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COMMUNICATION

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Diverse *Meta*-C–H Functionalization of Arenes Across Different Linker Lengths

Ramasamy Jayarajan,* Jayabrata Das, Sukdev Bag, Rajdip Chowdhury and Debabrata Maiti*

Abstract: Conformationally flexible long-chain arenes have been successfully functionalized at *meta*-position. Good to excellent *meta*-selectivity has been achieved up to twenty atoms between the target C–H bond and the coordinating heteroatom of the directing group. This palladium-catalyzed diverse functionalizations include alkylation, cyanation, olefination and acetoxylation. *Meta*-selectivity is exclusively governed by the design of flexible pyrimidine-based scaffolds.

Activation of inert C–H bonds of readily available starting materials to incorporate functionalities has certainly emerged as a key concept in order to elucidate the structure-reactivity relationships in molecules of interest in pharmaceuticals, industry and scientific research.[1] In the past few decades, *ortho*-C–H functionalization of arenes assisted by a native functionality or an installed directing group in a molecule has substantially thrived *via* five or six membered metallacycle.[2] In contrast, selective *meta*- and *para*-C–H bond activation remain difficult task owing to the formation of highly strained macrocyclic transition state (TS).[3] Recent reports demonstrated the significant efforts for directed distal C–H bond functionalization of arenes by employing nitrile-based templates.[4,5] Functionalizations that are difficult to accomplish at the *meta*-position of arenes using nitrile coordination, have been attained by the judicious design of relatively stronger coordinating directing groups.[6,7] However, the key to attain such selective *meta*-activation relies solely on the rigidity of the cyclophane-like TS, which might become fragile upon increase in the length of the linker that bridges the directing group and the target site. This has limited the application of such template-based strategies to cases where *meta*-C–H bonds are geometrically accessible and proximate. Consequently, a site selective installation of useful functional groups into arenes that contain a long alkyl chain is an extremely difficult task. In this context, striking a proper balance between the number of atoms required for maintaining the core metallacyclic TS and directing the coordinating nitrile group to the target *meta*- site has been identified to be crucial.[8] An increase in the number of involved atoms in the metallacycle raises the entropic barrier that offsets the situation of the catalyst at the optimum site for long-chain containing systems. Further, scientists aimed for a template that would facilitate a plethora of functionalization without any compromise in selectivity.

Herein, we disclose the use of an ether tethered conformationally flexible pyrimidine-based template to achieve diverse *meta*-functionalization of arenes (Figure 1) that is insensitive towards the location of the directing group (DG) from the target *meta*-C–H bond. Four distinct functionalizations, namely alkylation, cyanation, olefination and acetoxylation have been successfully executed.

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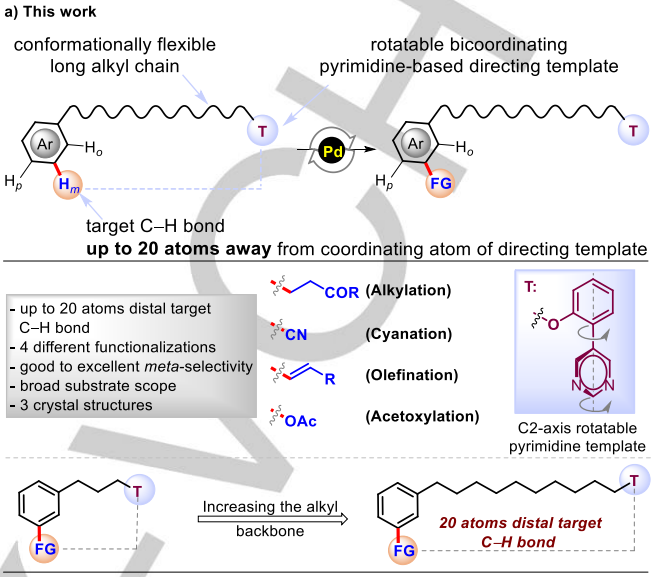
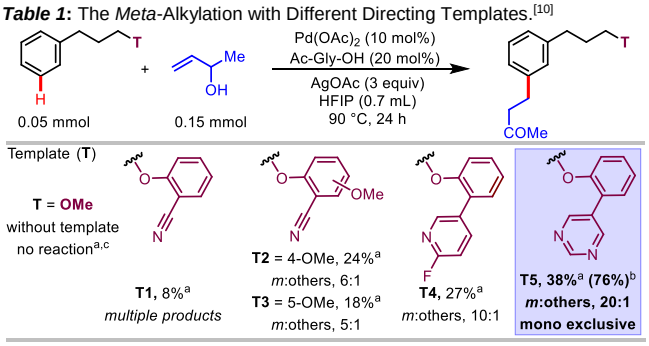


Figure 1. Selective *Meta*-C–H Functionalization of Conformationally Flexible Long-Chain Arenes.

The scope of this strategy has been demonstrated with a series of arenes such as propyl to octylbenzene, decylbenzene, ethyloxybenzene, hexyloxybenzene, benzyl alcohol and benzoic acid that depicts the competence of the present scaffold in enduring resistance to the entropic cost thus enabling the required selectivity.

We began our investigation towards *meta*-C–H functionalization of propylbenzene scaffold as a model substrate. Nitrile and heterocycle-based directing templates were tethered to phenylpropyl alcohol (**T1-T5**) for *meta*-C–H alkylation using 3-buten-2-ol as the coupling partner (Table 1).[7a,9] Very less conversion was observed with nitrile-based templates (**T1-T3**) whereas heterocycle-based templates (**T4** and **T5**) resulted in the desired *meta*-alkylated product in improved yield. Interestingly, both the scaffolds offered only mono alkylated (*β*-aryl ketone) product.

Table 1: The *Meta*-Alkylation with Different Directing Templates.[10]

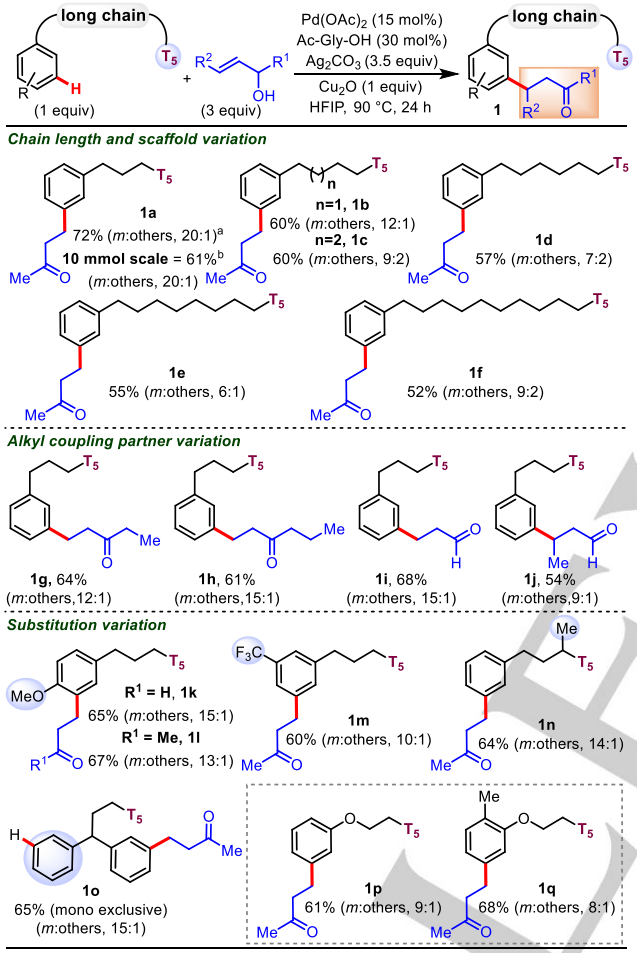


[a]Yields and ratio based on ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.
[b]Yield and selectivity under optimized condition.
[c]No desired product observed in combination of OMe protected substrate and *O*-methylated **T5**.

The biphenyl pyrimidine-based template **T5** has provided better yield and excellent *meta*-selectivity compared to **T4.** The observed high yield and regioselectivity can be explained by the hydrogen bonding interaction of solvent 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) with the pyrimidine-directing group

(DG) which decreases the basicity of DG and concurrently increases the π-acidity towards the palladium center.[11] The NMR studies reveal the existence of strong hydrogen bonding between pyrimidine DG and HFIP solvent (see Supporting Information).[7b]

A control experiment without using the directing template did not produce any alkylated product (Table **1**).[10] These findings indicate that the flexibility of the ether tethered pyrimidine-based template would be significant to encourage the formation of macrocyclic TS for the remote palladium-catalyzed C−H bond activation.

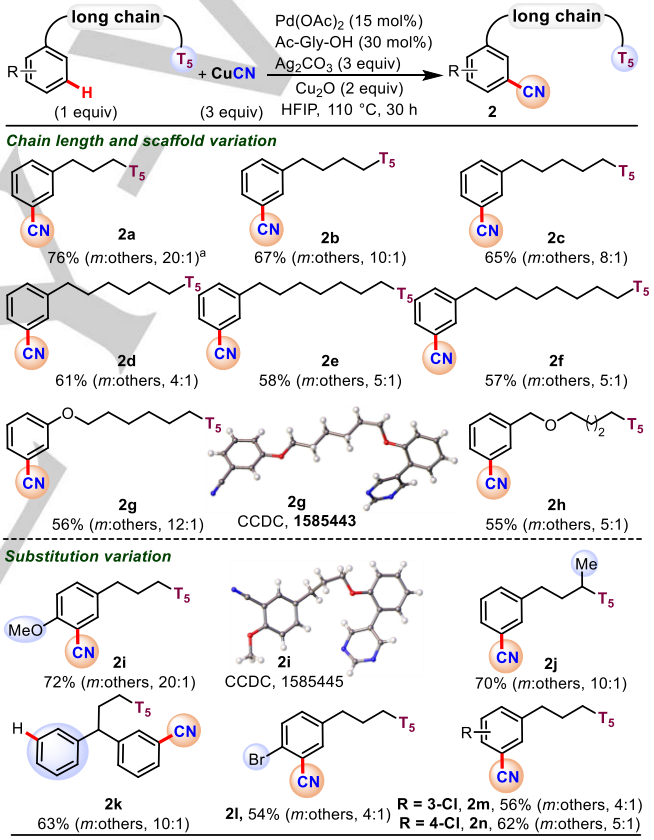


[a]Yield of isolated product; ratios are based on ^{1}H NMR analysis. [b]Isolated yield of large scale reaction (10 mmol) under optimized conditions.

Scheme 1. *Meta*-Alkylation of Long-Chain Tethered Arenes.[10]

In order to achieve the highest synthetic yield of *meta*-alkylation product, the reaction condition was extensively optimized.[10] A wide range of functional arenes possessing variable alkyl backbone has been subjected to the optimal *meta*-alkylation reaction conditions (Scheme 1). Arenes with variable linker length such as propyl (**1a**), butyl (**1b**), pentyl (**1c**), hexyl (**1d**), octyl (**1e**) and decyl (**1f**) were alkylated selectively at the *meta*-position. Exclusive mono selectivity was observed for all the scaffolds under the present reaction conditions. Scope of the reaction was explored using various alkenyl alcohols (**1g**-**1j**) and arenes containing different substitution (**1k**-**1n**). Mono product was observed with 3,3-diphenyl scaffold (**1o**) where one of the aryl rings was alkylated with good *meta*-selectivity. Remarkably, phenol-based scaffold (**1p** and **1q**) provided *meta*-coupled *β*-aryl keto product in good yield and selectivity. The practicality of this transformation was tested by a large-scale reaction (10 mmol scale, 2.9 g) which afforded the desired *meta*-alkylated product **1a** in 61% yield (Scheme 1).[10]

Arylnitrile is a key structural motif in natural products, pharmaceuticals and transformation of nitrile to other functionalities provide the precursor for several valuable compounds.[12] Our recent effort towards *meta*-selective cyanation led us to install a nitrile group in arenes possessing various lengths of alkyl chains which were previously inaccessible.[7b] Our initial attempt with propylbenzene scaffold provided a moderate yield and excellent *meta*-selectivity. After optimizing different parameters, it was observed that the yield and *meta*-selectivity remarkably increased when copper(I) cyanide was used as a cyanide source in the presence of silver carbonate and copper(I) oxide.[10, 13]

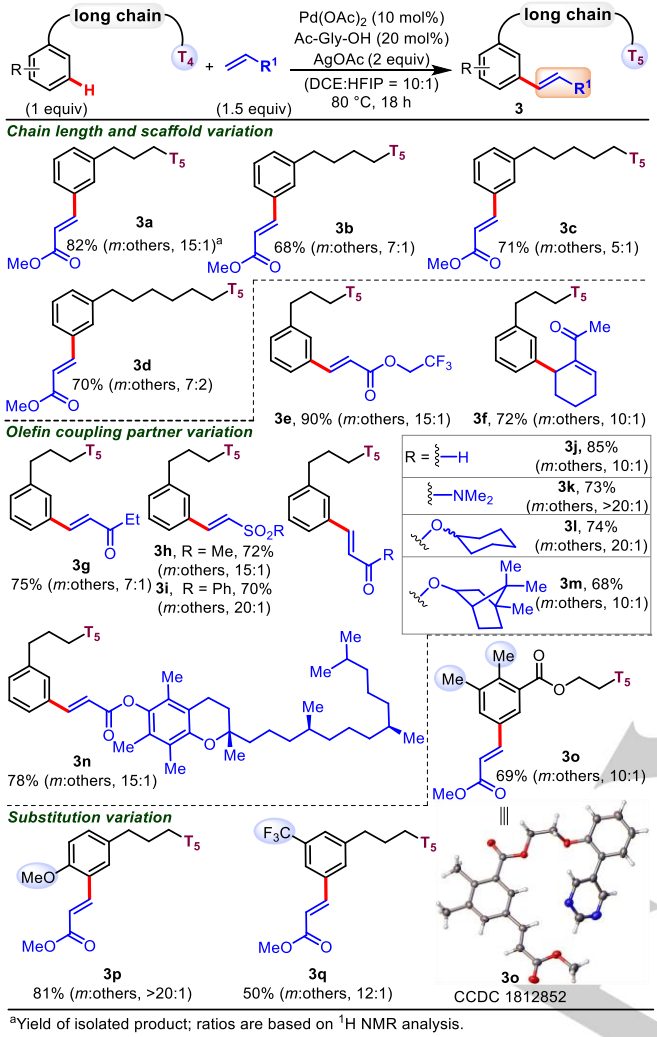


[a]Yield of isolated product; ratios are based on ^{1}H NMR analysis.

Scheme 2. *Meta*-Cyanation of Long-Chain Tethered Arenes.[10]

With optimized reaction conditions in hand, we have probed various scaffolds having elongated alkyl backbones (Scheme 2). We were delighted to find that the present reaction protocol provides selective *mono*-cyanation product. Almost similar reactivity pattern (yield and selectivity) was observed with propyl to octyl arene scaffolds (**2a**-**2f**) as noticed for alkylation. *Meta*-cyanation product for phenol-based hexyloxybenzene (**2g**) and benzyl alcohol-based scaffold **2h** was also obtained. The structure of **2g** was confirmed by X-ray crystallography. Further, the compatibility of substituents on aromatic ring has been examined with electron donating (**2i**), electron withdrawing (**2l, 2m** and **2n**) and sterically encumbered *α*-methyl propylbenzene

(**2j**). The structure of product **2i** was confirmed by X-ray crystallography (Scheme 2).



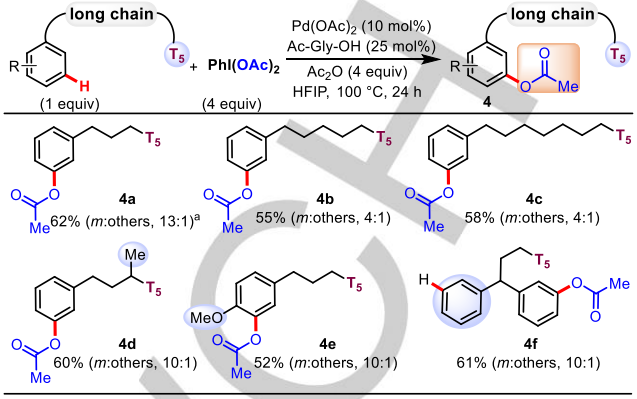
[a]Yield of isolated product; ratios are based on ^{1}H NMR analysis.

Scheme 3. *Meta*-Olefination with Diverse Scaffolds.[10]

After successful implementation of cyanation reaction, we have examined *meta*-C–H olefination with a wide variety of scaffolds (Scheme 3). The protocol is compatible with different alkyl benzenes (**3a**-**3d**), various activated olefins like acrylates (**3e**, **3l** and **3m**), vinylketone (**3g**), sulfone (**3h**-**3i**) and amide (**3k**). Interestingly, acrolein as a coupling partner yielded the alkenyl aldehyde (**3j**). Electron donating (**3p**) and withdrawing (**3q**) substituent on the arenes are also well tolerated. Substituted benzoic acid (**3o**) produced *meta*-olefinated product in synthetically useful yield and its structure was confirmed by X-ray crystallography (Scheme 3).

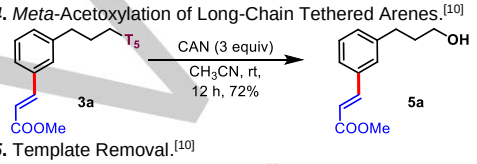
The *meta*-acetoxylation reaction was also found to be feasible with long-chain containing arenes (Scheme 4). Arenes with different chain lengths (**4a**, **4b** and **4c**) and substitution patterns (**4d**, **4e** and **4f**) have been acetoxylated under optimized reaction conditions. All scaffolds afforded mono acetoxylated product in synthetically useful yields and selectivity.

Finally, removal of the directing template was accomplished by oxidative cleavage of olefinated product **3a** using ceric ammonium nitrate (CAN) at room temperature to afford corresponding *meta*-functionalized 3-phenylpropanol (**5a**) (Scheme 5).



[a]Yield of isolated product; ratios are based on ^{1}H NMR analysis.

Scheme 4. *Meta*-Acetoxylation of Long-Chain Tethered Arenes.[10]



Scheme 5. Template Removal.[10]

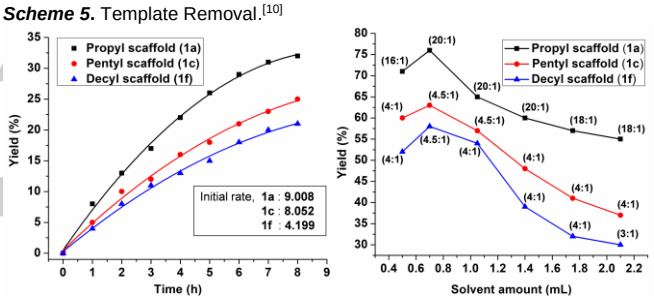
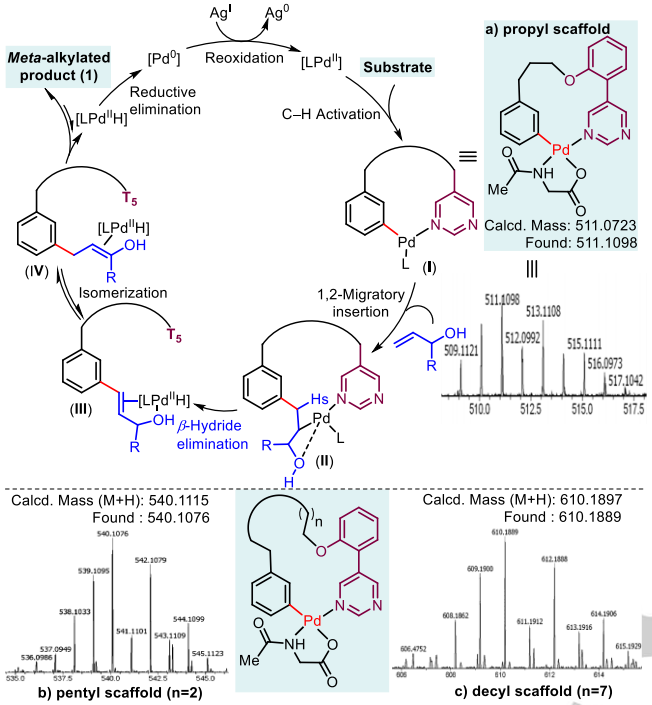


Figure 2. a) Rate of *meta*-alkylation with propyl (**1a**), pentyl (**1c**) and decyl (**1f**) scaffolds was measured by initial rate (i.e., slope of the plots). b) Concentration effect on yield and selectivity; Data points of both the plots represent the NMR yields and values in parentheses represents *meta*:others selectivity.[10]

To rationalize the effect of different linker lengths (propyl, pentyl and decyl), we further studied the rate of the reaction and concentration effect on yield and selectivity (Figure 2).[10] We performed three parallel sets of *meta*-alkylation reactions over 8 h, quenching them in 1 h interval and monitored the conversion by ^{1}H NMR spectroscopy of the crude reaction mixture (Figure 2a). The observed initial rate reveals that rate of the reaction drops down when linker length increases. Further, an effect of concentration on yield and selectivity was tested. Decrease in yields has been observed from optimum to lower or higher concentration. However, only a slight change in regioselectivity was observed with the change in concentration (Figure 2b).

A plausible catalytic cycle is depicted in Scheme 6 for the formation of *meta*-alkylation with long-chain arenes.[7a] The target *meta*-C–H bond of flexible arene might be selectively activated by conformationally well-defined reactive pyrimidine coordinated Pd-mono-*N*-protected amino acid species (**I**). The ESI-MS studies of individual reaction mixtures of propyl, pentyl and decyl scaffolds in the absence of alkyl coupling partner also suggested the formation of a macrocyclic palladacycle (**I**). Coordination followed by 1,2-migratory insertion of the allyl alcohol would give intermediate **II**. Thermodynamically stable β-hydride (H_S) elimination may lead to the formation of

intermediate **III**. Next, double bond isomerization (**IV**) and keto-enol tautomerization provides the desired *meta*-alkylated product (**1**). However, the formation of a bimetallic Pd-Ag adduct with substrate could facilitate the *meta*-functionalization with long chain scaffolds as proposed in recent reports.[8,10] A detailed mechanistic understanding remains our study of interest.



Scheme 6. Plausible Mechanistic Cycle for *meta*-C–H Alkylation.[10]

In conclusion, we have demonstrated Pd(II)-catalyzed diverse *meta*-C–H functionalization of long-chain arenes, where more conformational degrees of freedom make the C–H bond cleavage step entropically unfavourable. Alkylation, cyanation, olefination and acetoxylation have been accomplished at remote *meta*-position of arenes across different linker lengths.

Acknowledgements

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Keywords: • long-chain arenes • conformational flexibility • *meta*-functionalizations • palladium

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[10] See the Supporting Information for a detailed description.

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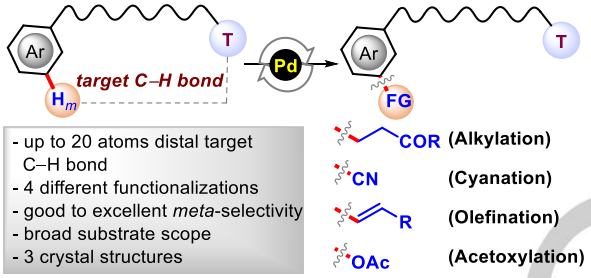
Palladium-catalyzed diverse *meta*-C–H functionalization of arenes that are located remotely (up to 10 methylene spaces) from a removable ether-tethered pyrimidine-based template have been described. This method is unique compared to classical cyclometallation due to its insensitivity of location of the DG from target C–H bond.



- up to 20 atoms distal target C–H bond
- 4 different functionalizations
- good to excellent *meta*-selectivity
- broad substrate scope
- 3 crystal structures

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