

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

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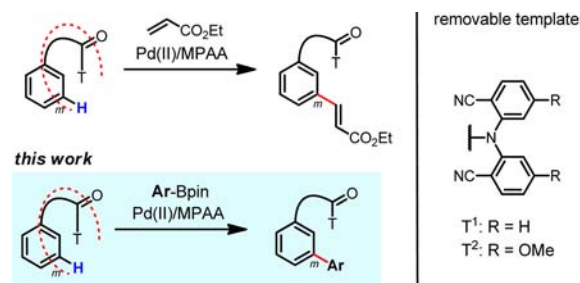
S Supporting Information

ABSTRACT: *meta*-C–H arylation and methylation of 3-phenylpropanoic 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.

Transition-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.¹ 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, σ -chelation-directed C–H activation has been successful in developing a wide range of C–H functionalization reactions.² 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.³ 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.⁴ 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.⁵ Herein we report the first example of Pd-catalyzed 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.^{6,7} Additionally, tuning the properties of the Pd(II) catalyst with a mono-protected 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

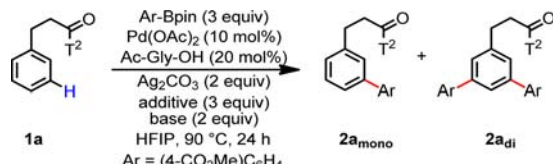


We have recently reported the first example of remote *meta*-C–H olefination of hydrocinnamic acids using an end-on nitrile template.⁶ This reaction provides important evidence for the formation of 12-membered cyclophane-like palladacycles, although Friedel–Crafts-type olefination catalyzed by Pd(II) 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 remote-*meta*-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.⁸ Through extensive screening of various reaction parameters including bases, oxidants, and solvents, we found that the combination of Pd(OAc)₂/Ac-Gly-OH/Ag₂CO₃/KHCO₃ and arylboronic ester facilitated the arylation of **1a** containing template T² to give the mono- and diarylated products **2a_{mono}** and **2a_{di}** 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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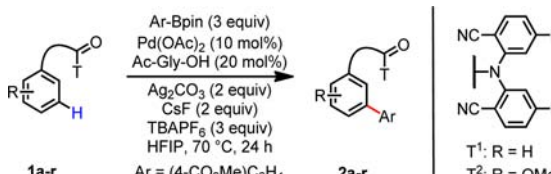
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Table 1. Screening of Additive and Base^{a,b}


entry	additive	base	yield (%)	
			mono	di
1	–	KHCO ₃	36	17
2	TBAF·3H ₂ O	KHCO ₃	11	2
3	TBAC	KHCO ₃	0	0
4	TBAB	KHCO ₃	16	4
5	TBAOAc	KHCO ₃	20	8
6	TBABF ₄	KHCO ₃	37	16
7	TBAPF ₆	KHCO ₃	41	21
8	TBAPF ₆	K ₂ CO ₃	26	14
9	TBAPF ₆	Cs ₂ CO ₃	0	0
10	TBAPF ₆	NaOAc	24	12
11	TBAPF ₆	KOAc	25	11
12	TBAPF ₆	CsOAc	42	17
13	TBAPF ₆	CsF	43	31
14 ^c	TBAPF ₆	CsF	48 (46) ^d	35 (34) ^d

^aConditions: **1a** (0.1 mmol), Ar-Bpin (0.3 mmol), Pd(OAc)₂ (10 mol %), Ac-Gly-OH (20 mol %), Ag₂CO₃ (0.2 mmol), additive (0.3 mmol), base (0.2 mmol), HFIP (1 mL), 90 °C, 24 h. ^bYield was determined by ¹H NMR analysis using CH₂Br₂ as internal standard. ^c70 °C. ^dIsolated yield.

Pd(0) species to form unreactive palladium black. Furthermore, the anionic counterion can play an important role in stabilizing cationic palladium intermediates.¹⁰ The addition of TBAPF₆ increased the total yield (**2a_{mono+di}**) 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,¹¹ 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.¹² Notably, the temperature could be decreased to 70 °C, affording 48% and 35% of **2a_{mono}** and **2a_{di}**, 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 (**2l**). The *meta*-selectivities of this reaction are in general excellent, although minor formation of different isomers were observed with nonsubstituted or *meta*-substituted 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 2. *meta*-Arylation of 3-Phenylpropanoic Acid and Phenolic Derivatives^{a,b}


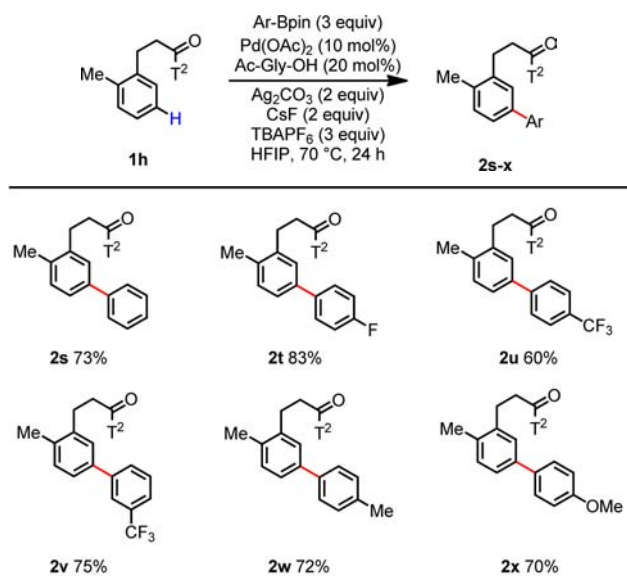
2a_{mono} , 46% <i>m</i> :(<i>p</i> + <i>o</i> + <i>o'</i>) = 96:4	2b , 56%	2c , 44% <i>m</i> :(<i>p</i> + <i>o</i> + <i>o'</i>) = 93:7
2a_{di} , 34% <i>m</i> :(<i>p</i> + <i>o</i> + <i>o'</i>) = 92:8	2e , 63% <i>m</i> :(<i>p</i> + <i>o</i> + <i>o'</i>) = 87:13	2f , 58%
2d_{mono} , 43% ^c 2d_{di} , 13%	2g , 65%	2i , 81% <i>m</i> :(<i>p</i> + <i>o</i> + <i>o'</i>) = 85:15
2j , 48% <i>m</i> :(<i>p</i> + <i>o</i> + <i>o'</i>) = 91:9	2k_{mono} , 42% 2k_{di} , 29%	2l , 57%
2m , traces	2n , 59%	2o , 42%
2p , 64%	2q , 53%	2r , 49%

^aConditions: substrate (0.1 mmol), Ar-Bpin (0.3 mmol), Pd(OAc)₂ (10 mol %), Ac-Gly-OH (20 mol %), Ag₂CO₃ (0.2 mmol), TBAPF₆ (0.3 mmol), CsF (0.2 mmol), HFIP (1 mL), 70 °C, 24 h. ^bIsolated yield. ^cMixture of *meta*-arylated isomers.

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

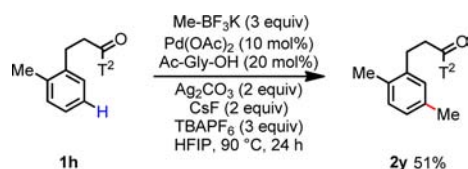
We have previously employed the nitrile template T¹ to perform *meta*-C–H olefination reactions of phenols.^{6b} We were pleased to find that *meta*-arylation of phenol substrates attached to T¹ also proceeded to give the desired products in moderate to good yields (**2n–2r**). Further optimizations 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

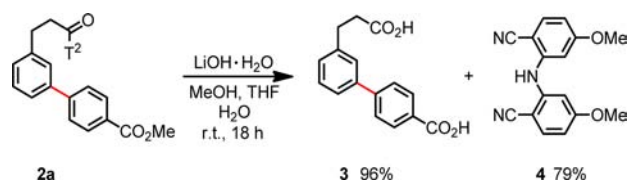
Table 3. *meta*-Arylation of **1h** with Arylboronic Acid Esters^{a,b}

^aConditions: **1h** (0.1 mmol), Ar-Bpin (0.3 mmol), Pd(OAc)₂ (10 mol%), Ac-Gly-OH (20 mol%), Ag₂CO₃ (0.2 mmol), TBAPF₆ (0.3 mmol), CsF (0.2 mmol), HFIP (1 mL), 70 °C, 24 h. ^bIsolated yield.

importance of methyl group in medicinal chemistry,¹³ we sought to determine if our method was compatible with methyl boron reagents. We found the use of MeBF₃K 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 β-hydride elimination side pathway.¹⁴

Scheme 2. *meta*-C–H Methylation of **1h**

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

Scheme 3. Hydrolysis of **2a**

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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