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

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Ⓢ *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 function-alized 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] Addition-ally, tuning the properties of the Pd(II) catalyst with a mono-protected amino acid (MPAA) ligand is vital to successful cross-coupling.

This coupling reaction affords synthetic chemists a novel C−H activation disconnection for biaryl synthesis. The trans-metalation 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
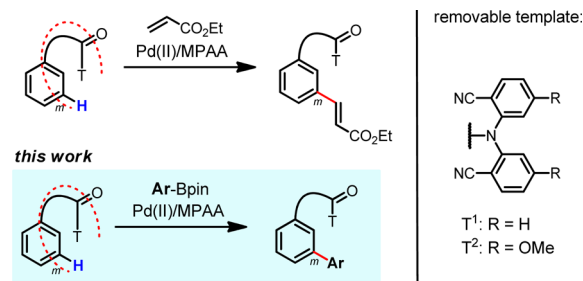
We have recently reported the first example of remote *meta*-C−H olefination of hydrocinnamic acids using an end-on nitrile template.[6] This reaction provides important evidence for the formation of 12-membered cyclophane-like palladacycles, although Friedel−Crafts-type olefination catalyzed by Pd(II) 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 reduc-tive 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/Ag$_2$CO$_3$/KHCO$_3$ and arylboronic ester facilitated the arylation of **1a** containing template T^2 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

Table 1. Screening of Additive and Base[a,b]

Ar-Bpin (3 equiv)
Pd(OAc)$_2$ (10 mol%)
Ac-Gly-OH (20 mol%)
Ag$_2$CO$_3$ (2 equiv)
additive (3 equiv)
base (2 equiv)
HFIP, 90 °C, 24 h
Ar = (4-CO$_2$Me)C$_6$H$_4$

1a → 2a$_{mono}$ + 2a$_{di}$

			yield (%)	
entry	additive	base	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]

[a]Conditions: 1a (0.1 mmol), Ar-Bpin (0.3 mmol), Pd(OAc)$_2$ (10 mol %), Ac-Gly-OH (20 mol%), Ag$_2$CO$_3$ (0.2 mmol), additive (0.3 mmol), base (0.2 mmol), HFIP (1 mL), 90 °C, 24 h. [b]Yield was determined by ^{1}H NMR analysis using CH$_2$Br$_2$ as internal standard. [c]70 °C. [d]Isolated 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 TBAPF$_6$ 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]

Ar-Bpin (3 equiv)
Pd(OAc)$_2$ (10 mol%)
Ac-Gly-OH (20 mol%)
Ag$_2$CO$_3$ (2 equiv)
CsF (2 equiv)
TBAPF$_6$ (3 equiv)
HFIP, 70 °C, 24 h

1a-r → 2a-r   Ar = (4-CO$_2$Me)C$_6$H$_4$

T^1: R = H
T^2: R = OMe

2a$_{mono}$, 46%
m:(p+o+o') = 96:4
2a$_{di}$, 34%
m:(p+o+o') = 92:8

2b, 56%

2c, 44%
m:(p+o+o') = 93:7

2d$_{mono}$, 43%[c]
2d$_{di}$, 13%

2e, 63%
m:(p+o+o') = 87:13

2f, 58%

2g, 65%

2h, 85%

2i, 81%
m:(p+o+o') = 85:15

2j, 48%
m:(p+o+o') = 91:9

2k$_{mono}$, 42%
2k$_{di}$, 29%

2l, 57%

2m, traces

2n, 59%

2o, 42%

2p, 64%

2q, 53%

2r, 49%

[a]Conditions: substrate (0.1 mmol), Ar-Bpin (0.3 mmol), Pd(OAc)$_2$ (10 mol%), Ac-Gly-OH (20 mol%), Ag$_2$CO$_3$ (0.2 mmol), TBAPF$_6$ (0.3 mmol), CsF (0.2 mmol), HFIP (1 mL), 70 °C, 24 h. [b]Isolated yield. [c]Mixture 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 T^1 to perform meta-C−H olefination reactions of phenols.[6b] 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

Table 3. *meta*-Arylation of 1h with Arylboronic Acid Esters[a,b]

2s 73%   2t 83%   2u 60%

2v 75%   2w 72%   2x 70%
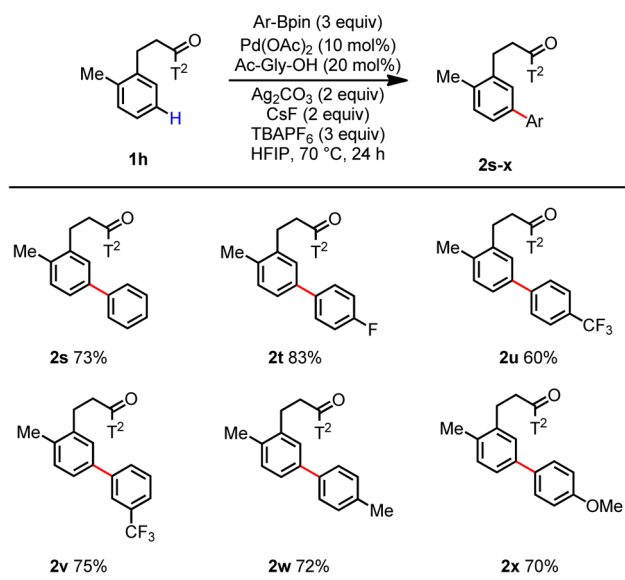
[a]Conditions: **1h** (0.1 mmol), Ar-Bpin (0.3 mmol), Pd(OAc)$_2$ (10 mol %), Ac-Gly-OH (20 mol%), Ag$_2$CO$_3$ (0.2 mmol), TBAPF$_6$ (0.3 mmol), CsF (0.2 mmol), HFIP (1 mL), 70 °C, 24 h. [b]Isolated yield.

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 MeBF$_3$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 *β*-hydride elimination side pathway.[14]

Scheme 2. *meta*-C−H Methylation of 1h
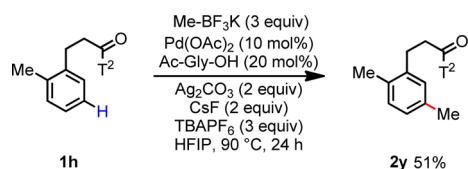
Finally, the template was removed under mild conditions, furnishing **3** in 96% yield while nitrile template **4** was recovered in 79% yield (Scheme 3).

Scheme 3. Hydrolysis of 2a
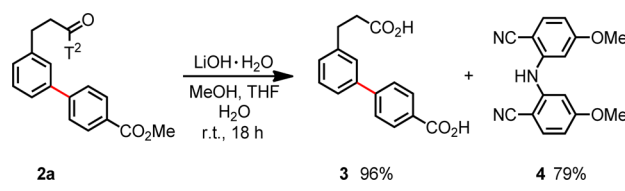
In summary, we have developed the first example of coupling *meta*-C−H bonds with organoborons using a removable U-shaped template. This *meta*-arylation reaction provides a novel method for preparing of 3-phenylpropanoic acid and phenolic derivatives. The observed reactivity provides strong evidence 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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