ACS Catalysis

pubs.acs.org/acscatalysis Letter

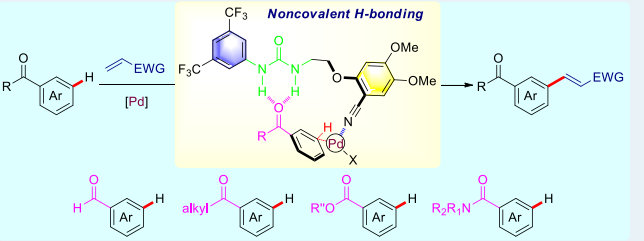
Palladium-Catalyzed *meta*-Selective C−H Functionalization by Noncovalent H-Bonding Interaction

Guoshuai Li, Yifei Yan, Pengfei Zhang, Xiaohua Xu,* and Zhong Jin*

Cite This: *ACS Catal.* 2021, 11, 10460−10466 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Controlling positional selectivity represents one of the most important aspects in transition-metal-catalyzed C−H bond functionalization. However, the conventional directing template strategies via a covalent binding to the substrates are always hindered by prior stoichiometric installation and removal of the directing groups. Herein, we report a palladium-catalyzed *meta*-selective C−H olefination of aromatic carbonyl compounds by noncovalent hydrogen-bonding interaction. N,N′-Substituted ureas were engineered to serve as a H-bonding donor for binding to the substrates and, meanwhile, achieve site-selective control by the integrated directing group.

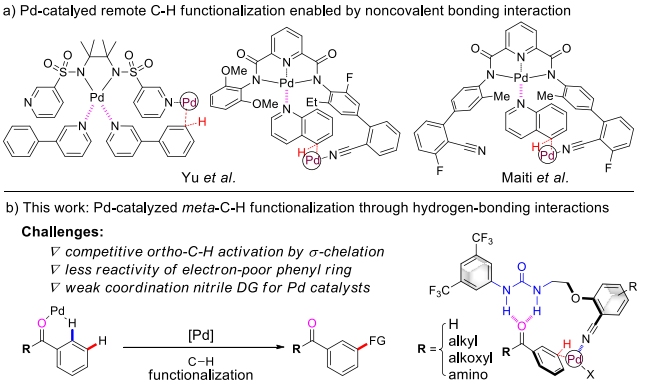


KEYWORDS: *palladium, noncovalent H-bonding interaction, C−H activation, olefination, urea*

Transition-metal-catalyzed remote *meta*- or *para*-C−H bond functionalization of arenes[1,2] has attracted the extensive interest from both chemical and medicinal communities in recent years owing to its vast potentials for step- and atom-economic synthesis of active pharmacophores, as well as late-stage diversification of pharmaceuticals. To render the catalyst proximal to the distal C−H bond efficiently, the C−H activation process frequently requires the participation of a deliberated σ-bonding directing group (DG) in the formation of a metal-embedded macrocyclic transition state. However, the stoichiometric installation and removal of a DG consistently influence the synthetic efficacy of the C−H functionalization strategy.[3,4] Moreover, some kinds of substrates such as aromatic aldehydes/ketones and esters, among others, are incompatible with the DG's methodology because they lack a site for the installation of DG. In contrast, the employment of noncovalent bonding interactions to direct transition-metal-catalyzed C−H functionalization remarkably solves these irreconcilable conflicts. For instance, through various noncovalent bonding interactions,[5−8] iridium-catalyzed *meta*-C−H borylation of arenes has been successfully achieved by several research groups to date.

Relative to the high reactivity of iridium catalysts, palladium-catalyzed remote C−H activation based on noncovalent bonding interactions still remains extremely challenging to date. In 2017, a class of bifunctional directing templates based on noncovalent Lewis acid/base coordination was elegantly designed by the Yu group for Pd-catalyzed distal C−H alkenylation of heteroarenes,[9] for example, quinolines (Scheme 1a). In such a template, one palladium atom fixed in the template central scaffold is in charge of reversibly anchoring substrates by heteroatom coordination, and the other

Scheme 1. Noncovalent Bonding Strategies for Pd-Catalyzed Distal C−H Functionalization



regioselectively cleaves the distal C−H bonds by coordination to the DG. Subsequently, through utilizing symmetrically bidentate nitrile templates (Scheme 1a), the Maiti group also realized Pd-catalyzed distal C−H alkenylation and alkylation in the same heteroarenes based on the template designed by Yu's group.[10] To date, the intermolecular hydrogen-bonding approach to achieve the palladium-catalyzed remote C−H

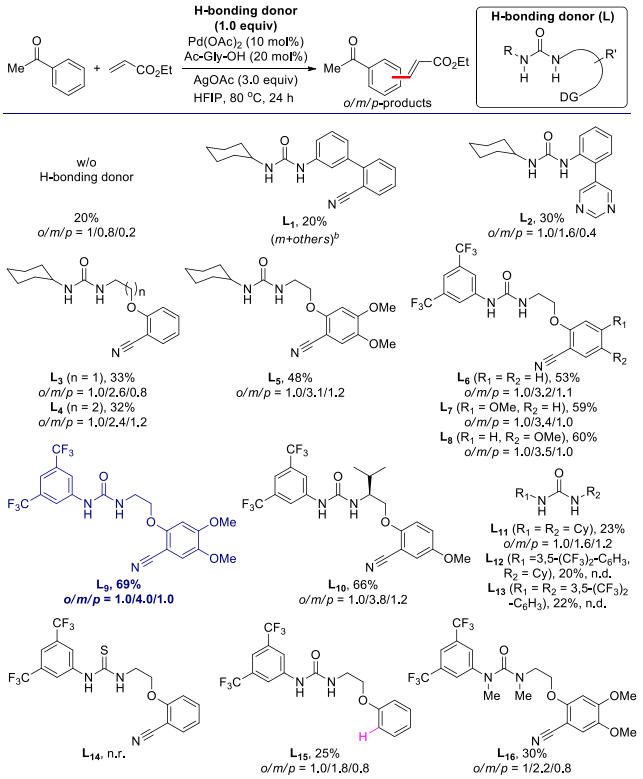
Received: July 2, 2021
Revised: July 26, 2021

https://doi.org/10.1021/acscatal.1c02974
ACS Catal. 2021, 11, 10460−10466

activation of arenes is yet to be exploited probably because of the perceived lower reactivity. To address this, we sought to investigate aromatic carbonyl compounds in palladium-catalyzed remote *meta*-C−H activation, envisaging that the carbonyl group serving as a hydrogen-bond acceptor would be able to pair with a hydrogen-bond donor bearing a suitable directing template. N,N′-Substituted ureas behave as the strong double hydrogen-bond donors, shown thus far to be capable of assembling a lot of guest acceptor molecules including aldehydes, ketones, esters, imines, *N*-acyliminium ions, and nitro compounds.[11] Herein, we report that the N,N′-substituted urea scaffold is highly proficient as a hydrogen-bond donor to direct palladium-catalyzed C−H functionalization to the *meta* position in a series of arene substrates bearing the carbonyl group as hydrogen-bond acceptors.

Based on the Yu's pioneering work[3a] on remote *meta*-selective C−H functionalization directed by a covalently U-shaped template, a range of DGs for transition-metal-catalyzed distal C−H functionalization have been developed since then. Over the past few years, We,[12] Yu,[13] Maiti,[14] and others[15] have identified a substituted salicylonitrile moiety as the versatile template to direct palladium-catalyzed *meta*-C−H functionalization in various arene derivatives. In approaching the development of an efficient hydrogen-bonding donor template, we began by elaborating an appropriate *N,N′*-substituted urea framework for Pd-catalyzed remote C−H functionalization of arenes, according to the experimental and computational results established for the covalently binding templates.[12a,13b,16] By integrating a salicylonitrile-bearing tether into the urea backbone, a powerful double hydrogen-bonding interaction appears plausible with an aromatic carbonyl substrate promoting C−H activation at the *meta* position of the phenyl ring. Therefore, we first synthesized a series of *N*-cyclohexyl ureas, $\mathbf{L_1}$−$\mathbf{L_5}$, containing an additional directing functional group on the other nitrogen atom (Scheme 2). Using acetophenone as a model substrate, C−H olefination only gave the poor reactivity with a mixture of *o*-, *m*-, and *p*-products (*o*/*m*/*p* = 1/0.8/0.2) in the absence of a hydrogen-bonding donor. The major *o*-olefinated product obtained is probably attributed to the natively Pd-catalyzed carbonyl-directed *ortho*-C−H activation.[17] While an equivalent H-bonding donor ($\mathbf{L_2}$−$\mathbf{L_4}$) bearing a *meta*-selective DG was added into the reaction, the desired products were afforded with significantly improved regioselectivity, albeit in just a slightly higher yield. By modifying the salicylonitrile moiety in hydrogen-bonding donors ($\mathbf{L_5}$), C−H olefination achieved the *m*-product in up to 48% yield with a regioselectivity of *o*/*m*/*p* = 1.0/3.1/1.2. Pleasingly, replacing the cyclohexyl group in the urea with a 3,5-(bis)trifluoromethyl phenyl group led to a dramatic improvement in both reactivity and regioselectivity ($\mathbf{L_6}$−$\mathbf{L_{10}}$). Hydrogen-bonding donor $\mathbf{L_9}$ was the most effective, affording the olefinated products at 69% yield with a regioselectivity of *o*/*m*/*p* = 1.0/4.0/1.0. A possible explanation for the enhanced reactivity of hydrogen-bonding donors ($\mathbf{L_6}$−$\mathbf{L_{10}}$) is that a very weak, not detectable by routine spectroscopic and crystallographic methods, intramolecular C−H--O interaction between the weakly acidic *ortho*-C−H proton and the urea carbonyl group takes place,[11a−c] which drastically increases the binding potential of hydrogen-bonding donors to guest molecules. The dimethoxy substituent on the nitrile template ($\mathbf{L_9}$) affords improved reactivity and regioselectivity, probably because of the enhanced electron density of the phenyl ring which prompts the metal binding of

Scheme 2. Evaluation of Hydrogen-Bonding Donors for Pd-Catalyzed *meta*-C−H Olefination[a]



[a]NMR yield, and regioselectivity was determined by ^{1}H NMR analysis with reference to an internal standard. [b]C−H olefination occurring in the template was also observed. n.d.: regioselectivity not detected, n.r.: no reaction.

the cyano group.[18] The use of symmetrical *N,N′*-dicyclohexyl, *N,N′*-diaryl ureas ($\mathbf{L_{11}}$ and $\mathbf{L_{13}}$), or unsymmetrical urea ($\mathbf{L_{12}}$) only provided comparable yields to the blank experiment but with slightly higher *meta* regioselectivities. C−H olefination in the presence of thiourea ($\mathbf{L_{14}}$) failed to give the desired products, which is certainly due to the poisoning deactivation of Pd catalysts by the coordination of sulfur atoms in the thiourea molecules. As the control experiments, removal of the nitrile group in the hydrogen-bonding donor ($\mathbf{L_{15}}$ vs $\mathbf{L_6}$) led to a significant decline in both reactivity and regioselectivity, indicating the essential directing effect of the nitrile group. Replacement of two hydrogen atoms on the urea N−H bonds by two methyl groups ($\mathbf{L_{16}}$) also afforded a diminished yield and *meta* selectivity. As observed in the previous reports,[19] as a solvent hexafluoroisopropanol (HFIP) shows a significant influence on the yield and regioselectivity of C−H olefination (for details, see Supporting Information).

It is well-established that N,N′-disubstituted ureas as hydrogen-bond donors may associate with guest molecules, such as triphenylphosphine oxide (TPPO), dimethyl sulfoxide (DMSO), and benzophenone,[11b] to form 1:1 complexes through double hydrogen bonds. The solution NMR and IR analyses proved to be particularly useful for hydrogen-bonding interaction. As compared with $\mathbf{L_9}$ (5.81 ppm, 7.62 ppm) in *d*-chloroform solution, the chemical shifts of two urea N−H protons move downfield to 6.62 ppm, 9.18 ppm in $\mathbf{L_9}$/TPPO 1:1 complex and 6.70 ppm, 9.45 ppm in d_6-DMSO solution, respectively (Figure 1), consistent with the previous

https://doi.org/10.1021/acscatal.1c02974
ACS Catal. 2021, 11, 10460−10466

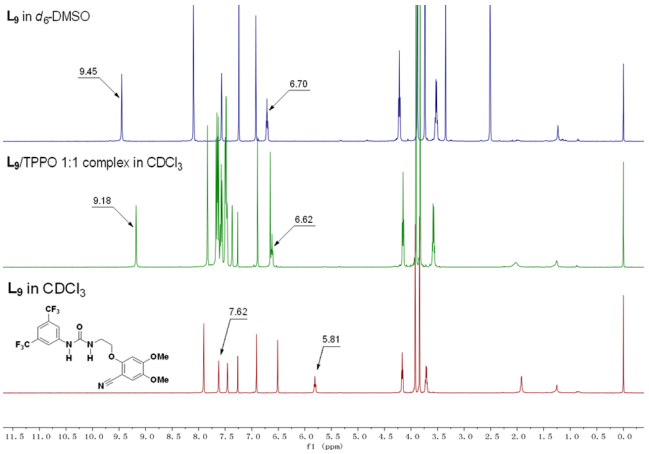


Figure 1. Chemical shift variations of urea **L$_9$** N−H protons resulted from intermolecular H-bonding interaction.

observation by Kuninobu and Kanai.[5a] The ^{31}P chemical shift of TPPO also moves downfield by 2.32 ppm in the complex, which is obviously resulted from deshielding by hydrogen-bonding interactions. Carbonyl stretching frequencies for **L$_9$** are highly sensitive to hydrogen bonding, varying from 1658 cm^{-1} in **L$_9$** to 1712 cm^{-1} in both 1:1 complexes of **L$_9$** with TPPO and benzophenone (Figure 2). The high-frequency

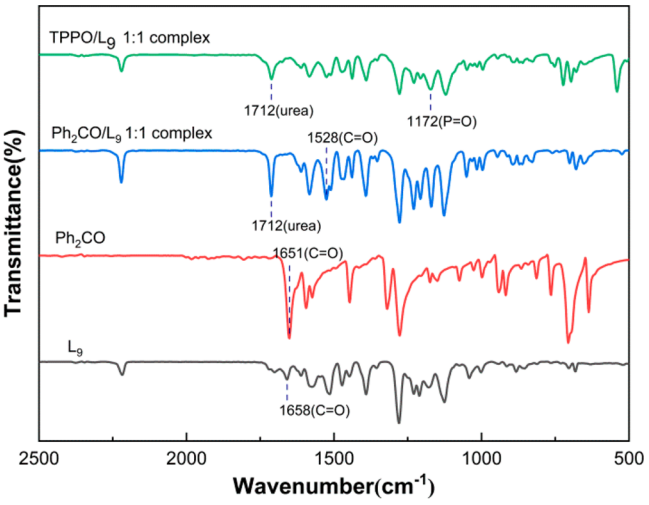


Figure 2. IR analyses of intermolecular H-bonding interaction.

bands occur in both complexes where the P═O or carbonyl oxygen forms two strong hydrogen bonds to the N−H protons of urea **L$_9$**. Meanwhile, the carbonyl stretching frequency of benzophenone varies from 1651 to 1528 cm^{-1} in **L$_9$**/benzophenone 1:1 complex. Similarly, urea carbonyl stretching frequencies in 1:1 cocrystals of **L$_9$** and aromatic aldehyde, ester and amide also vary from 1658 cm^{-1} in **L$_9$** to 1712 cm^{-1} (Figure 3). All IR and NMR data unambiguously supports the occurrence of hydrogen-bonding interaction between **L$_9$** and hydrogen-bond acceptors.

Next, we investigate the application of hydrogen-bond donor **L$_9$** in Pd-catalyzed *meta*-C−H olefination of aromatic carbonyl derivatives. For acetophenones and benzaldehydes (Scheme 3), the methoxyl substituents on the *ortho*, *para* positions of the phenyl ring were well tolerated, giving similar yields and excellent *meta* selectivities (**3b**, **3c**, **3m**, **4b**, and **4c**). Substrates

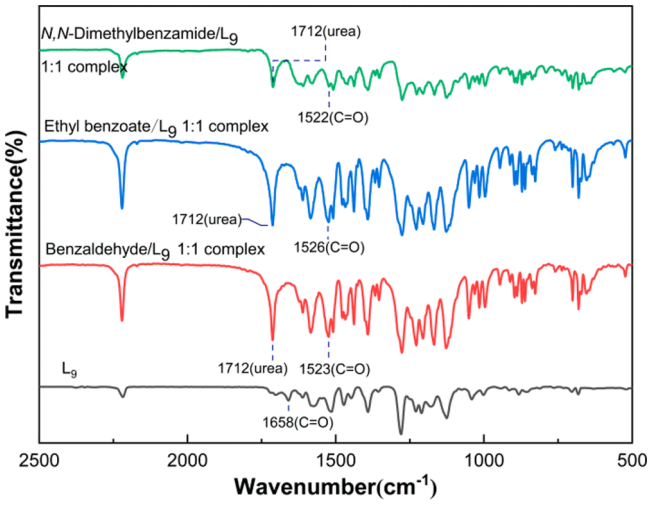
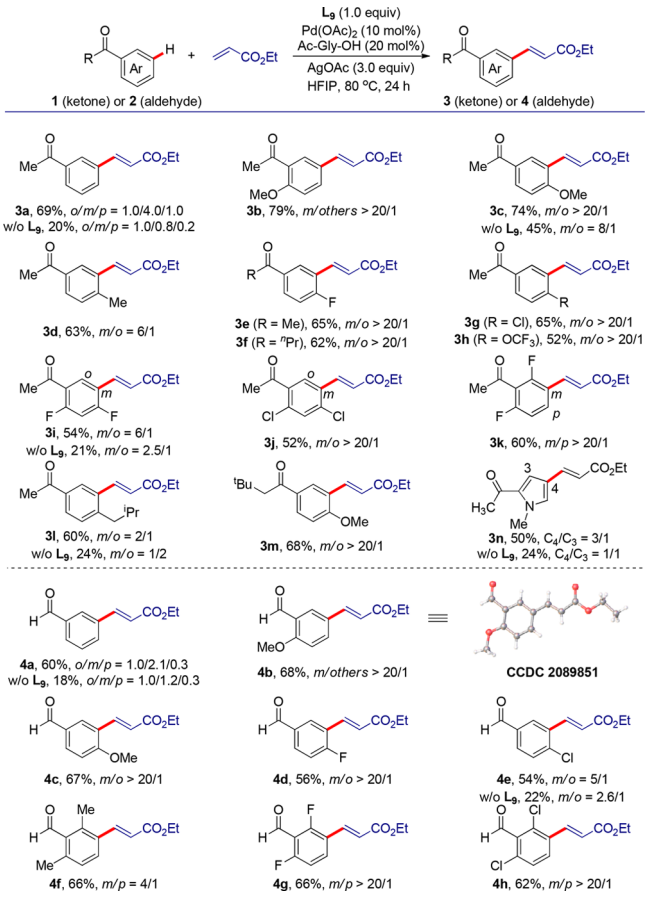


Figure 3. IR spectra of 1:1 cocrystals of **L$_9$** and aromatic aldehyde, ester, and amide.

Scheme 3. Pd-Catalyzed *meta*-C−H Olefination of Aromatic Ketones and Aldehydes[a]



[a]Isolated yield.

bearing electron-withdrawing fluorine, chlorine, and trifluoromethoxyl groups on the *para* position of the phenyl ring are compatible with the protocol, affording the *meta* products in yields of 52%−65% with regioselectivities of up to >20/1 (**3e**−**3h**, **4d**, and **4e**). C−H olefination proceeds smoothly with the substrates owning difluoro or dichloro groups in different substitution patterns to provide the desired *meta* products in

https://doi.org/10.1021/acscatal.1c02974
ACS Catal. 2021, 11, 10460−10466

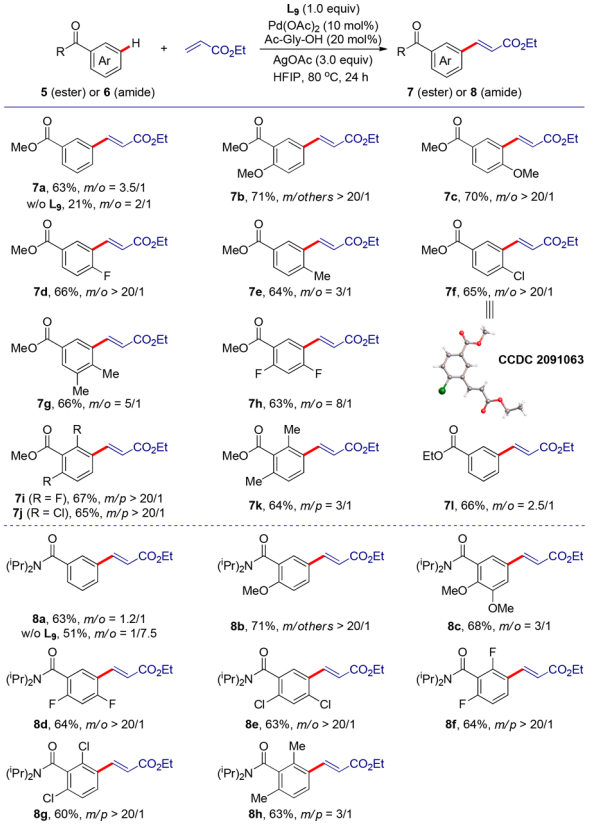
52%−66% yields (**3i**−**3k**, **4g**, and **4h**). Compared with 2,4-dichloro benzophenone (**3j**), 2,4-difluoro benzophenone (**3i**) gave rise to a decreased *meta* selectivity. Notably, *N*-methyl 2-acetyl pyrrole (**3n**) is also compatible with the protocol, providing the olefinated product in 50% yield with a regioselectivity of C_4/C_3 = 3/1. In general, a *meta* group on the phenyl ring led to the drastic decrease of *meta* selectivity in the C−H olefination process. This phenomenon was previously observed in template-enabled *meta*-C−H olefination of 3-arylpyridines by Yu,[9] probably attributed to the *meta* substitution in substrates interfering with the optimal conformational orientation because of steric repulsion. Besides acetophenones, other aromatic ketones, such as **3f** and **3m**, are also suitable substrates for the present protocol. The presence of a bulky substituent liking the methyl (**3d**) and *iso*-butyl (**3l**) group led to the obvious decline of product regioselectivity due to the steric effect. Owing to the enhanced electron-deficient nature, the substrates bearing an additionally electron-withdrawing group such as NO_2, CF_3, and ester group only provided a trace amount of olefinated products.

Besides ketones and aldehydes, we also examined the generality of hydrogen-bond donor L_9 in Pd-catalyzed *meta*-C−H olefination of benzoate esters and benzamides (Scheme 4). Similar to ketones and aldehydes, the methoxyl group at either *ortho* or *para* position of the phenyl ring was reactive to provide the olefination products in more than 70% isolated yields and excellent regioselectivities (**7b**, **7c**, and **8b**). Substrates incorporating difluoro or dichloro groups in different substitution patterns are compatible with the protocol, giving rise to the desired olefinated products in 60%−67% yields with regioselectivities of 8/1 to >20/1 (**7h**−**7j** and **8d**−**8g**). In addition to methyl ester, other alkyl esters are also suitable substrates in C−H olefination, albeit in decreased *meta* selectivity (**7l**). For benzamide substrates (**8a**), in the absence of L_9, *ortho*-olefinated product was obtained as the major product (*o*/*m* = 7.5/1) due to the proximal *σ*-chelation of the amide group. In contrast, regioselectivity of C−H olefination was improved to *o*/*m* = 1/1.2 with L_9 as a hydrogen-bond donor.

The scope of C−H olefination was further studied using different olefin partners with acetophenone **1b** (Scheme 5). To our delight, in the presence of hydrogen-bond donor L_9, *meta*-selective C−H olefination was shown to be compatible with a diverse set of olefins containing ketones (**9a** and **9l**), esters (**9c**), aldehydes (**9f**), amides (**9g**), multiple-fluoro substituted aryl and alkyl (**9e**, **9h**, and **9i**) functional groups. The diverse olefins derived from naturally occurring terpenes were also well tolerated in the protocol (**9j**−**9n**).

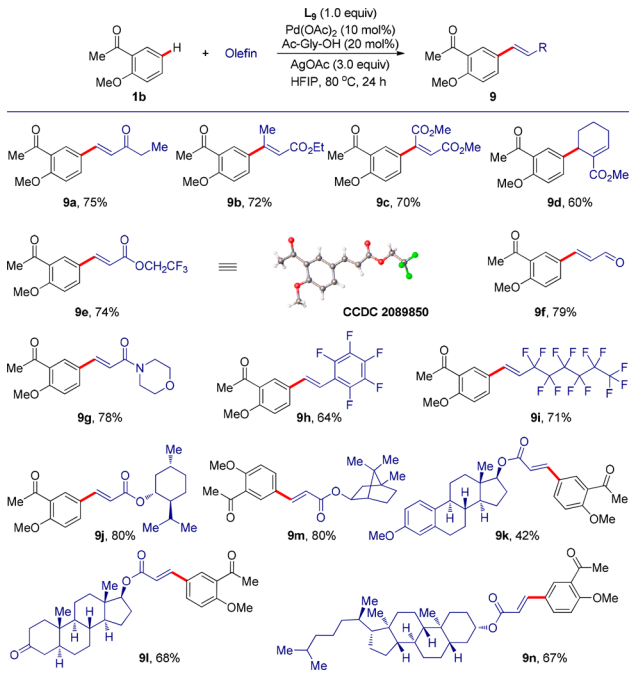
To elucidate the roles of hydrogen-bond donors in the reaction, we further carried out three sets of parallel experiments (Figure 4). In the absence of hydrogen-bond donor L_9, the olefination reaction gave no more than 20% of the olefinated products **3a** after 20 h, while under the same conditions, close to 65% of the products were obtained with 1.0 equiv of L_9. Both the reactivity and *meta* selectivity (53% yield, *o*/*m*/*p* = 1/3.3/1) declined obviously when reducing the loadings of hydrogen-bond donor L_9 to 0.5 equiv. It was found that with a loading of 0.5 equiv L_9, C−H olefination products were provided in slightly higher yield (58% yield) when further extending the reaction time to 48 h. In regard to *meta*-C−H olefination products, kinetic isotope effect (KIE) was also measured, and the value of k_H/k_D was 3.93 (Scheme 6), indicating that C−H-bond cleavage is probably the rate-determining step as observed in the previous reports.[12,13b]

Scheme 4. Pd-Catalyzed *meta*-C−H Olefination of Benzoate Esters and Benzamides[a]



[a]Isolated yield.

Scheme 5. Scope of the Olefins[a]



[a]Isolated yield.

https://doi.org/10.1021/acscatal.1c02974
ACS Catal. 2021, 11, 10460−10466

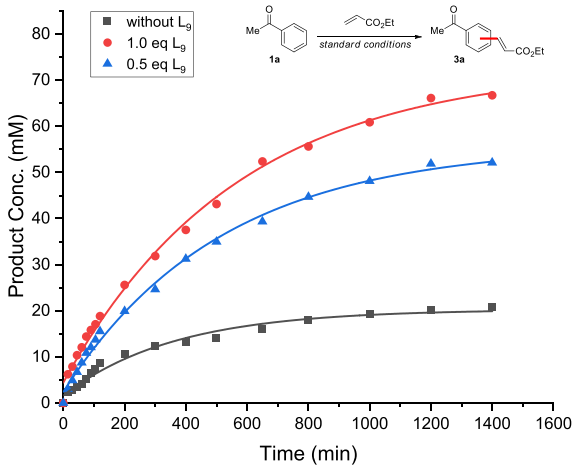
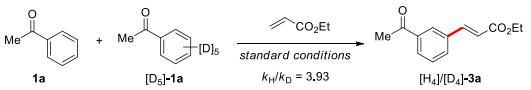


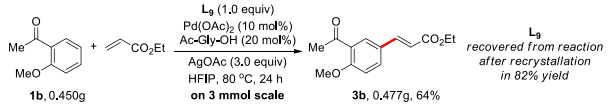
Figure 4. Effect of H-bonding interaction on C−H olefination.

Scheme 6. KIE Experiment



Finally, hydrogen-bonding donor enabled C−H olefination was carried out on a 3 mmol scale to provide the *meta*-olefinated product **3b** in 64% isolated yield, accompanied by 82% recovery of hydrogen-bond donor $\mathbf{L_9}$ from the reaction (Scheme 7).

Scheme 7. Up-Scaled Reaction and Recovery of H-Bonding Donor



In conclusion, we have described the first example of Pd-catalyzed *meta*-selective C−H functionalization of aromatic carbonyl compounds through noncovalent hydrogen-bonding interaction. The N,N′-substituted ureas as hydrogen-bond donors were demonstrated to be capable of forming the double hydrogen bonds with aromatic ketones, aldehydes, benzoate esters, and benzamides, thereby achieving C−H functionalization on the *meta* position of the phenyl ring by an embedded nitrile directing group. We believe that the present noncovalent hydrogen-bonding strategy for Pd-catalyzed distal C−H bond functionalization will prove to be applicable in other types of substrates and/or reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c02974.

General information, experimental procedures, analytical data, and NMR spectra for products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Zhong Jin − *State Key Laboratory of Elementoorganic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China; Laboratory of Xinjiang Native Medicinal and Edible Plant Resource Chemistry, College of Chemistry and Enviromental Science, Kashi University, Kashgar 844007, China;* orcid.org/0000-0001-5722-7175; Email: zjin@nankai.edu.cn

Xiaohua Xu − *State Key Laboratory of Elementoorganic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China*; Email: xiaohuaxu@nankai.edu.cn

Authors

Guoshuai Li − *State Key Laboratory of Elementoorganic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China*

Yifei Yan − *State Key Laboratory of Elementoorganic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China*

Pengfei Zhang − *State Key Laboratory of Elementoorganic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.1c02974

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the National Natural Science Foundation of China (Nos. 32072440, 21672116, 21172111) for financial support.

■ DEDICATION

Dedicated to the 100th anniversary of chemistry at Nankai University and 60th anniversary of Kashi University.

■ REFERENCES

(1) (a) Julia-Hernandez, F.; Simonetti, M.; Larrosa, I. Metalation dictates remote regioselectivity: Ruthenium-catalyzed functionalization of *meta* C_{Ar}−H bonds. *Angew. Chem., Int. Ed.* **2013**, *52*, 11458−11460. (b) Ye, J.; Lautens, M. Palladium-catalysed norbornene-mediated C−H functionalization of arenes. *Nat. Chem.* **2015**, *7*, 863−870. (c) Li, J.; De Sarkar, S.; Ackermann, L. *meta*- and *para*-Selective C−H functionalization by C−H activation. *Top. Organomet. Chem.* **2015**, *55*, 217−258. (d) Mihai, M. T.; Genov, G. R.; Phipps, R. J. Acess to the *meta* position of arenes through transition metal catalysed C−H bond functionalisation: a focus on metals other than palladium. *Chem. Soc. Rev.* **2018**, *47*, 149−171. (e) Dey, A.; Sinha, S. K.; Achar, T. K.; Maiti, D. Accessing remore *meta*- and *para*-C(sp^2)-H bonds with covalently attached directing groups. *Angew. Chem., Int. Ed.* **2019**, *58*, 10820−10843. (f) Meng, G.; Lam, N. Y. S.; Lucas, E. L.; Saint-Denis, T. G.; Verma, P.; Chekshin, N.; Yu, J.-Q. Achieving site-selectivity for C−H activation processes based on distance and geometry: A carpenter's approach. *J. Am. Chem. Soc.* **2020**, *142*, 10571−10591. (g) Ali, W.; Prakash, G.; Maiti, D. Recent development in transition metal-catalysed C−H olefination. *Chem. Sci.* **2021**, *12*, 2735−2759. (h) Dutta, U.; Maiti, S.; Bhattacharya, T.; Maiti, D. Arene diversification through distal C(sp^2)−H functionalization. *Science* **2021**, *372*, eabd5992.

(2) (a) Dey, A.; Maity, S.; Maiti, D. Reaching the south: metal catalyzed transformation of the aromatic *para*-position. *Chem. Commun.* **2016**, *52*, 12398−12414. (b) Sasmal, S.; Dutta, U.; Lahiri, G. K.; Maiti, D. Transition metals and transition metals/

https://doi.org/10.1021/acscatal.1c02974
ACS Catal. 2021, 11, 10460−10466

Lewis acid cooperative catalysis for directing group assisted *para*-C−H functionalization. *Chem. Lett.* **2020**, *49*, 1406−1420.

(3) (a) Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. Activation of remote *meta*-C−H bonds assisted by an end-on template. *Nature* **2012**, *486*, 518−522. (b) Hofmann, N.; Ackermann, L. *meta*-Selective C−H bond alkylation with secondary alkyl halides. *J. Am. Chem. Soc.* **2013**, *135*, 5877−5884. (c) Wang, X.-C.; Gong, W.; Fang, L.-Z.; Zhu, R.-Y.; Li, S.; Engle, K. M.; Yu, J.-Q. Ligand-enabled *meta*-C−H activation using a transient mediator. *Nature* **2015**, *519*, 334−338. (d) Dong, Z.; Wang, J.; Dong, G. Simple amine-directed *meta*-selecitve C−H arylation via Pd/norbornene catalysis. *J. Am. Chem. Soc.* **2015**, *137*, 5887−5890. (e) Chu, L.; Shang, M.; Tanaka, K.; Chen, Q.; Pissarnitski, N.; Streckfuss, E.; Yu, J.-Q. Remote *meta*-C−H activation using a pyridine-based template: Achieving site-selectivity via the recognition of distance and geometry. *ACS Cent. Sci.* **2015**, *1*, 394−399. (f) Wang, P.; Li, G.-C.; Jain, P.; Farmer, M. E.; He, J.; Shen, P.-X.; Yu, J.-Q. Ligand-promoted *meta*-C−H amination and alkynylation. *J. Am. Chem. Soc.* **2016**, *138*, 14092−14099. (g) Bag, S.; Jayarajan, R.; Mondal, R.; Maiti, D. Template-assisted *meta*-C−H alkylation and alkenylation of arenes. *Angew. Chem., Int. Ed.* **2017**, *56*, 3182−3186. (h) Achar, T. K.; Zhang, X.; Mondal, R.; Shanavas, M. S.; Maiti, S.; Maity, S.; Pal, N.; Paton, R. S.; Maiti, D. Palladium-catalyzed directed *meta*-selective C−H allylation of arenes: Unactivated internal olefins as allyl surrogates. *Angew. Chem., Int. Ed.* **2019**, *58*, 10353−10360. (i) Shi, H.; Herron, A. N.; Shao, Y.; Shao, Q.; Yu, J.-Q. Enantioselective remote *meta*-C−H arylation and alkylation via a chiral transient mediator. *Nature* **2018**, *558*, 581−585. (j) Li, S.; Wang, H.; Weng, Y.; Li, G. Carboxy group as a remote and selective chelating group for C−H activation of arenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 18502−18507. (k) Bag, S.; K, S.; Mondal, A.; Jayarajan, R.; Dutta, U.; Porey, S.; Sunoj, R. B.; Maiti, D. Palladium-catalyzed *meta*-C−H allylation of arenes: A unique combination of a pyrimidine-based template and hexafluoroisopropanol. *J. Am. Chem. Soc.* **2020**, *142*, 12453−12466.

(4) (a) Bag, S.; Patra, T.; Modak, A.; Deb, A.; Maity, S.; Dutta, U.; Dey, A.; Kancherla, R.; Maji, A.; Hazra, A.; Bera, M.; Maiti, D. Remote *para*-C−H functionalization of arenes by a D-shaped biphenyl templated-based assembly. *J. Am. Chem. Soc.* **2015**, *137*, 11888−11891. (b) Patra, T.; Bag, S.; Kancherla, R.; Mondal, A.; Dey, A.; Pimparkar, S.; Agasti, S.; Modak, A.; Maiti, D. Palladium-catalyzed directed *para*-C−H functionalization of phenols. *Angew. Chem., Int. Ed.* **2016**, *55*, 7751−7755. (c) Yang, L.; Semba, K.; Nakao, Y. *para*-Selective C−H borylation of (hetero)arenes by cooperative iridium/aluminum catalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 4853−4857. (d) Maji, A.; Dahiya, A.; Lu, G.; Bhattacharya, T.; Brochetta, M.; Zanoni, G.; Liu, P.; Maiti, D. H-Bonded reusable template assisted *para*-selective ketonisation using soft electrophilic vinyl ethers. *Nat. Commun.* **2018**, *9*, 3582−3592. (e) Li, M.; Shang, M.; Xu, H.; Wang, X.; Dai, H.-X.; Yu, J.-Q. Remote *para*-C−H acetoxylation of electron-deficient arenes. *Org. Lett.* **2019**, *21*, 540−544. (f) Chen, X.; Fan, S.; Zhang, M.; Gao, Y.; Li, S.; Li, G. Palladium-catalyzed remote *para*-C−H activation of arenes assisted by a recyclable pyridine-based template. *Chem. Sci.* **2021**, *12*, 4126−4131.

(5) For review, see: (a) Pandit, S.; Maiti, S.; Maiti, D. Noncovalent interactions in Ir-catalyzed remote C−H borylation: a recent update. *Org. Chem. Front.* **2021**, *8*, 4349. (b) Kuninobu, Y.; Ida, H.; Nishi, M.; Kanai, M. A *meta*-selective C−H borylation directed by a secondary interaction between ligand and substrate. *Nat. Chem.* **2015**, *7*, 712−717. (c) Davis, H. J.; Genov, G. R.; Phipps, R. J. *meta*-Selective C−H borylation of benzylamine, phenethylamine-, and phenylpropylamine-derived amides enbaled by a single anionic ligand. *Angew. Chem., Int. Ed.* **2017**, *56*, 13351−13355. (d) Lu, X.; Yoshigoe, Y.; Ida, H.; Nishi, M.; Kanai, M.; Kuninobu, Y. Hydrogen bond-accelerated *meta*-selective C−H borylation of aromatic compounds and expression of functional group and substrate specificities. *ACS Catal.* **2019**, *9*, 1705−1709.

(6) Bisht, R.; Hoque, M. E.; Chattopadhyay, B. Amide effects in C−H activation: Noncovalent interactions with L-shaped ligand for *meta* borylation of aromatic amides. *Angew. Chem., Int. Ed.* **2018**, *57*, 15762−15766.

(7) (a) Davis, H. J.; Mihai, M. T.; Phipps, R. J. Ion pair-directed regiocontrol in transition-metal catalysis: A *meta*-selective C−H borylation of aromatic quaternary ammonium salts. *J. Am. Chem. Soc.* **2016**, *138*, 12759−12762. (b) Mihai, M. T.; Phipps, R. J. Ion-pair-directed *meta*-selecitve C−H borylation of aromatic quaternary ammonium salts. *Synlett* **2017**, *28*, 1011−1017. (c) Mihai, M. T.; Davis, H. J.; Genov, G. R.; Phipps, R. J. Ion pair-directed C−H activation on flexible ammonium salts: *meta*-Selective borylation of quaternized phenethylamines and phenylpropylamines. *ACS Catal.* **2018**, *8*, 3764−3769. (d) Lee, B.; Mihai, M. T.; Stojalnikova, V.; Phipps, R. J. Ion-pair-directed borylation of aromatic phosphonium salts. *J. Org. Chem.* **2019**, *84*, 13124−13134. (e) Genov, G. R.; Douthwaite, J. L.; Lahdenpera, A. S. K.; Gibson, D. C.; Phipps, R. J. Enantioselective remote C−H activation directed by a chiral cation. *Science* **2020**, *367*, 1246−1251.

(8) (a) Bisht, R.; Chattopadhyay, B. Formal Ir-catalyzed ligand-enabled *ortho* and *meta* borylation of aromatic aldehydes via in situ-generated imines. *J. Am. Chem. Soc.* **2016**, *138*, 84−87. (b) Yang, L.; Uemura, N.; Nakao, Y. *meta*-Selective C−H borylation of benzamides and pyridines by an iridium-Lewis acid bifunctional catalyst. *J. Am. Chem. Soc.* **2019**, *141*, 7972−7979.

(9) Zhang, Z.; Tanaka, K.; Yu, J.-Q. Remote site-selective C−H activation directed by a catalytic bifunctional template. *Nature* **2017**, *543*, 538−542.

(10) (a) Achar, T. K.; Ramakrishna, K.; Pal, T.; Porey, S.; Dolui, P.; Biswas, J. P.; Maiti, D. Regiocontrolled remoted C−H olefination of samll heterocycles. *Chem. - Eur. J.* **2018**, *24*, 17906−17910. (b) Ramakrishna, K.; Biswas, J. P.; Jana, S.; Achar, T. K.; Porey, S.; Maiti, D. Coordination assisted distal C−H alkylation of fused heterocycles. *Angew. Chem., Int. Ed.* **2019**, *58*, 13808−13812.

(11) (a) Etter, M. C.; Panunto, T. W. 1,3-Bis(*m*-nitrophenyl)urea: An exceptionally good complexing agent for proton acceptors. *J. Am. Chem. Soc.* **1988**, *110*, 5896−5897. (b) Etter, M. C.; Urbanczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. Hydrogen bond directed cocrystallization and molecular recognition properties of diarylureas. *J. Am. Chem. Soc.* **1990**, *112*, 8415−8426. (c) Etter, M. C. Encoding and decoding hydrogen-bond patterns of organic compounds. *Acc. Chem. Res.* **1990**, *23*, 120−126. (d) Taylor, M. S.; Jacobsen, E. N. Asymmetric catalysis by chiral hydrogen-bond donors. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520−1543. (e) Volz, N.; Clayden, J. The urea renaissance. *Angew. Chem., Int. Ed.* **2011**, *50*, 12148−12155.

(12) (a) Zhang, L.; Zhao, C.; Liu, Y.; Xu, J.; Xu, X.; Jin, Z. Activation of remote *meta*-C−H bonds in arenes with tethered alcohols: A salicylonitrile template. *Angew. Chem., Int. Ed.* **2017**, *56*, 12245−12249. (b) Wang, B.; Zhou, Y.; Xu, N.; Xu, X.; Xu, X.; Jin, Z. Palladium(II)-catalyzed remote *meta*-C−H functionalization of aromatic tertiary amines. *Org. Lett.* **2019**, *21*, 1885−1889. (c) Xie, S.; Li, S.; Ma, W.; Xu, X.; Jin, Z. Chelation-directed remote *meta*-C−H functionalization of aromatic aldehydes and ketones. *Chem. Commun.* **2019**, *55*, 12408−12411.

(13) (a) Tang, R.-Y.; Li, G.; Yu, J.-Q. Conformation-induced remote *meta*-C−H activation of amines. *Nature* **2014**, *507*, 215−220. (b) Fang, L.; Saint-Denis, T. G.; Taylor, B. L. H.; Ahlquist, S.; Hong, K.; Liu, S.; Han, L.; Houk, K. N.; Yu, J.-Q. Experimental and computational development of a conformationally flexible template for the *meta*-C−H functionalization of benzoic acids. *J. Am. Chem. Soc.* **2017**, *139*, 10702−10714.

(14) (a) Bera, M.; Modak, A.; Patra, T.; Maji, A.; Maiti, D. *meta*-Selective arene C−H bond olefination of arylacetic acid using a nitrile-based directing group. *Org. Lett.* **2014**, *16*, 5760−5763. (b) Bera, M.; Maji, A.; Sahoo, S. K.; Maiti, D. Palladium(II)-catalyzed *meta*-C−H olefination: Constructing multisubstituted arenes through homo-diolefination and sequential hetero-diolefination. *Angew. Chem., Int. Ed.* **2015**, *54*, 8515−8519. (c) Maji, A.; Bhaskararao, B.; Singha, S.; Sunoj, R. B.; Maiti, D. Directing group assisted *meta*-hydroxylation by C−H activation. *Chem. Sci.* **2016**, *7*, 3147−3153. (d) Bera, M.; Sahoo, S. K.; Maiti, D. Room-temperature *meta*-functionalization:

https://doi.org/10.1021/acscatal.1c02974
ACS Catal. 2021, 11, 10460−10466

Pd(II)-catalyzed synthesis of 1,3,5-trialkenyl arene and *meta*-hydroxylated olefin. *ACS Catal.* **2016**, *6*, 3575−3579. (e) Casali, E.; Kalra, P.; Brochetta, M.; Borsari, T.; Gandini, A.; Patra, T.; Zanoni, G.; Maiti, D. Overriding *ortho* selectivity by template assisted *meta*-C−H activation of benzophenones. *Chem. Commun.* **2020**, *56*, 7281−7284.

(15) Williams, A. F.; White, A. J. P.; Spivey, A. C.; Cordier, C. J. *meta*-Selective C−H functionalisation of aryl boronic acids directed by a MIDA-derived boronate ester. *Chem. Sci.* **2020**, *11*, 3301−3306.

(16) Yang, Y.-F.; Cheng, G.-J.; Liu, P.; Leow, D.; Sun, T.-Y.; Chen, P.; Zhang, X.; Yu, J.-Q.; Wu, Y.-D.; Houk, K. N. Palladium-catalyzed *meta*-selective C−H bond activation with a nitrile-containing template: Computational study on mechanism and origins of selectivity. *J. Am. Chem. Soc.* **2014**, *136*, 344−355.

(17) (a) Xiao, B.; Gong, T.-J.; Xu, J.; Liu, Z.-J.; Liu, L. Palladium-catalyzed intermolecular directed C−H amidation of aromatic ketones. *J. Am. Chem. Soc.* **2011**, *133*, 1466−1474. (b) Shan, G.; Yang, X.; Ma, L.; Rao, Y. Pd-catalyzed C−H oxygenation with TFA/TFAA: Expedient access to oxygen-containing heterocycles and late-stage drug modification. *Angew. Chem., Int. Ed.* **2012**, *51*, 13070−13074. (c) Mo, F.; Trzepkowski, L. J.; Dong, G. Synthesis of *ortho*-acyphenols through the palladium-catalyzed ketone-directed hydroxylation of arenes. *Angew. Chem., Int. Ed.* **2012**, *51*, 13075−13079. (d) Sun, X.; Shan, G.; Sun, Y.; Rao, Y. Regio- and chemoselective C−H chlorination/bromination of electron-deficient arenes by weak coordination and study of relative directing-group abilities. *Angew. Chem., Int. Ed.* **2013**, *52*, 4440−4444. (e) Choy, P. Y.; Kwong, F. Y. Palladium-catalyzed *ortho*-CH-bond oxygenation of aromatic ketones. *Org. Lett.* **2013**, *15*, 270−273.

(18) (a) Maji, A.; Guin, S.; Feng, S.; Dahiya, A.; Singh, V. K.; Liu, P.; Maiti, D. Experimental and computational exploration of *para*-selective silylation with a hydrogen-bonded template. *Angew. Chem., Int. Ed.* **2017**, *56*, 14903−14907. (b) Dutta, U.; Maiti, S.; Pimparkar, S.; Maiti, S.; Gahan, L. R.; Krenske, E. H.; Lupton, D. W.; Maiti, D. Rhodium catalyzed template-assisted distal *para* C-H olefination. *Chem. Sci.* **2019**, *10*, 7426−7432. (c) Pimparkar, S.; Bhattacharya, T.; Maji, A.; Saha, A.; Jayarajan, R.; Dutta, U.; Lu, G.; Lupton, D. W.; Maiti, D. *para*-Selective cyanation of arenes by H-bonded template. *Chem. - Eur. J.* **2020**, *26*, 11558−11564.

(19) (a) Sinha, S. K.; Bhattacharya, T.; Maiti, D. Role of hexafluoroisopropanol in C−H activation. *React. Chem. Eng.* **2019**, *4*, 244−253. (b) Bhattacharya, T.; Ghosh, A.; Maiti, D. Hexafluoroisopropanol: the magical solvent for Pd-catalyzed C−H activation. *Chem. Sci.* **2021**, *12*, 3857−3870.

https://doi.org/10.1021/acscatal.1c02974
ACS Catal. 2021, 11, 10460−10466