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Ligand-Enabled *meta*-C–H Activation Using a Transient Mediator

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Abstract

Achieving site selectivity in C–H functionalization reactions is a significant challenge, especially when the target C–H bond is distant from existing functional groups.^{1–5} Coordination of a functional group to a metal catalyst is often a key driving force and control element in many important reactions including asymmetric hydrogenation,⁶ epoxidation^{7, 8}, and lithiation⁹. Exploitation of this effect has led to the development of a broad range of directed C–H activation reactions.^{10–14} However, such C–H activation methods are limited to proximal C–H bonds, which are spatially and geometrically accessible from the directing functional group. Development of *meta*-selective C–H functionalizations remains a significant challenge.^{1–5, 15–17} We recently developed a U-shaped template that can be used to overcome this constraint and have shown that it can be used to selectively activate remote *meta*-C–H bonds.^{1, 2} While this approach has proven applicable for a diverse set of substrates and catalytic transformations,^{3–5} the need for a covalently attached complex template is a significant drawback for synthetic applications. In this manuscript, we report an alternative approach, one that employs norbornene as a transient mediator to achieve *meta*-selective C–H activation with a simple and common *ortho*-directing group. The use of a newly developed pyridine-based ligand is crucial for relaying the palladium catalyst to the *meta* position by norbornene following initial *ortho*-C–H activation. Thus, this catalytic reaction demonstrates the feasibility of switching *ortho*-selectivity to *meta*-selectivity in C–H activation of the same substrate by catalyst control.

Inspired by the unique reactivity of norbornene in palladium-catalyzed reactions discovered by Catellani (Fig. 1b),^{18–22} we hypothesized that *ortho*-palladacycle **I** (Fig. 1c) could react with norbornene to provide an intermediate that can undergo activation of the *meta*-C–H bond (intermediate **II**). Reaction of palladacycle **II** with a coupling partner would form a new C–C or C–heteroatom bond and subsequent β -carbon elimination of norbornene followed by protodemetalation of the aryl-palladium bond would regenerate the palladium catalyst. As such, this reaction pathway would provide a new approach to achieve catalytic

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Author Contributions X.-C.W. and R.-Y.Z. developed the reactions. W.G. and S.L. synthesized the ligands. L.-Z.F. examined the substrate scope. K.M.E. performed preliminary studies. J.-Q.Y. conceived this concept and prepared this manuscript with feedback from X.-C.W.

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meta-selective C–H activation using standard *ortho*-directing groups with norbornene as a transient mediator. Herein we report the realization of this concept through the design of a pyridine-based ligand that suppresses several undesired reaction pathways and promotes *meta*-selective alkylation and - arylation of phenylacetic acid derivatives. We anticipate that this approach will enable many previously reported *ortho*-C–H activation reactions to be achieved with high levels of *meta*- selectivity.

At the outset, we were cognizant that our proposed *meta*-C–H activation with norbornene as a transient mediator would face several key challenges (Fig. 1c). First, it was unclear if 1,2-migratory insertion with norbornene could occur from a cyclopalladated intermediate (**I**) and whether this pathway would be faster than the competitive reaction of the palladacycle with a terminal electrophile. In a recent report from the Bach's group, the C2-selective C–H alkylation of indoles *via* the initial aminopalladation of norbornene with the indolyl N–H bonds is inspiring.^{23, 24} Second, the resultant intermediate **II** could undergo reductive elimination to form a benzocyclobutene thereby preventing the desired *meta*-C–H functionalization (Fig. 1c).²⁵ Third, rather than undergoing protodemetalation, intermediate **III** could be further functionalized to afford the undesired *ortho*, *meta*-difunctionalized products.

We initiated our investigation with a phenylacetic acid–derived *N*-2,3,5,6-tetrafluoro-4-trifluoromethylphenyl amide substrate. This auxiliary has been proven effective in the *ortho*-C–H activation of C(sp²)–H bonds by Pd(II) catalysts.¹² To probe the feasibility of each step in the proposed catalytic cycle, we first treated substrate **1a** with Pd(OAc)₂ and norbornene under various conditions in an attempt to identify conditions for 1,2-migratory insertion without success (see supplementary information). Although, *ortho*-C–H activation of **1a** does not require ligands,²⁶ our recent finding that 9-methylacridine promotes directed *ortho*-C–H activation²⁷ prompted us to search for pyridine-type ligands that would facilitate the 1,2-migratory insertion. We found that the addition of pyridine as a ligand enables 1,2-migratory insertion of norbornene into the putative *ortho*-palladacycle intermediate. Subsequent *meta*-C–H palladation and reductive elimination presumably then took place to give benzocyclobutene **2a** in 61% yield (Fig. 2a). Notably, formation of **2a** was not observed in the absence of pyridine ligand.

Having established the first step in the proposed catalytic cycle (1,2-migratory insertion), we next sought to identify conditions to prevent benzocyclobutene formation and promote *meta*-functionalization with an electrophile. Encouragingly, in the presence of methyl iodide, the desired *meta*-methylated product **3a** was obtained in 15% yield, and formation of **2a** was reduced to 15% yield (Fig. 2b, **L1**). Further screening of simple pyridine ligands revealed that alkyl substitution at the 2-position improved the yield of *meta*-methylation (**L2** and **L5**, 29% and 37% yield, respectively). We further found that pyridine ligands with electron-donating substituents lead to improved product selectivity (**L6–L9**) while electron-deficient pyridine ligands provided both poor selectivity and reactivity (**L10–L12**). Prompted by our recent progress in developing quinoline-based ligands for C–H activation,^{28, 29} we subsequently examined this class of ligands. Although the use of 2-methylquinoline (**L14**) and acridine (**L15**) as ligands led to increased reactivity, formation of benzocyclobutene **2a**

was favored. Since electron-donating substituents enhance selectivity for the *meta*-methylation pathway, we tested several quinoline ligands containing alkoxy groups at the 2-position. Although 2-(isobutoxy)quinoline (**L16**) is an ineffective ligand, the use of ligand **L17**, containing a 2-alkoxy group with a constrained conformation in a fused ring, leads to full conversion, affording **3a** in 80% yield. Installation of a highly electron-donating amine substituent on a similar ligand **L18** did not improve the selectivity. Ligand **L19**, containing a fused cyclopentane ring, further improves the selectivity for *meta*-methylation, providing **3a** in 85% yield. Selective *meta*-alkylation with ethyl iodoacetate is also achieved under optimized conditions to give the desired product **4a** in 67% yield (Fig. 2c).

The scope of this norbornene-mediated *meta*-alkylation was investigated using methyl iodide (**3a–3x**) and ethyl iodoacetate (**4a–4x**) as coupling partners (Fig. 3). Electron-donating and -withdrawing *ortho*-substituents are tolerated in this transformation, providing moderate to excellent yields (**3a–3h** and **4a–4h**). An *ortho*-bromide substituent is also compatible with this protocol (**3d** and **4d**). Alkylation of 1-naphthylacetic amide **1i** occurs exclusively at the 3- position, rather than the 8-position (**3i** and **4i**). When an unsubstituted amide substrate **1j** is used, methylation occurs at both *meta* positions to provide dimethylated product **3j** in 80% yield. Coupling of ethyl iodoacetate with this substrate, however, mainly produces the benzocyclobutene byproduct; the yield of the desired dialkylated product **4j** was <10%. This result demonstrates the subtle reactivity differences between these two alkylating reagents. Substrates bearing electron-donating or -withdrawing *meta*-substituents are also reactive with this protocol (**3k–3n** and **4k–4n**). Methylation of the more sterically hindered *p*-MeO-substituted substrate **1o** is sluggish and poor yielding, providing **3o** in <10% yield. Interestingly, mono- alkylation of **1o** with ethyl iodoacetate affords **4o** in 68% yield. Substrate containing the less steric hindered *p*-F-group reacted well with both coupling partners to afford di-alkylated products **3p** and **4p** in 85% and 59% yields, respectively. Methylation reaction was found to proceed effectively with a broad range of α -substituents, including methyl, acetoxyl, benzyloxy and phthaloyl-protected amino groups to give the di-methylated products in good yields (**3q–3t**). Thus, this transformation enables the direct *meta*-functionalization of key biologically-active building-blocks, such as mandelic acid (**3r** and **3s**) and phenylglycine (**3t**). In contrast, ethoxycarbonylmethylation reaction is effective only for **1s**, containing a benzyloxy group at the benzylic position (**4s**). Notably, both alkylation reactions are compatible with tetrahydronaphthalene (**1u**) and tetralone (**1v**) substrates, despite the amide directing groups being out of plane with the target C(aryl)–H bonds. We were pleased to observe that *meta*-methylation is effective for the heterocyclic dihydrobenzofuran- and indoline-containing substrates **1w** and **1x**. However, ethoxycarbonylmethylation of these heterocycles provides only trace product.

We subsequently examined the generality of this *meta*-C–H functionalization strategy by investigating additional organohalide coupling partners (Fig. 4). Ethylation with ethyl iodide under standard conditions leads to exclusive formation of the undesired benzocyclobutene byproduct. Increasing the loading of ethyl iodide (6 eq) affords *meta*-ethylated product **5** in 21% yield, with the benzocyclobutene still formed as the major product. We were pleased to find that *meta*-alkylation with benzyl bromide, a more reactive electrophile, proceeds

smoothly to afford **6a** in 66% yield. Both electron-donating and -withdrawing substituents on the *ortho*-, *meta*- and *para*- positions of the benzyl bromide coupling partner are tolerated, providing *meta*-benzylated products **6b–6g** in 60–75% yield.

Finally, we examined whether this approach for *meta*-C–H functionalization could be adapted to achieve *meta*-C–H arylation, thereby providing a method for the synthesis of biaryl compounds. Gratifyingly, arylation with methyl 2-iodobenzoate in *t*-butyl methyl ether (TBME) provides the *meta*-arylated product **7a** in 64% yield. The use of methyl 3-iodobenzoate or methyl 4-iodobenzoate, however, results in the formation of the benzocyclobutene adduct as the major product. These experiments suggest that the presence of an *ortho*-coordinating group is required to promote oxidative addition of the aryl halide, consistent with previous studies.^{19, 30} As such, we examined other substituted 2-iodobenzoates and were able to obtain the desired products in moderate yields (**7b–7d**). Similarly, 2'-iodoacetophenone is a competent coupling partner, affording **7e** in 48% yield. Arylation with highly reactive, electron-deficient 3,5- bis(trifluoromethyl)iodobenzene is also effective, providing the *meta*-arylated product **7f** in 76% yield. The successful *meta*-arylation of substrates containing dihydrobenzofuran (**8**, 82% yield) and indoline (**9**, 69% yield) groups with methyl 2-iodobenzoate is especially noteworthy in terms of demonstrating late-stage diversification of heterocycles with possible applications in medicinal chemistry. We anticipate that further development of the ancillary pyridine ligand will broaden the scope of alkyl and aryl halides in this reaction, ultimately leading to a broadly useful method for *meta*-C–H functionalization using common *ortho*-directing groups and norbornene as a transient mediator.

Supplementary Material

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Acknowledgments

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Figure 1. Design of a new approach for *meta*-C–H activation

a, Previously reported remote *meta*-C–H activation directed by a U-shaped template. **b**, The norbornene-mediated Catellani reaction functionalizes *ortho*-positions of aryl iodides. **c**, The development of a tailor-made ligand that switches the *ortho*-selectivity to *meta*-selectivity using norbornene as a transient mediator (this work). Ar_F, 4-(CF₃)C₆F₄. The activated C–H bonds (blue) and the newly formed bonds (red) are highlighted.

Figure 2. Discovery of a ligand that enables *meta*-C–H alkylation using norbornene as a transient mediator

a, Pyridine promotes Pd-catalyzed reaction of phenylacetic amide with norbornene to afford benzocyclobutene via a Catellani pathway. DCE, 1,2-dichloroethane. **b**, A modified pyridine-type ligand enables selective *meta*-C–H methylation. Yields are determined by crude ^1H NMR analysis. **c**, *meta*-C–H alkylation with ethyl iodoacetate.

The values under each structure indicate percent isolated yields.

For **1j** and **1p-1t**, di-alkylation is observed; Reaction conditions: 20 mol% Pd(OAc)_2 , 40 mol% **L19**, 5 eq R-I, 5 eq AgOAc, 3 eq of norbornene.

15 mol% Pd(OAc)_2 , 30 mol% **L19**.

† 20 mol% Pd(OAc)_2 , 40 mol% **L19**.

Figure 3. meta-C-H alkylation of phenylacetic amides

R-I, methyl iodide or ethyl iodoacetate; X, Y, generic substituents; Ac, acetyl; Bn, benzyl;

Phth, phthaloyl; Ts, 4-toluenesulfonyl.

The values under each structure indicate percent isolated yields.

[#] 15 mol% Pd(OAc)₂, 30 mol% **L19**.

[⊥] Dichloromethane as solvent.

[‡] 6 eq Ar-I; AgOPiv used instead of AgOAc.

Figure 4. Scope of organohalide coupling partners

a, *meta*-C–H Alkylation with alkyl halides. Alkyl-X, iodoethane or benzyl bromides. **b**, *meta*-C–H arylation with aryl iodides. TBME, *t*-butyl methyl ether.