

# Cross-Coupling of Remote meta-C-H Bonds Directed by a U-Shaped Template

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**S** Supporting Information

ABSTRACT: meta-C-H arvlation and methylation of 3phenylpropanoic acid and phenolic derivatives were developed using an easily removable nitrile template. The combination of a weakly coordinating U-shaped template and mono-protected amino acid ligand was crucial for the cross-coupling of C-H bonds with organoborons.

ransition-metal-catalyzed functionalization of unactivated C-H bonds is a highly attractive strategy for the synthesis of organic molecules, owing to the omnipresent nature of C-H bonds in organic substances.<sup>1</sup> Due to the subtle difference in reactivity of multiple C-H bonds in a given molecule, however, controlling the regioselectivity or positional selectivity remains a central challenge in the field. In addition, when an intrinsically less reactive C-H bond needs to be preferentially functionalized to meet a synthetic task, a chemical approach must be developed to override the intrinsic bias. In this context,  $\sigma$ chelation-directed C-H activation has been successful in developing a wide range of C-H functionalization reactions.<sup>2</sup> While these reactions are broadly useful, the tremendous opportunity of activating C-H bonds that are relatively distal to existing functional groups remains to be exploited. Notably, functionalizations of C-H bonds with different distance from a functional group will lead to distinct structural motifs.<sup>3</sup> In our efforts to seek solutions for this problem, we found that the development of remote C-H functionalization reactions using C-H palladation process suffers from the difficulty of forming palladacycles larger than six-membered rings which has been a major obstacle.<sup>4</sup> More arduous still is the formation of palladacycles consisting of strained ring systems, as is the case with cyclophanes formed from directed palladation of meta- and para-C-H bonds.<sup>5</sup> Herein we report the first example of Pdcatalyzed cross-coupling of meta-C-H bonds with arylboronic acids (Scheme 1). The observed meta-selectivity was achieved through directed C-H palladation via an U-shaped nitrile template weakly coordinated to a Pd(II) catalyst.<sup>6,7</sup> Additionally, tuning the properties of the Pd(II) catalyst with a monoprotected amino acid (MPAA) ligand was vital to successful cross-coupling.

This coupling reaction affords synthetic chemists a novel C-H activation disconnection for biaryl synthesis. The transmetalation process required for the coupling also provides concrete evidence in support of a C-H palladation pathway directed by remote weak coordination.

# Scheme 1. meta-C-H Functionalization Using Nitrile Template



We have recently reported the first example of remote meta-C-H olefination of hydrocinnamic acids using an end-on nitrile template.<sup>6</sup> This reaction provides important evidence for the formation of 12-membered cyclophane-like palladacycles, although Friedel-Crafts-type olefination catalyzed by Pd(II) salts as Lewis acids cannot be ruled out. To further establish the feasibility of remote C-H activation via large and strained palladacycles, we embarked on the development of remotemeta-C-H cross-coupling with aryl boronic acids which would require the formation of discrete arylpalladium species. Whether this highly strained cyclophane organopalladium intermediates could accommodate transmetalation and reductive elimination steps remained to be tested. This reaction would provide a novel C-H activation disconnection for the synthesis of biaryls with different substitution patterns to those prepared from ortho-C-H arylation reactions. Thus, we began to develop remote-meta-C-H cross-coupling with aryl boronic acids using our recently designed nitrile template.

Our exploratory experiments were guided by our previous discovery that MPAA ligands promote C-H coupling with organoborons.<sup>8</sup> Through extensive screening of various reaction parameters including bases, oxidants, and solvents, we found that the combination of Pd(OAc)2/Ac-Gly-OH/ Ag<sub>2</sub>CO<sub>3</sub>/KHCO<sub>3</sub> and arylboronic ester facilitated the arylation of 1a containing template  $T^2$  to give the mono- and diarylated products 2amono and 2adi in 36% and 17% yield, respectively (Table 1, entry 1). In order to increase the yield, we started to examine different additives. It has been shown that tetrabutylammonium (TBA) salts can have a dramatic influence on the catalytic performance of palladium in cross coupling reactions.9 The enhanced reactivity can be attributed to the ability of surfactants to prevent undesired agglomeration of

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## Ar-Bpin (3 equiv) Pd(OAc)<sub>2</sub> (10 mol%) Ac-Gly-OH (20 mol% Ag<sub>2</sub>CO<sub>3</sub> (2 equiv) ČsF (2 equiv) NC TBAPF<sub>6</sub> (3 equiv) HFIP, 70 °C, 24 h T<sup>1</sup>: R = H 1a-r $Ar = (4-CO_2Me)C_6H_4$ 2a-1 T<sup>2</sup>: R = OMe **2b**. 56% **2a<sub>mono</sub>, 46%** 2c. 44% m:(p+o+o') = 93:7 m:(p+o+o') = 96:42a<sub>di</sub>, 34% m:(p+o+o') = 92:82d<sub>mono</sub>, 43%<sup>4</sup> **2e,** 63% **2f**, 58% *m*:(*p*+*o*+*o*') = 87:13 **2d<sub>di</sub>,** 13% F₂C **2g**, 65% **2h**, 85% **2i**, 81% *m*:(*p*+*o*+*o*') = 85:15 **2I**, 57% **2**j, 48% 2kmono, 42% m:(p+o+o') = 91:9 2k<sub>di</sub>, 29% **2n**, 59% **20,** 42% 2m. traces Me Me Me MeC

Table 2. meta-Arylation of 3-Phenylpropanoic Acid and

Phenolic Derivatives<sup>*a,b*</sup>

<sup>*a*</sup>Conditions: substrate (0.1 mmol), Ar-Bpin (0.3 mmol),  $Pd(OAc)_2$  (10 mol%), Ac-Gly-OH (20 mol%), Ag<sub>2</sub>CO<sub>3</sub> (0.2 mmol), TBAPF<sub>6</sub> (0.3 mmol), CsF (0.2 mmol), HFIP (1 mL), 70 °C, 24 h. <sup>*b*</sup>Isolated yield. <sup>*c*</sup>Mixture of *meta*-arylated isomers.

**2q**, 53%

2r, 49%

**2p**, 64%

diarylation. In contrast to the *meta*-olefination reaction,<sup>6</sup> the reactivity of di-*ortho*-substituted (2m) substrates are poor under these conditions.

We have previously employed the nitrile template  $T^1$  to perform *meta*-C–H olefination reactions of phenols.<sup>6b</sup> We were pleased to find that *meta*-arylation of phenol substrates attached to  $T^1$  also proceeded to give the desired products in moderate to good yields (**2n**-**2r**). Further optimizations of conditions and template may lead to a novel route for preparing *meta*arylated phenols.

The scope of the arylboron coupling partners was also surveyed (Table 3). We found that arylboronic acid esters containing both electron-withdrawing (2t-2v) and donating (2w, 2x) substituents afforded good yields. In light of the





			yield (%)	
entry	additive	base	mono	di
1	_	KHCO3	36	17
2	TBAF · 3H₂O	KHCO3	11	2
3	TBAC	KHCO3	0	0
4	TBAB	KHCO3	16	4
5	TBAOAc	KHCO3	20	8
6	$TBABF_4$	KHCO3	37	16
7	$TBAPF_6$	KHCO3	41	21
8	TBAPF <sub>6</sub>	$K_2CO_3$	26	14
9	TBAPF <sub>6</sub>	$Cs_2CO_3$	0	0
10	$TBAPF_6$	NaOAc	24	12
11	TBAPF <sub>6</sub>	KOAc	25	11
12	$TBAPF_6$	CsOAc	42	17
13	$TBAPF_6$	CsF	43	31
14 <sup>c</sup>	TBAPF <sub>6</sub>	CsF	$\frac{48}{(46)^d}$	$(35)^{(34)^d}$

<sup>*a*</sup>Conditions: **1a** (0.1 mmol), Ar-Bpin (0.3 mmol),  $Pd(OAc)_2$  (10 mol %), Ac-Gly-OH (20 mol%), Ag<sub>2</sub>CO<sub>3</sub> (0.2 mmol), additive (0.3 mmol), base (0.2 mmol), HFIP (1 mL), 90 °C, 24 h. <sup>*b*</sup>Yield was determined by <sup>1</sup>H NMR analysis using CH<sub>2</sub>Br<sub>2</sub> as internal standard. <sup>*c*</sup>70 °C. <sup>*d*</sup>Isolated yield.

Pd(0) species to form unreactive palladium black. Furthermore, the anionic counterion can play an important role in stabilizing cationic palladium intermediates.<sup>10</sup> The addition of TBAPF<sub>6</sub> increased the total yield (2a<sub>mono+di</sub>) from 53% to 62% (entry 7), while TBA halides, such as fluoride (13%), chloride (0%), and bromide (20%), inhibited the reaction (entries 2-4). Additionally, we tested different bases in our transformation because, according to our experience, the nature of the base can have a crucial impact on cross-coupling reactions. CsF (entries 13 and 14), a mild base successfully employed in different cross-coupling reactions,<sup>11</sup> proved to be the most effective compared to carbonates and acetates (entries 8-12), which did not show a positive effect. It has been reported that fluoride can play an important role in activating the boronic acid ester, facilitating the transmetalation step.<sup>12</sup> Notably, the temperature could be decreased to 70 °C, affording 48% and 35% of 2a<sub>mono</sub> and 2a<sub>di</sub>, respectively (entry 14). Next, we investigated the scope of the reaction, testing different substituted 3-phenylpropanoic acids (Table 2). We were delighted to find that this reaction proved general for both electron withdrawing (2b-2g) and electron-donating substituents (2h-2j). Substitution of the benzylic position with a methyl group was also tolerated  $(2k_{mono+di})$ . Interestingly, [1,1'-biphenyl]-2-carboxylic acid was also smoothly arylated at the remote-meta-position instead of the meta-position that is closer to the template (21). The *meta*-selectivities of this reaction are in general excellent, although minor formation of different isomers were observed with nonsubstituted or metasubstituted substrates. As expected, only mono-meta-arylation was observed in the case of ortho-substituted substrates (2b, 2f, **2h**). With the exception of the *ortho*-fluorinated substrate (**2d**) the remaining *meta*-position is sterically hindered, preventing Table 3. *meta*-Arylation of 1h with Arylboronic Acid Esters<sup>a,b</sup>



<sup>*a*</sup>Conditions: **1h** (0.1 mmol), Ar-Bpin (0.3 mmol),  $Pd(OAc)_2$  (10 mol %), Ac-Gly-OH (20 mol%),  $Ag_2CO_3$  (0.2 mmol), TBAPF<sub>6</sub> (0.3 mmol), CsF (0.2 mmol), HFIP (1 mL), 70 °C, 24 h. <sup>*b*</sup>Isolated yield.

importance of methyl group in medicinal chemistry,<sup>13</sup> we sought to determine if our method was compatible with methyl boron reagents. We found the use of MeBF<sub>3</sub>K as the methylating reagent afforded the *meta*-methylated product **2y** in 51% yield, while Me-Bpin gave slightly lower yield (Scheme 2). Further optimizations are required to encompass broad range of alkylborons due to the well-known  $\beta$ -hydride elimination side pathway.<sup>14</sup>



Finally, the template was removed under mild conditions, furnishing 3 in 96% yield while nitrile template 4 was recovered in 79% yield (Scheme 3).



In summary, we have developed the first example of coupling *meta*-C-H bonds with organoborons using a removable U-shaped template. This *meta*-arylation reaction provides a novel method for preparing of 3-phenylpropanoic acid and phenolic derivatives. The observed reactivity provides strong evidence for the formation of an arylpalladium intermediate directed by

remote weak coordination and signals future development of a wide range of transformations based upon the template-assisted remote C–H activation.

# ASSOCIATED CONTENT

### **Supporting Information**

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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#### Notes

The authors declare no competing financial interest.

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