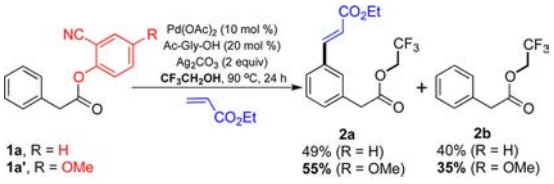
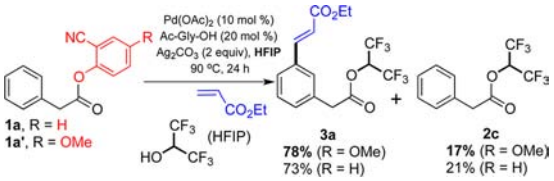
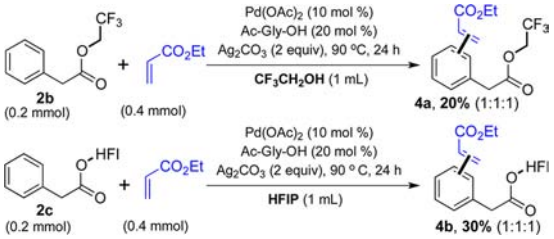
Scheme 2. *Meta*-Selective Olefination in CF_3CH_2OH[7]



Scheme 3. *Meta*-Selective Olefination in HFIP[7]



Scheme 4. Olefination without Nitrile Directing Group



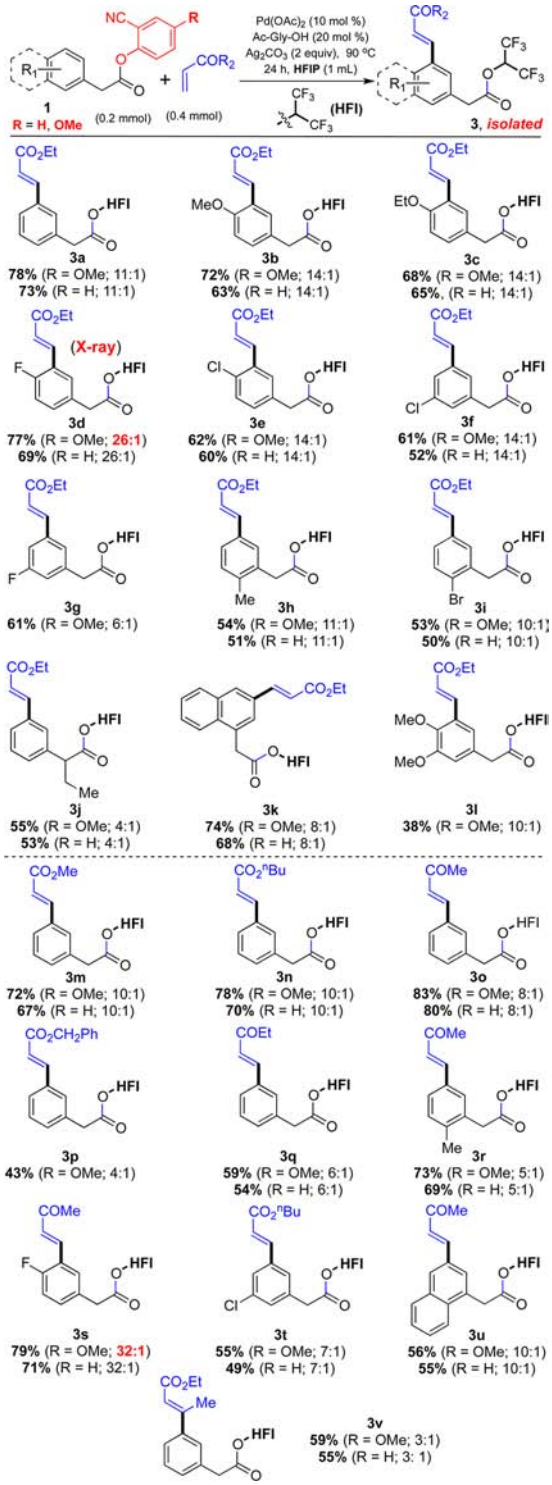
C−H functionalization auxiliary—which could easily be attached to phenylacetic acid to furnish benzyl ester **1a** as the model substrate (Scheme 2).

Initial investigation with **1a** included optimization of reaction conditions (GC) with respect to Pd-catalysts, solvent, temperature, and oxidant.[7] These GC studies revealed that the combination of catalytic $Pd(OAc)_2$/*N*-acetyl-glycine (Ac-Gly-OH)[5] and Ag_2CO_3 (as the oxidant) in trifluoroethanol (90 °C, 24 h) can afford alkenylated product **2a** in 49% isolated (54%, GC) yield with a good level of *meta*-selectivity. Further the 3,5-diolefination compound was also obtained in a small quantity in trifluoroethanol. Upon *meta*-olefination, *trans*-esterification removed the 2-hydroxybenzonitrile template under the optimized conditions (Scheme 2).

Importantly, due to facile *trans*-esterification,[8] **2b** was obtained from **1a** in 40% yield. From this observation, a single lead emerged that prompted us to further focus on reducing the *trans*-esterification of the substrate, which will in turn boost the desired *meta*-alkenylated product. Expectedly, dry solvent gave better yields of the olefinated product. Use of different additives was ineffective to reduce the *trans*-esterification.[7] Introduction of an electron-donating methoxy (OMe) substituent at the *para* position to the hydroxyl group in the template (**1a**′) enhanced the reactivity, and the desired product **2a** was isolated in 55% yield. Upon further optimization, higher conversion was achieved (Scheme 3) by replacement of trifluoroethanol solvent with 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP; $(CF_3)_2CHOH$). Position-selective desired monoalkenylated product **3a** was isolated in 73% (R = H) or 78% (R = OMe) yield. Note that minor amounts of *meta* diolefinated products were detected by GC-MS and NMR analysis of the crude reaction mixture; however, isolation in pure form could not occur.

Notably, generation of a mixture of isomeric products (1:1:1; *o*:*m*:*p*) from **2b** and **2c** (Scheme 4) under the optimization conditions further confirmed the necessity of the nitrile-directing group for *meta*-selectivity.

Scheme 5. Substrates Scope[7] [a]



[a]Isomeric ratio in the isolated materials. *Meta*: others. HFIP: hexafluoroisopropanol. HFI: hexafluoroisopropyl

With the optimal reaction conditions, a wide range of arylacetic acid substrates were found to be compatible with this protocol (Scheme 5). Various benzyl esters were prepared from the corresponding arylacetic acid and 2-hydroxybenzonitrile and/or 2-hydroxy-5-methoxy benzonitrile in one step. A series of

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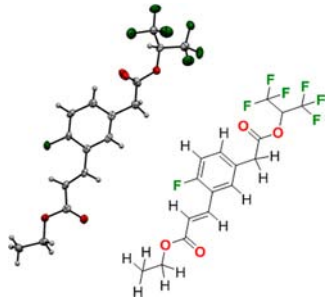
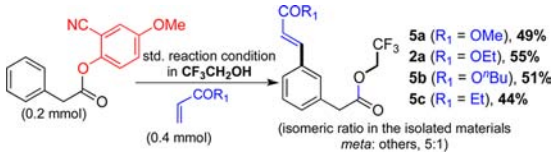
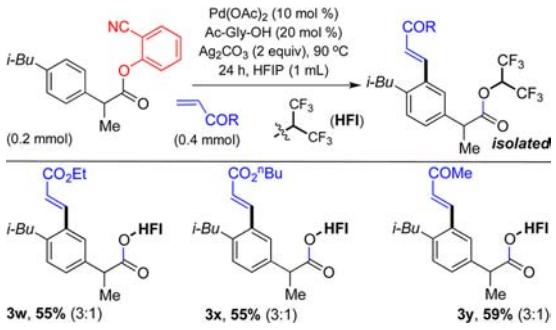


Figure 2. X-ray structure of *meta*-olefinated product **3d**.

Scheme 6. Substrates Scope in CF_3CH_2OH

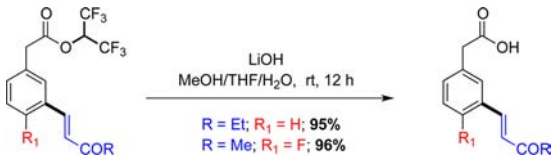


Scheme 7. Drug Diversification[a]



[a]Isomeric ratio in the isolated materials. *Meta*: others. HFI: hexafluoroisopropyl.

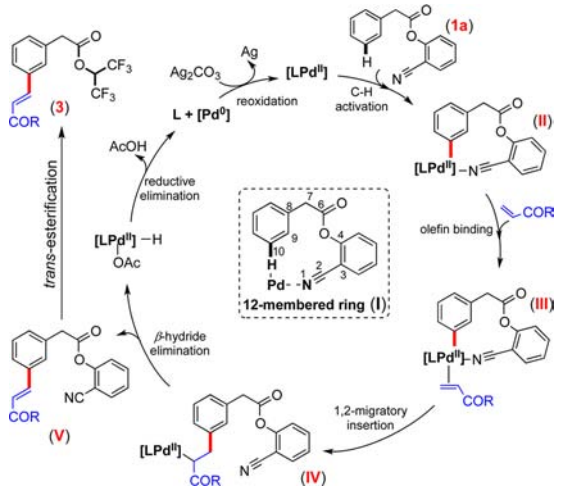
Scheme 8. Hydrolysis of Hexafluoroisopropyl Ester



para-substituted phenyl actetic acids including electron-donating (OMe and OEt) and electron-withdrawing (F and Cl) substituents produced alkenylated products (**3b**−**3e**) in moderate to good yields. Most importantly, a good level of *meta*-selectivity (26:1 for **3d**) was obtained regardless of the electronic properties of the substituents. *Meta*-chloro and -fluoro substituted phenylacetic acids were olefinated selectively at the 5-position (**3f** and **3g**). With an *ortho*-substituted arene substrate, high *meta*-selectivity was achieved with both an electron-donating methyl group (**3h**) and electron-withdrawing bromo group (**3i**). Intriguingly, the cyano ester template can guide the catalyst to reach and activate the *meta*-C−H bond in a selective manner in the presence of α-ethyl substitution on the phenylacetic acid substrate (**3j**).

Notably, a naphthylacetic acid derived substrate also displayed similar reactivity (**3k**). Despite the steric hindrance, a 3,4-dimethoxy substituted arene was also olefinated at the remaining *meta* position (**3l**). Such an example demonstrated that

Scheme 9. Proposed Catalytic Cycle for *Meta*-C−H Olefination



tetrasubstituted arenes could be constructed by employing the *meta*-C−H functionalization strategy as a synthetic tool. Further investigations revealed that commonly used electron-deficient α,β-unsaturated esters and ketones can deliver *meta*-functionalized compounds with good yields and high selectivity (**3m**−**3u**). The 1,2-disubstituted *trans*-ethyl crotonate also proceeded well, affording the corresponding *meta*-selective product **3v**. The highest level of selectivity for the *meta*-olefination reaction was obtained in the case of **3s**.

Compounds in Scheme 5 were characterized by 1D and/or 2D NMR studies. Furthermore, olefination product **3d** was characterized by X-ray crystallography (Figure 2),[9] which confirmed the formation of a *meta*-alkenylated product.

The *meta*-alkenylation reaction was less efficient in trifluoroethanol (Scheme 2) compared to HFIP (Scheme 3). Since trifluoroethanol is synthetically more useful, we thought to explore the reactivity using this solvent. We found that moderate yields and selectivity for the desired alkenylated products were obtained (Scheme 6).

This position-selective *meta*-C−H olefination protocol was then applied to ibuprofen, one of the best-selling analgesic and antipyretic drugs presently available on the market. Although a moderate yield and selectivity were obtained (Scheme 7, **3w**−**3y**), these results display the potential for applying *meta*-C−H olefination in drug diversification.

The *meta* diolefinated products in Schemes 5−7 were detected in small quantities by GC-MS, ^{1}H NMR, and TLC. However, we could not isolate these products in pure form.

The hexafluoroisopropyl group was readily removed by hydrolysis at rt using LiOH to produce *meta*-substituted phenylacetic acid in high yield (Scheme 8).

A proposal on the reaction course is presented in Scheme 9 on the basis of previous reports.[5] Interaction with **1a** is expected to orient the Pd-center selectively toward the *meta*-position of the arene ring. The linear weakly binding nitrile group is proposed to make a 12-membered cyclophane-like pretransition state (**I**). Due to the high electrophilicity, the nitrile-bound Pd(II) center is likely to be reactive toward the C−H bond. Generation of **V** from **II** (Scheme 9) will involve (i) C−H activation, (ii) olefin binding, (iii) 1,2-migratory insertion, and (iv) β-hydride elimination. Subsequently, a facile *trans*-esterification of **V** will afford the final product **3**.

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In conclusion, we developed a method for *meta*-selective olefination of the substituted phenylacetic acid motif with a 2-hydroxybenzonitrile template. Substituents are tolerated at all positions on the phenylacetic acid framework. This strategy for directing remote C−H activation provides a novel route for the preparation of *meta*-olefinated phenylacetic acid derivatives and drug molecules that are difficult to access using conventional methods. Although our attempts to perform *meta*-selective acetoxylation or arylation reactions[5] with **1a** gave little/no desired product, development of *meta*-selective functionalization reactions with related scaffolds is presently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(7) See Supporting Information for detailed description.

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(9) X-ray data CCDC 1019210 (**3d**) can be obtained via http://www.ccdc.cam.ac.uk/data_request/cif.ed.