Communication

Sequential Functionalization of meta-C–H and ipso-C–O Bonds of Phenols

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J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 22 Jan 2019

Sequential Functionalization of *meta*-C–H and *ipso*-C–O Bonds of Phenols

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Supporting Information Placeholder

ABSTRACT: The use of a template as a linchpin motif in directed remote C–H functionalization is a versatile yet relatively underexplored strategy. We have developed a template-directed approach to realizing one-pot sequential palladium-catalyzed *meta*-selective C–H olefination of phenols, and nickel-catalyzed *ipso*-C–O activation and arylation. Thus, this bifunctional template converts phenols to synthetically useful 1,3-disubstituted arenes.

Realizing remote selective C–H functionalization is essential for broad application of directed C–H activation reactions in the presence of multiple C–H bonds.[1] Over the past two decades, transition-metal-catalyzed arene *ortho*-C–H functionalization has been extensively exploited via σ-chelation-assisted directing effect.[2] More recently, directed remote *meta*- and *para*-C–H functionalization of arenes has also been achieved using distance and geometry as the key recognition parameters.[3–5] However, the installation and removal of these templates for remote C–H activation reduces the step economy in synthetic applications. Therefore, a one-pot procedure that can both directly remove the directing group and install additional desired functionality would greatly improve the synthetic efficacy of directed arene C–H activation. In this context, Chatani and others have demonstrated a commendable example with the *ortho*-selective directing group 2-pyridyloxy (OPy) (Figure 1a).[6] Herein we report the development of a palladium-catalyzed remote *meta*-C–H olefination of phenols enabled by a novel bifunctional template, which can also be directly converted into other functional groups, *i.e.* an aryl group (*vide infra*), via the catalytic cleavage of the *ipso*-C–O bonds in the *meta*-functionalized phenols (Figure 1b). Notably, this template is easily installed in a single step from the commercially available 2,4-dichloro-6-methoxy-1,3,5-triazine (Figure 1c).

It is well established that the positional selectivity of template-assisted remote C–H activation is highly associated with the template geometry.[3,4] An appropriate template facilitates the assembly of a conformationally favored macrocyclic metallocycle that enables the metal catalyst to activate the remote C–H bond of the arene through an agnostic interaction.[7] Moreover, a rigid backbone in the template readily forms a large yet less strained macrocyclic pre-transition state, and therefore provides the palladacycle intermediate with higher stability and a longer lifetime.[3f] For example, we[3f,8] and others[9] have found that the use of a relatively ri-

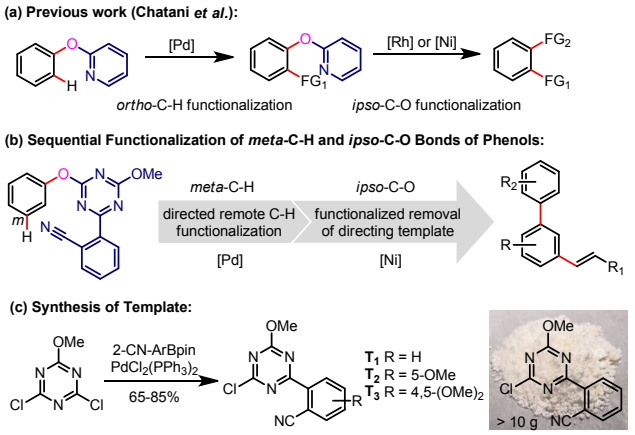


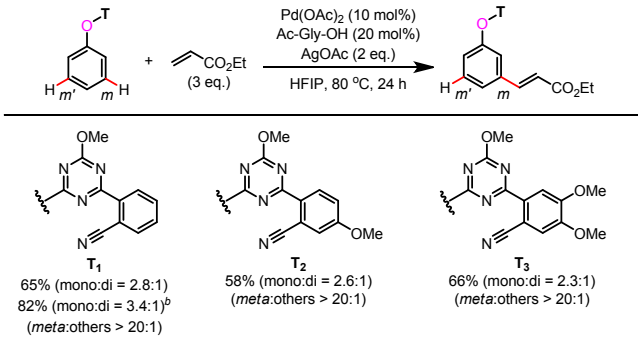
Figure 1. Development of new bifunctional templates for sequential *meta*-C–H/*ipso*-C–O functionalization of phenols.

gid template could functionalize remote *meta*-C–H bonds in long-chain aromatic alcohols. Bearing in mind that the unreactive C–O bonds in phenols may be directly functionalized via transition-metal-catalyzed C–O cleavage of aryl ethers, such as 2-pyridyloxy,[6,10] and 2-triazinyloxy groups[11], we strove to develop a bifunctional template that could both direct the *meta*-C–H functionalization of phenols and be subsequently removed through a transition-metal-catalyzed *ipso*-C–O cleavage, consisting of a 1,3,5-triazine-derived rigid biaryl scaffold (Figure 1b).

Initially, the biaryl templates $\mathbf{T_1}$–$\mathbf{T_3}$ were synthesized via a Suzuki coupling from the commercially available 2,4-dichloro-6-methoxy-1,3,5-triazine (Figure 1c), and the latter can also be prepared from inexpensive cyanuric chloride in almost quantitative yield (see the SI). The substrate bearing the template $\mathbf{T_1}$ was subjected to the previously established *meta*-C–H olefination conditions.[3,8] Much to our delight, the C–H olefination occurred exclusively at the *meta*-position with *meta*:others > 20:1 regioselectivity. *Ortho*-C–H functionalization directed by the donor heteroatom of 1,3,5-triazine was not observed under the reaction conditions.[12] Not surprisingly, using templates $\mathbf{T_2}$ and $\mathbf{T_3}$ also afforded the products in >20:1 *meta*-selectivity. Increasing the electron density of the phenyl rings in the templates $\mathbf{T_2}$ and $\mathbf{T_3}$

did not significantly improve the reactivity, but led to a lower ratio of mono- to di-olefinated products (Scheme 1). With the template **T$_1$**, however, the desired *meta*-C–H olefination product could be obtained in 82% yield after an elongated reaction time (36 h). Thus, **T$_1$** was selected as the optimal template.

Scheme 1. Design of New Template for *meta*-C-H Olefination of Phenol[a]

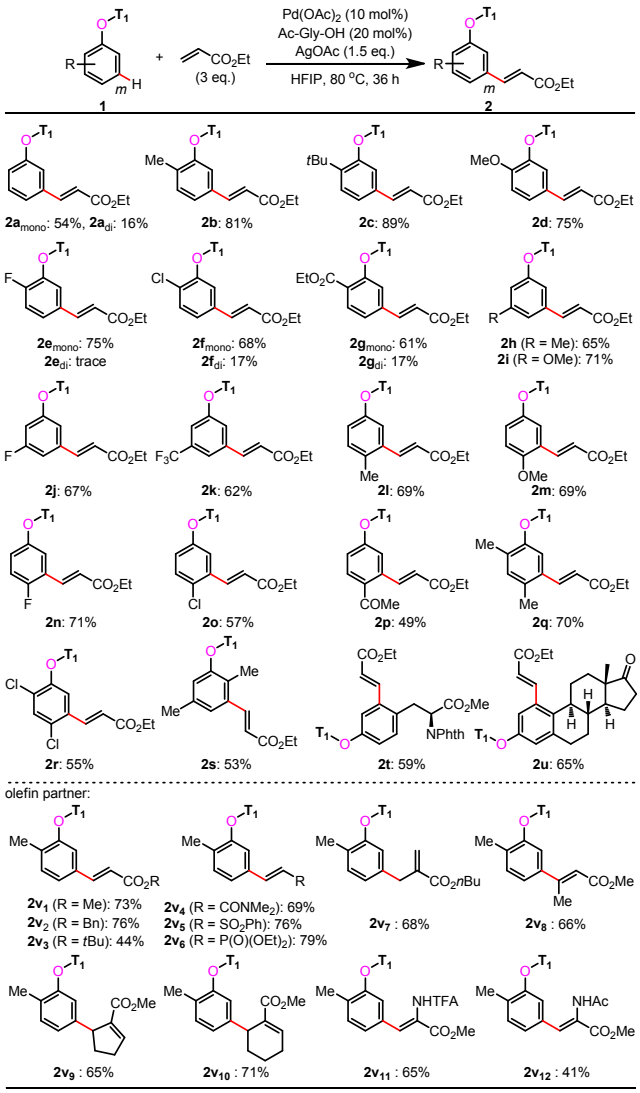


[a]Yield and regioselectivity were determined by ^{1}H NMR with CH_2Br_2 as an internal standard. [b]Reaction time: 36 h.

Having identified the optimal template, we further investigated the generality of the template-assisted *meta*-C–H olefination (Table 1). Both electron-donating and -withdrawing groups are well tolerated with predominant *meta*-selectivity. Excluding alkyl and alkoxyl groups, a variety of functional groups such as halogen (**2e**, **2f**, **2j**, **2n** and **2o**), ester (**2g**), and acetyl (**2p**) groups afforded the *meta*-olefinated products in isolated yields of 49–89%. Substrates bearing two groups in different substitution patterns are also compatible with the present protocol (**2q**–**s**). Compared with *meta*- and *para*-substituted phenols, substrates derived from *ortho*-substituted phenols delivered the *meta*-C–H olefination products in higher yields (**2b**–**g**). The presence of an *ortho*-substituent significantly improves the mono-selectivity as the di-*meta*-C–H olefination will be subjected to steric hindrance from the adjacent *ortho*-substituent. It is noteworthy that, using template **T$_1$**, naturally occurring L-tyrosine (**2t**) and estrone (**2u**) also yielded the corresponding olefination products in exclusive *meta*-selectivity. The synthetically valuable *meta*-olefinated phenols could be readily obtained through removing the template (See SI for details). In addition, the olefin coupling partner scope was examined. Various α,β-unsaturated esters, amide, sulfone, and phosphonate olefins were reactive, affording the *meta*-olefinated products in good yields (**2v$_1$**–**2v$_6$**). Under the reaction conditions, α- or β-substituted olefins proved to be compatible substrates (**2v$_7$** and **2v$_8$**). Moreover, C–H olefination with cyclic α,β-unsaturated esters and 2-amidoacrylates also provided the desired *meta*-products with exclusive *Z*-selectivity in satisfactory yields (**2v$_9$**–**2v$_{12}$**). The stereochemistry of the double bond is determined by the two competing transition state energy of the β-hydride elimination, analogous to the Heck Coupling. The transition state with the electron-withdrawing ester group being *anti* to the phenyl group is generally favored which accounts for the observed *Z*-selectivity of *meta*-C–H olefinated products (for stereochemistry assignment, see the SI).

In template-directed C–H functionalization, an additional step is typically required to remove the template and release the C–H functionalized product.[3–5] We wonder whether the template could serve as a linchpin to enable further elaboration of the product *via* C–O activation. Undoubtedly, direct functionalization via template-induced *ipso*-C–O bond cross-coupling will not only reduce the cost of the process, but also improve the synthetic efficacy. Therefore, transition-metal-catalyzed direct *ipso*-C–O cross-coupling of the *meta*-C–H olefinated phenol **2a** with arylboronic acid was investigated. Reaction parameters such as metal catalysts, ligand, base, solvent, and temperature were examined (see SI for details), showing that Ni(xantphos)Cl$_2$ (10 mol%), K_3PO_4 (7.0 eq), in toluene at 120 °C comprised the optimal reaction conditions.

Table 1. Pd-Catalyzed Template-Directed *meta*-C–H Olefination of Phenols[a]

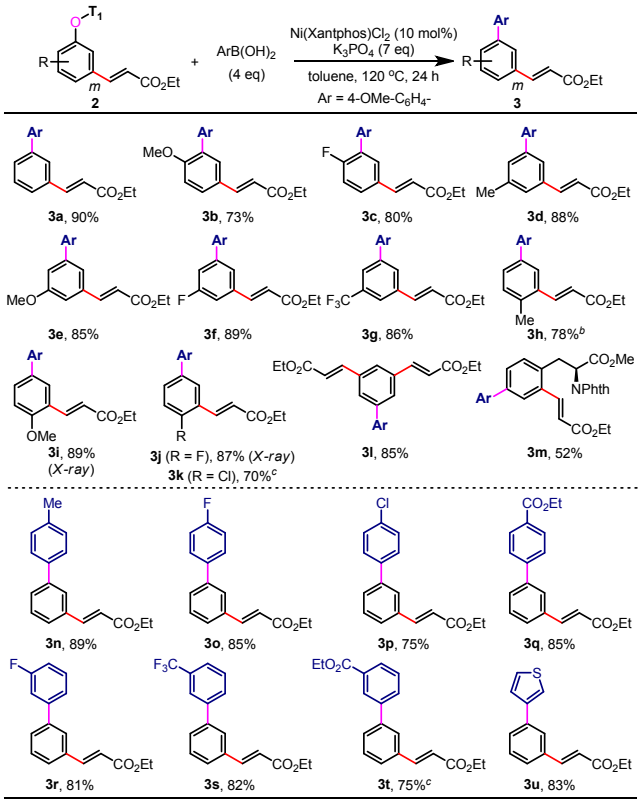


[a]Isolated yield. Regioselectivity was determined to be *meta*:others > 20:1 by ^{1}H NMR using CH_2Br_2 as an internal standard.

Next, the substrate scope and the functional group tolerance of this nickel-catalyzed transformation were also surveyed (Table 2). Using *p*-methoxyl phenylboronic acid as a coupling partner, Ni-catalyzed C–O cross-coupling with various *o*-, *m*-, and *p*-substituted phenol substrates provided the biaryl products **3** in good to excellent yields under the optimized reaction conditions (**3b**–**k**). Various functional groups, such as alkyl, alkoxyl, halogen, trifluoromethyl, and ester groups, are tolerated in this transformation. Moreover, *m*-, *m*′-diolefinated phenol substrates successf-ully underwent the reaction in good yield (**3l**). Using the *meta*-C–H olefinated product of *N*-protected L-tyrosine, it was also possible to synthesize an unnatural amino acid (**3m**). Single crystal X-ray diffraction analyses of compounds **3i** (*p*-OMe) and **3j** (*p*-F) validated the exclusive *meta*-selectivity of C–H functionalization and *ipso*-C–O cross-coupling (see SI for details).

The scope of organoboron reagents was also evaluated: both *m*- and *p*-substituents on arylboronic acids including alkyl, halogen, trifluoromethyl, and ester groups were tolerated (**3n**–**t**). Notably, heteroarylboronic acid (**3u**) afforded the biaryl product in 83% yield. Regrettably, *o*-substituted arylboronic acids give the target products in poor yields, probably due to the steric congestion.

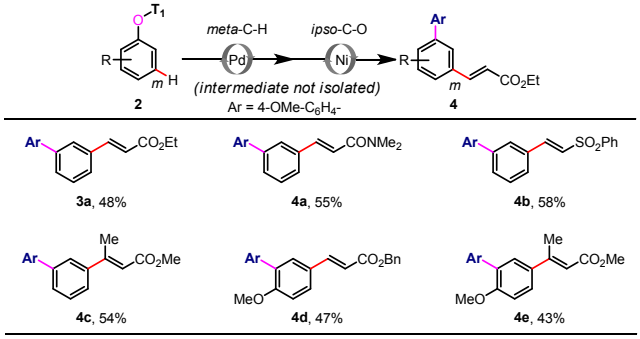
Table 2. Ni-Catalyzed C–O Cross-Coupling of *meta*-Olefinated Phenols[a]



[a]Isolated yield. [b]110 °C, 36 h. [c]110 °C.

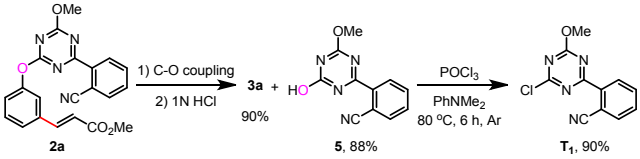
To improve the synthetic utility of this strategy and avoid the tedious separation of C–H olefination products, a one-pot *meta*-C–H/*ipso*-C–O functionalization procedure was pursued (Table 3). Following palladium-catalyzed *meta*-C–H olefination, the unpurified intermediate was subjected to nickel-catalyzed *ipso*-C–O cross-coupling reaction with an arylboronic acid. Gratifyingly, this one-pot procedure furnished the desired *m*-substituted biaryls in good overall yields (**3a**, **4a**–**e**). These results further demonstrated the synthetic applicability of this template-assisted transformation. More importantly, template $\mathbf{T_1}$ can be recovered and regenerated after nickel-catalyzed C–O coupling in excellent yield (Scheme 2), which further enhances the synthetic efficacy and atom-economy of the strategy.

Table 3. Template-Assisted Tandem *meta*-C–H/*ipso*-C–O Functionalization of Phenols[a]



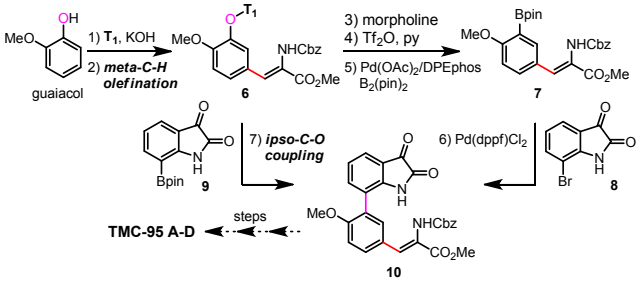
[a]Overall yield for two steps.

Scheme 2. Recovery and Regeneration of Template



Finally, this template-directed remote C–H functionalization strategy was tested in the synthesis of key building blocks of natural products. Template-assisted *meta*-C–H olefination of the substrate derived from guaiacol afforded the olefinated product **6** in 68% yield. While direct C–O coupling of compound **6** with arylboronate **9** under the present conditions gave the biaryl scaffold **10** in low yield (18%), an alternative route featuring quantitative removal of the template $\mathbf{T_1}$, borylation, and palladium-catalyzed Suzuki coupling with bromide **8** efficiently delivered the left-hand moiety **10** of TMC-95 A–D (Scheme 3), a small class of naturally occurring selective proteasome inhibitors with IC_{50} values of 5–60 nM.[13] The synthetic strategy allows for facile modification of the biaryl units and the amino acid residue, for such purposes as a structure-activity relationship (SAR) study for this family of natural products.

Scheme 3. Application to Synthesis of the Central Scaffold of Natural Antibiotic TMC-95[a]



[a]Conditions: (1) $\mathbf{T_1}$ (1 eq), KOH (1 eq), THF, rt, 95%. (2) olefin (3 eq), $Pd(OAc)_2$ (10 mol%), Ac-Gly-OH (20 mol%), AgOAc (1.5 eq), HFIP (0.2 M), 80 °C, 36 h, 68%. (3) morpholine (1 eq), dioxane, 100 °C, 12 h, 99%. (4) Tf_2O (1.1 eq), Pyridine (2.5 eq), CH_2Cl_2, 0 °C to rt, 3 h, 75%. (5) $B_2(pin)_2$ (2 eq), $Pd(OAc)_2$ (10 mol%), DPEphos (20 mol%), TEA (4 eq), dioxane, 80 °C, 16 h, 90 %. (6) ArBr **8** (1.1 eq), $Pd(dppf)Cl_2$ (20 mol%), K_2CO_3 (4 eq), DME, 80 °C, 14 h, 92%. (7) ArBpin **9** (4 eq), Ni(xantphos)Cl_2 (10 mol%), K_3PO_4 (7 eq), toluene, 120 °C, 24 h, 18%.

In summary, a robust bifunctional template has been developed for the palladium-catalyzed remote *meta*-C–H olefination of phenols. The template can be synthesized concisely in a two-step sequence from inexpensive cyanuric chloride, and is easily

installed and removed. In addition, this bifunctional template is amenable to nickel-catalyzed *ipso*-C–O cross-coupling. This template-assisted one-pot sequential *meta*-C–H/*ipso*-C–O functionalization methodology allows for the expedited synthesis of multiply substituted arenes from simple phenol substrates. Further applications of this template-assisted strategy are under investigation in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures, characterization data, NMR spectra for new compounds (PDF)
Crystal data for compounds **3i** and **3j** (CIF)

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We thank the NSF of China (20502012, 21172111 and 21672116) for financial support of this work. We gratefully acknowledge The Scripps Research Institute, the NIH ((National Institute of General Medical Sciences grant 5R01GM102265).

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