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Pd-Catalyzed Remote *Meta*-C−H Functionalization of Phenylacetic Acids Using a Pyridine Template

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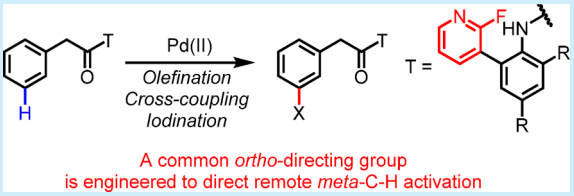
Supporting Information

ABSTRACT: An effective pyridine based U-shaped template has been developed to enable a diverse range of *meta*-C−H functionalizations of phenylacetic acid scaffolds. This new template has extended the reaction scope to cross-coupling with $ArBF_3K$ as well as iodination using 1,3-diiodo-5,5-dimethylhydantoin as the iodination reagent.



Although cyclometalation to generate rigid five- or six-membered palladacycle intermediates has been extensively exploited to achieve *ortho*-selectivity in a wide range of C−H activation reactions, *meta*-selective C−H activation through directed metal insertion remains highly limited. Such a challenge escalates when the directing functional groups are further away from the arenes.[1] One potential advantage of directed *meta*-C−H activation over other nondirected *meta*-C−H activation[2] lies in its ability to override the innate steric or electronic bias of arenes. While a number of relay strategies have been established to direct *meta*-selective C−H activation,[3,4] we have also initiated efforts to develop directed metal insertion into the *meta*-C−H bond using a U-shaped nitrile-directing template (Figure 1).[1,5] Importantly, by recognition of

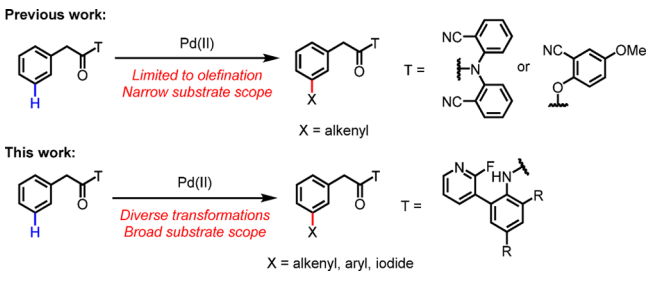


Figure 1. *Meta*-C−H functionalization using a U-shaped template.

distance and geometry, *meta*-selectivity can be achieved regardless of the substitution pattern or electronic nature of the substrate. Notably, this approach is compatible with substrates when the directing functional groups are 10 bonds away from the arene. Recently, such a remote directing effect has also been incorporated into catalyst design to achieve *meta*-C−H[6,7] or even remote C−H activation[8] at other locations without the installation of a non-native directing group. However, in all of these cases, the substrate scope and the number of transformations that could be achieved are limited due to the relatively weak directing effect.

To overcome these limitations, we have recently developed a novel pyridine-based template for the *meta*-C−H activation of benzyl alcohols and phenyl ethyl alcohols based on the following rationale: the strongly coordinating pyridyl group is beneficial for recruiting metal catalysts in the presence of other coordinating functional groups; on the other hand, the large ring size as well as the cyclophane structure of the cyclopalladacycle affords these intermediates with lower stability and hence high reactivity.[9] This new template enabled the development of the first example of *meta*-C−H iodination, thereby demonstrating the utility of this pyridine-based template. Considering the prevalence of the phenylacetic acid scaffold in synthetic intermediates and drug molecules, we have launched extensive efforts to develop both *ortho*- and *meta*-C−H functionalization reactions of these substrates. However, only *meta*-C−H olefination of phenyl acetic acids has been achieved to date.[5e,g] Herein, we report a new pyridine-based template that enables *meta*-C−H olefination, cross-coupling, and iodination of phenylacetic acids, thus providing highly versatile methods for rapid diversification of phenylacetic acid scaffolds that are of importance in drug discovery. These results demonstrate that pyridyl groups can be engineered to direct remote C−H activation by tuning the distance and geometry. The well-defined coordination of the pyridyl group also provides valuable insights into the geometry of the pretransition state required for *meta*-C−H activation.

To overcome the limitations of the U-shaped nitrile-based templates, we have recently developed a pyridine-based template. Through engineering the distal and geometric relationship between the 3-pyridyl group and the target C−H bonds, *meta*-C−H activation of benzyl alcohols has been made possible. Prompted by the broad synthetic utility of phenylacetic acid scaffolds, we began our investigation by testing the *meta*-C−H functionalizations of a variety of phenylacetic acid derivatives containing a 3-subsituted pyridine-based templates (Table S1). Under C−H olefination conditions, a mixture of

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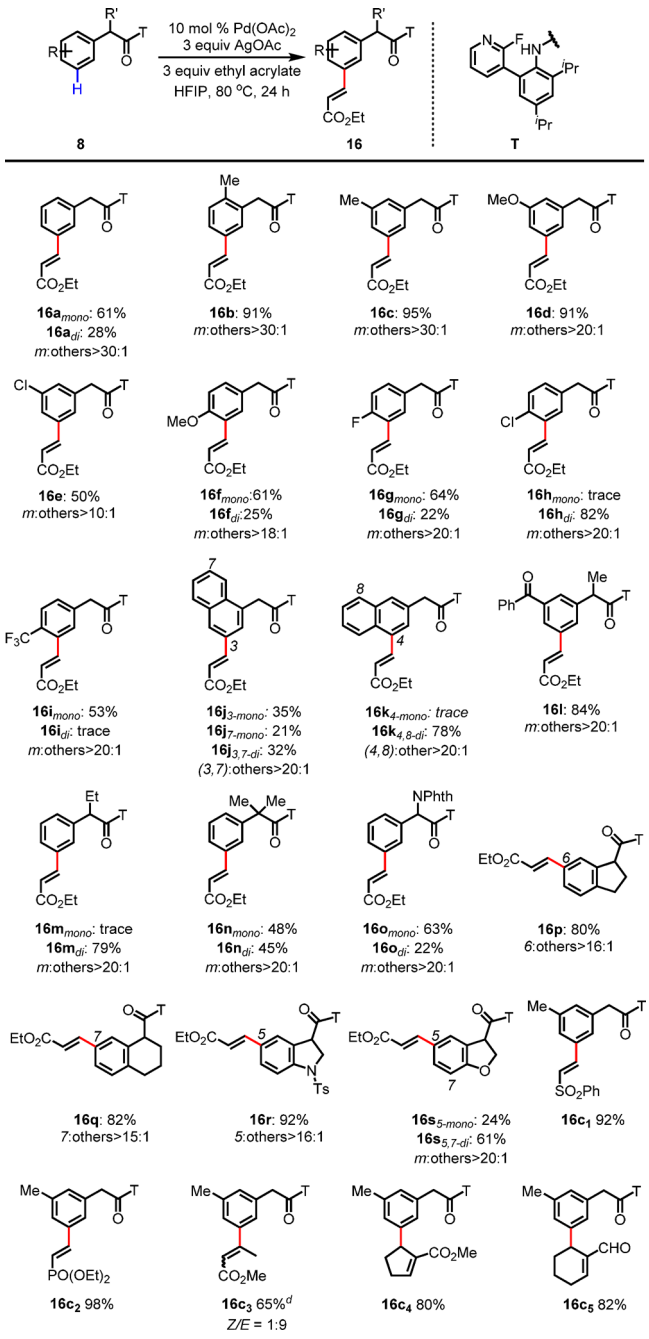
products was obtained with pyridine-based template **1**. Careful analysis showed that the C−H olefination reaction occurred mainly on the aniline moiety. To prevent undesired competitive C−H activation on the aniline ring, a methyl group was introduced at the *ortho*-position of the aniline group in substrate **2**. However, this template failed to promote the *meta*-C−H olefination. Incorporating an electron-withdrawing fluoro group at the C-2 position of the pyridine ring (**3**) provided C−H olefination products in 58% yield, albeit with moderate *meta*-selectivity (*meta*/others = 7:1). Changing the fluoro group to an electron-donating methoxy group (**4**) shuts down the reaction. Satisfyingly, switching the 2-fluoro-5-pyridyl group to a 2-fluoro-3-pyridyl group improved both yield and *meta*-selectivity (**5**, 84% yield, *meta*/others >20:1). Introducing a second fluoro group on the pyridine ring decreased both the yield and regioselectivity (**6**, 46% yield, *meta*/others = 9:1). Notably, incorporation of two bulky ^{i}Pr groups on the aniline ring led to significantly improved yield and *meta*-selectivity (**8a**, 93% yield, *meta*/others >30:1). This improvement is presumably attributed to the conformational restriction posed by the bulky isopropyl group, which promotes a more rigid transition state conformation.

With the optimal template in hand, a variety of phenylacetic acids were covalently linked to the template and subjected to the *meta*-C−H olefination reaction conditions (Scheme 1). *meta*-C−H olefination of phenylacetic acid provided the *meta*-olefinated products in an overall yield of 89% (**16**$_{amono}$, 61%, **16**$_{adi}$, 28%) with high regioselectivity. Phenylacetic acids bearing methyl or methoxy substitutions at the 2- or 3-position gave exclusively the mono *meta*-olefinated product in high yields (**16b−d**). *m*-Chloro-substituted phenylacetic acidic provided moderate yield and regioselectivity (**16e**). *Para*-substitutions were well tolerated, affording both the mono- and di-products in moderate to good isolated yields regardless of its electronic properties (**16f−i**). For 1-naphthalenylacetic acid **16j**, olefination occurred at both the 3- and 7-position, affording the mono- and di-products **16j**$_{3\text{-mono}}$, **16j**$_{7\text{-mono}}$, and **16j**$_{3,7\text{-di}}$ in isolated yields of 35%, 21%, and 32%, respectively. In contrast, olefination of 2-naphthalenylacetic acid **8k** gave exclusively 4,8-diolefinated product (**16k**). Furthermore, olefination of α-substituted phenylacetic acids afforded excellent yields and regioselectivities (**16l−o**). More importantly, this protocol is also compatible with cyclic and heterocyclic substrates, thus opening new avenues for its potential utility in C−H functionalization of advanced intermediates and late-stage modifications (**16p−s**). The scope of the olefin partners was also examined using substrate **8c**. α,β-Unsaturated olefins containing various functional groups such as sulfone (**16**$_{c1}$), phosphonate (**16**$_{c2}$), and aldehyde (**16**$_{c5}$) are all well tolerated, providing the desired products in good yields. Reaction with *di*-substituted olefin **16c**$_3$ afforded the corresponding product with moderate to good yields. Notably, this reaction is also compatible with cyclic α,β-unsaturated olefins, providing the nonconjugated products in good yields (**16c**$_4$, **16**$_{c5}$). Excellent *meta*-selectivities were obtained in all cases (*meta*/others >20:1).

To demonstrate the versatility of this new pyridine-based template, we next developed a new protocol for *meta*-C−H cross-coupling of phenylacetic acids. Notably, the previous nitrile-based template is not compatible with the *meta*-C−H coupling of phenylacetic acid derivatives. We began by evaluating different pyridine-based templates with our previously established cross-coupling conditions using 4-

Scheme 1. Scope of Phenylacetic Acids for *Meta*-C−H Olefination[a−c]



[a]Reaction conditions: substrate **8** (0.1 mmol), $Pd(OAc)_2$ (0.1 mmol), ethyl acrylate (0.3 mmol), AgOAc (0.3 mmol), HFIP (1.0 mL), air, 80 °C, 24 h. [b]Isolated yield. [c]*Meta*-regioselectivity based on analysis of crude ^{1}H NMR spectra. [d]**16**$_{c3}$ was isolated as a *Z*/*E* mixture (*Z*/*E* = 1:9) based on analysis of ^{1}H NMR.

methoxycarbonyl phenylboronic acid pinacol ester as the coupling partner (Table S2). Template **8a** was identified as the optimal template, giving the *meta*-arylated product in 30% overall yield with >20:1 *meta*-selectivity. The use of potassium trifluoroborate improved the yield to 46% (Table S3). Reaction optimization revealed that silver carbonate was the best oxidant (Table S4). A combination of cesium fluoride and potassium trifluoroacete could improve the overall yield to 50%. Tetrabutylammonium (TBA) salts have been shown to

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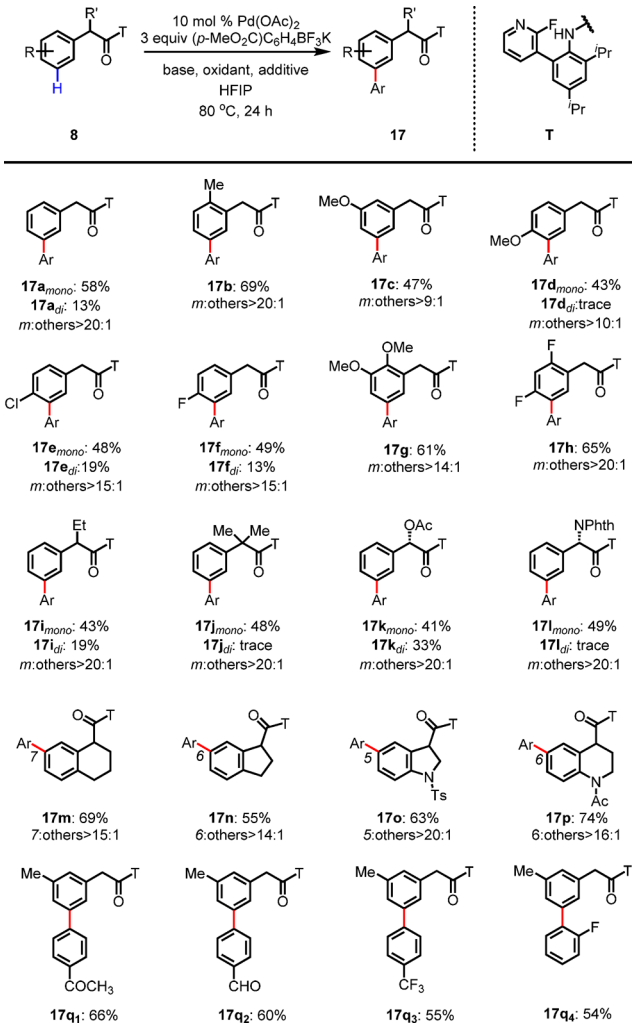
improve C−H cross-coupling reactions dramatically.[10,5a] Evaluation of different TBA salts showed that the addition of tetrabutylammonium tetrafluoroborate improved the yield to 57% with (entry 12, Table S4). Addition of catalytic amounts of sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate further improved the yield to 75% (entry 17, Table S4). The overall yield was improved to 81% when the temperature was lowered to 80 °C (entry 18, Table S4).

The substrate scope of this *meta*-C−H cross-coupling protocol was subsequently investigated (Scheme 2). Phenylacetic acid derivatives containing electron-donating and electron-withdrawing substitutions were all tolerated to give moderate to good yields (**17a**−**f**). Disubstituted phenylacetic acids afforded the corresponding arylation products in moderate yield (**17g**,**h**). α-Substituted phenylacetic acids were also compatible in this reaction (**17i**−**l**), providing the desired products in moderate to good yields. The versatility of this protocol was further validated by *meta*-C−H cross-coupling of cyclic and heterocyclic substrates (**17m**−**p**). The scope of the arylboron coupling partners was then investigated. Electron-deficient arylborons containing ketone, aldehyde, trifluoro, and fluoro groups were all tolerated (**17q$_1$**−**q$_4$**). Excellent *meta*-selectivity was observed in all cases.

Aryl iodides are versatile intermediates in organic synthesis. Using a recently developed protocol,[9a] *meta*-iodination of phenylacetic acid derivatives could be achieved with high yields and regioselectivity. Both electron-donating (Scheme 3, **18b**,**e**) and electron-withdrawing substitutions (**18c**,**d**,**f**,**g**) were tolerated to give moderate to good yields and high regioselectivity. Finally, the directing template could be removed with high yield using a previously reported procedure.[11]

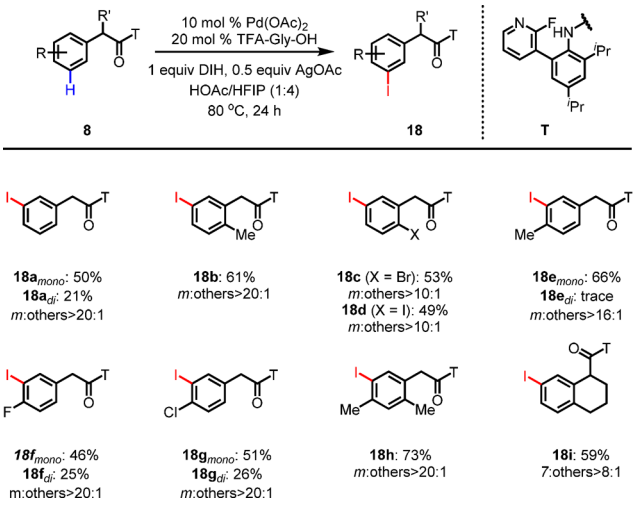
In summary, we have developed a new class of pyridine-based template for the *meta*-C−H activation of phenylacetic acids, demonstrating that a commonly used *ortho*-directing group can be engineered to activate remote C−H bonds by tuning the distance and geometry.

Scheme 2. Scope of Phenylacetic Acids for *Meta*-C−H Arylation[a,b]



[a]Reaction conditions: substrate **8** (0.1 mmol), $ArBF_3K$ (0.3 mmol), $Pd(OAc)_2$ (0.01 mmol), Ag_2CO_3 (0.2 mmol), CsF (0.2 mmol), KTFA (0.2 mmol), Bu_4NBF_4 (0.05 mmol), $NaB(3,5\text{-}CF_3Ph)_4$ (0.02 mmol), HFIP (2 mL), air, 80 °C, 24 h. [b]Isolated yield.

Scheme 3. Scope of Phenylacetic Acids for *Meta*-C−H Iodination[a,b]



[a]Reaction conditions: substrate **8** (0.1 mmol), 1,3-diiodo-5,5-dimethylhydantoin (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), AgOAc (0.05 mmol), TFA-Gly-OH (0.02 mmol), HOAc (0.2 mL), HFIP (0.8 mL), air, 80 °C, 24 h. [b]Isolated yield.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03336.

Experimental procedures and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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