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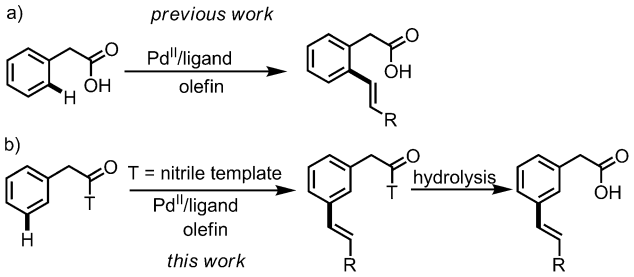
Remote *meta*-C–H Olefination of Phenylacetic Acids Directed by a Versatile U-Shaped Template**

*Youqian Deng and Jin-Quan Yu**

In memory of Carlos F. Barbas III

Abstract: *meta-C–H olefination of phenylacetic acid derivatives has been achieved using a commercially available nitrile-containing template. The identification of N-formyl-protected glycine as the ligand (Formyl-Gly-OH) was crucial for the development of this reaction. Versatility of the template approach in accommodating macrocyclopalladation processes with different ring sizes is demonstrated.*

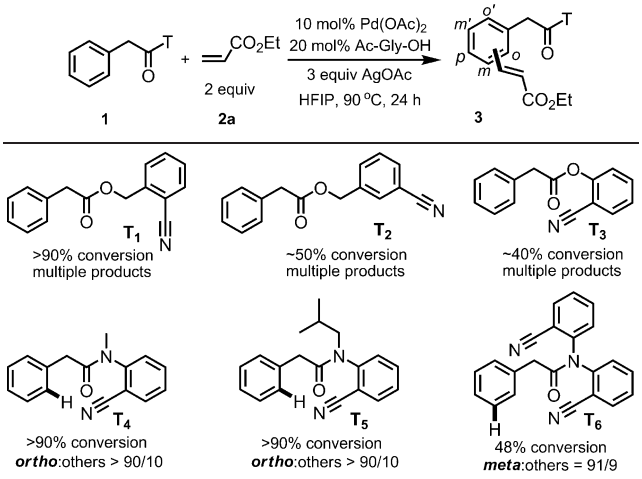
C–H activation directed by chelating groups has been exploited to develop a diverse range of carbon–carbon and carbon–heteroatom bond-forming reactions.[1] While these reactions display reliable and useful *ortho*-selectivity, achieving *meta*-selectivity through various approaches will greatly expand the synthetic utility of C–H activation reactions by providing novel disconnections.[2–5] We have recently developed a nitrile-based template to direct *meta*-C–H activation of phenols, anilines, and carboxylic acids.[4,5] These nitrile-containing templates successfully override the intrinsic electronic and steric biases of substrates as well as the *ortho*-directing effect via a metallocyclophane-like transition state. However, a significant remaining challenge is to demonstrate that this template can direct the activation of *meta*-C–H bonds that are located at different distance from the directing nitrile group. For example, our *meta*-C–H activations of hydrocinnamic acids and α-phenoxyacetic acids involve abstraction of hydrogen atoms that are 12 bonds away from the directing nitrogen atom. Therefore, a 13-membered cyclic transition state is proposed for the palladation step. As one might expect that the assembly of these macrocyclic transition states is sensitive to ring size, we wondered if the *meta*-selectivity could be reproduced when the C–H bonds are closer to the directing nitrile. In this context, phenylacetic acid is an ideal test substrate, as the same template linkage can be adopted. In addition, *ortho*-C–H functionalizations of phenylacetic acids have been extensively developed in recent years and their synthetic utility has also been demonstrated (Scheme 1 a).[6] Thus, extending these reactions to *meta*-C–H functionalizations will greatly expand the synthetic utility of readily available phenylacetic acid analogues. Herein we report the first example of *meta*-C–H olefination of a wide range of phenylacetic acids using our template and a newly identified ligand (Scheme 1 b). Surprisingly, this protocol can also install α,β-unsaturated aldehydes, previously shown to have been unreactive in *ortho*-C–H olefination of phenylacetic acids.[6a–c]



Scheme 1. *ortho*- and *meta*-C–H olefinations of phenylacetic acid.

Based on our previous experimental and computational studies on remote *meta*-C–H activation reactions of hydrocinnamic acids,[4a,f] our initial efforts were centered on identifying a new nitrile template suitable for phenylacetic acid (Table 1). Commercially available templates ($\mathbf{T_1}$–$\mathbf{T_3}$) attached to phenylacetic acid through an ester linkage are

Table 1: Investigation of templates to direct *meta*-C–H olefination.[a,b,c]



[a] Conditions: **1** (0.1 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), Ac-Gly-OH (20 mol%), AgOAc (0.3 mmol), HFIP (1 mL), 90 °C, 24 h. [b] Selectivity was determined by crude ^1H NMR spectroscopy. [c] Yields were determined with CH_2Br_2 as internal standard.

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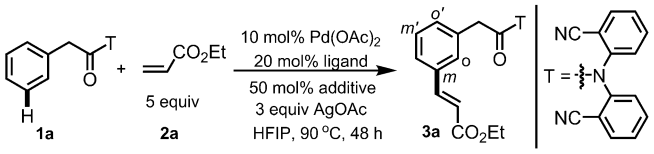
reactive but show poor site selectivity.[7] The previously effective templates ($\mathbf{T_4}$ and $\mathbf{T_5}$) for *meta*-C–H olefination of hydrocinnamic acid[4a] afforded *ortho*-selectivity instead. Finally, we found that previously reported template $\mathbf{T_6}$ proved most promising, affording the olefinated products in 48% total yield (mono/di 3.0/1) with good *meta*-selectivity (*meta*/others 91/9) (Table 1).

We thus began extensive optimizations using template $\mathbf{T_6}$. The first significant improvement was made by increasing the amount of ethyl acrylate **2a** to 5 equiv and extending the reaction time to 48 h, which enhanced the yield to 60% (Table 2, entry 3). A control experiment showed that the mono-protected amino acid ligand Ac-Gly-OH is required for this reaction (Table 2, entry 2) to proceed.[8] We hence screened a series of structurally related mono-protected amino acid ligands (Table 2, entries 4–12). Formyl-Gly-OH was identified to be the optimum choice in terms of both yield and *meta*-selectivity (Table 2, entry 12). Although the use of bases was not beneficial in the *meta*-C–H olefination of hydrocinnamic acid, we found through screening that addition of 50 mol% of KH_2PO_4 improved the total yield to 76% (Table 2, entry 19). The role of the base is most likely related to the promotion of ligand coordination as only the ligand contains acidic protons. Shortening the reaction time to 24 h did not significantly affect the yield (Table 2, entry 21). Ag_2CO_3 was also found to be an effective oxidant but gave inferior *meta*-selectivity (Table 2, entry 23). The mono- and di-olefinated products were easily separated by silica gel chromatography.

With these optimized conditions in hand, we examined the scope of phenylacetic acid analogues using ethyl acrylate as the reacting partner (Table 3). Various substrates containing electron-withdrawing or -donating substituents were prepared by reacting the corresponding phenylacetic acyl chloride with the amine template $\mathbf{T_6}$ in the presence of sodium hydride in dimethylformamide or acetonitrile (see the Supporting Information). High mono-selectivities were obtained with *ortho*-

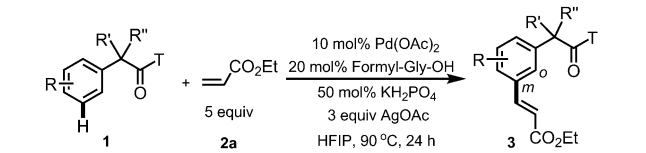
Table 2: Optimization of reaction conditions.[a,b]

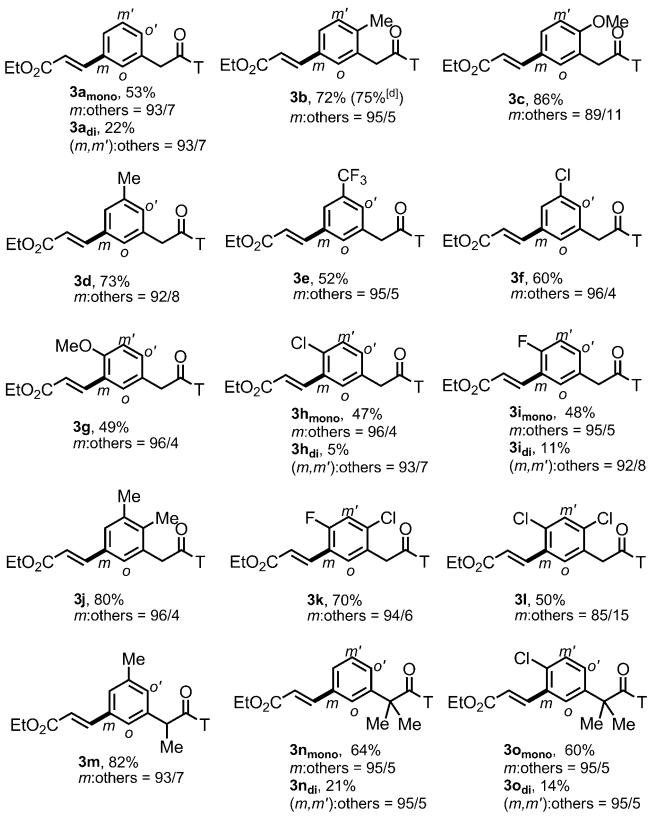


Entry	Ligand (20 mol%)	Additive (50 mol%)	Yield [%]	mono/di	Selectivity[c] *meta*/others
1[d,e]	Ac-Gly-OH	–	48	3.0/1	91/9
2	–	–	trace	–	–
3	Ac-Gly-OH	–	60	3.0/1	91/9
4	Ac-Ala-OH	–	54	3.5/1	80/20
5	Ac-Val-OH	–	35	6.0/1	91/9
6	Ac-Leu-OH	–	38	8.5/1	91/9
7	Ac-β-Ala-OH	–	23	22.0/1	91/9
8	TFA-Gly-OH	–	19	5.3/1	84/16
9	MeO_2C-Gly-OH	–	20	>20/1	86/14
10	2-furoyl-Gly-OH	–	0	–	–
11	Formyl-Ala-OH	–	58	3.8/1	92/8
12	Formyl-Gly-OH	–	66	3.1/1	93/7
13	Formyl-Gly-OH	BQ	61	4.5/1	91/9
14	Formyl-Gly-OH	TFA	60	3.0/1	90/10
15	Formyl-Gly-OH	$BF_3{\cdot}Et_2O$	42	4.3/1	80/20
16	Formyl-Gly-OH	K_2CO_3	0	–	–
17	Formyl-Gly-OH	KOAc	51	3.6/1	95/5
18	Formyl-Gly-OH	K_2HPO_4	54	5.0/1	91/9
19	Formyl-Gly-OH	KH_2PO_4	76	2.5/1	93/7
20	Formyl-Gly-OH	NaH_2PO_4	73	2.7/1	93/7
21[d]	**Formyl-Gly-OH**	**KH_2PO_4**	**80**	**2.2/1**	**93/7**
22[d,f]	Formyl-Gly-OH	KH_2PO_4	67	3.2/1	93/7
23[g]	Formyl-Gly-OH	KH_2PO_4	70	2.2/1	90/10

[a] Conditions: **1a** (0.1 mmol), **2a** (0.5 mmol), $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), additive (50 mol%), AgOAc (0.3 mmol), HFIP (1 mL), 90 °C, 48 h. [b] Crude ^{1}H NMR yields determined with CH_2Br_2 as internal standard. [c] Selectivity refers to the ratio of *meta*:others mono-olefinated products, as determined by crude ^{1}H NMR spectroscopy. [d] 24 h. [e] **2a** (0.2 mmol). [f] **2a** (0.3 mmol). [g] Ag_2CO_3 (0.2 mmol) was used instead of AgOAc. Ac = acetyl, Gly = glycine, Ala = L-alanine, Val = L-valine, Leu = L-leucine. BQ = 1,4-benzoquinone, TFA = CF_3CO_2H.

Table 3: Pd^{II}-catalyzed *meta*-C–H olefination of aryl acetic acid amides.[a,b,c]



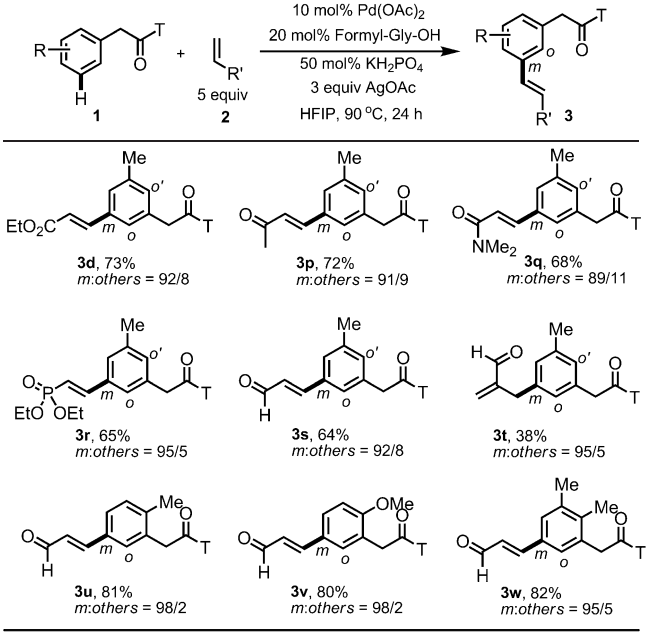


[a] Conditions: **1** (0.1 mmol), **2a** (0.5 mmol), $Pd(OAc)_2$ (10 mol%), Formyl-Gly-OH (20 mol%), KH_2PO_4 (50 mol%), AgOAc (0.3 mmol), HFIP (1 mL), 90 °C, 24 h. [b] Selectivity was determined by crude ^{1}H NMR spectroscopy. [c] Yields of isolated products. [d] Isolated yield of 2 mmol scale reaction.

methyl- (**3b**) or *ortho*-methoxy-substituted (**3c**) phenylacetic acid substrates. Substrates containing a methyl (**3d**), trifluoromethyl (**3e**) and chloro group (**3f**) at the *meta*-position afforded the desired products in good yields with excellent *meta*-selectivities. The protocol is also compatible with functional groups at the *para*-positions, such as methoxy (**3g**), chlorine (**3h**) and fluorine (**3i**), albeit affording lower yields. However, bromo and iodo substituents inhibit this reaction. *Meta*-olefination of 2,3- or 2,4-disubstituted substrates (**3j–3l**) also gave synthetically useful yields. Importantly, α-substitutions were also tolerated (**3m–3o**) thus allowing for broader synthetic applications of this reaction. Although *ortho*-disubstituted hydrocinnamic acids were previously olefinated at the *meta*-position using this template,[4a] *ortho*-dimethylated phenylacetic acid is not compatible with this protocol, which could be attributed to the steric congestion of this phenyl acetic acid substrate.

The scope of olefins was also briefly surveyed using substrate **1d** (Table 4). Commonly used olefin coupling partners[9] such as an α,β-unsaturated ester, ketone, amide, and phosphonate afforded the corresponding *meta*-olefinated

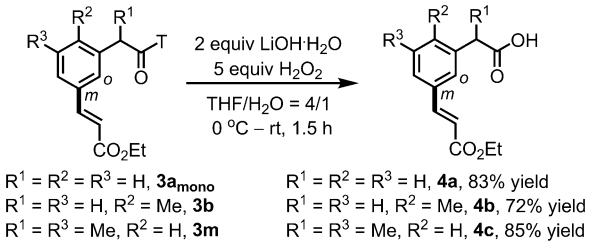
Table 4: Scope of olefin coupling partners.[a,b,c]



[a] Conditions: **1** (0.1 mmol), **2** (0.5 mmol), $Pd(OAc)_2$ (10 mol%), Formyl-Gly-OH (20 mol%), KH_2PO_4 (50 mol%), AgOAc (0.3 mmol), HFIP (1 mL), 90°C, 24 h. [b] Selectivity was determined by crude ^{1}H NMR spectroscopy. [c] Yields of isolated products.

products in good yields and with good *meta*-selectivities. While our previous conditions for *ortho*-directed C–H olefination often proved incompatible with acrolein, interestingly, both acrolein and metacrolein are effective reacting partners for this *meta*-C–H olefination reaction (**3s** and **3t**). It is worth noting that C–H olefination reactions with acrolein have only been demonstrated through non-directed C–H activation[10a–c] with an exceptional single example of directed C–H activation.[10d] Olefination with acrolein was also carried out with other methylated and methoxylated substrates to give the desired products in excellent yields (**3u**, **3v**, and **3w**). Unfortunately, this reaction is not compatible with simple alkenes such as 1-hexene.

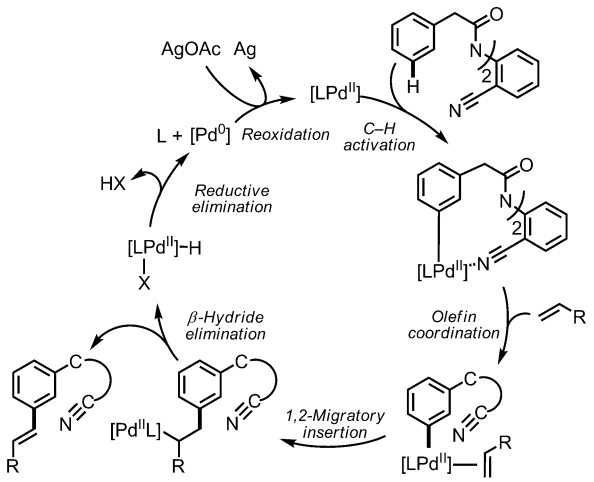
Removal of the template under previously reported conditions utilizing LiOH in MeOH/THF/H_2O[4a] resulted in an unidentified mixture of compounds. Extensive screening of conditions led us to find that treatment of *meta*-olefinated products $\mathbf{3a_{mono}}$, **3b**, and **3m** under Evans' hydrolytic conditions (LiOH/H_2O_2) at room temperature[11] provided phenylacetic acid **4a**, **4b**, and **4c** in 83%, 72%, and 85% yields, respectively (Scheme 2). The remaining vinylic ester group that remained unaffected by the hydrolysis conditions renders this transformation especially useful.



Scheme 2. Removal of nitrile template.

The observed *meta*-selectivity can be explained by a selective C–H palladation directed by a remote end-on coordinating nitrile group (Scheme 3). The C–H palladation step involves the formation of a 11-membered palladacycle. In light of the bisdentate coordination mode with mono-protected amino acid ligand, the nitrile group is mostly likely displaced by the olefin prior to the migratory insertion. Pd^0 species formed from the β-hydride elimination step is recycled by the Ag^+ oxidant.

In conclusion, we have developed a protocol for *meta*-C–H olefination of phenylacetic acids. This protocol affords a series of synthetically valuable *meta*-olefinated phenylacetic acids that are otherwise not readily available. The identifica-



Scheme 3. Catalytic cycle of *meta*-C–H olefination of phenylacetic acid.

tion of N-formyl-protected glycine (Formyl-Gly-OH) as the ligand and KH_2PO_4 as the additive was crucial for the development of this reaction. This new development demonstrates a high level of versatility of the template approach in accommodating macrocyclopalladation processes with different ring size.

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Keywords: C–H activation · olefination · palladium · phenylacetic acid · template synthesis

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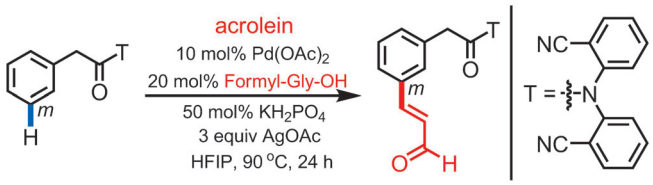
Communications

C–H Activation

Y. Deng, J.-Q. Yu* _____ ■■■■–■■■■

Remote *meta*-C–H Olefination of Phenylacetic Acids Directed by a Versatile U-Shaped Template



It's T time: The title reaction has been achieved using a commercially available nitrile-containing template. The identification of N-formyl-protected glycine as the ligand (Formyl-Gly-OH) was crucial for the development of this reaction. Versatility of the template approach in accommodating macrocyclopalladation processes with different ring sizes is demonstrated.