OL Organic Letters

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Remote and Selective C(sp^2)−H Olefination for Sequential Regioselective Linkage of Phenanthrenes

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01208 Read Online

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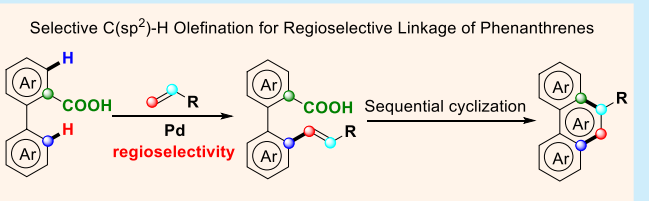
ABSTRACT: Biphenylcarboxylic acid with two competing C-(sp^2)-H sites was designed for site selective C(sp^2)-H functionalization by developing carboxylic acids assisted remote and selective olefination via 7-membered palladacycle. Mechanism investigation and DFT calculations reveal a kinetics-determined process, which could be utilized to explore a variety of remote site selectivity. The practicability of this method was highlighted by the precise construction of phenathrene under sequential site selectivity.

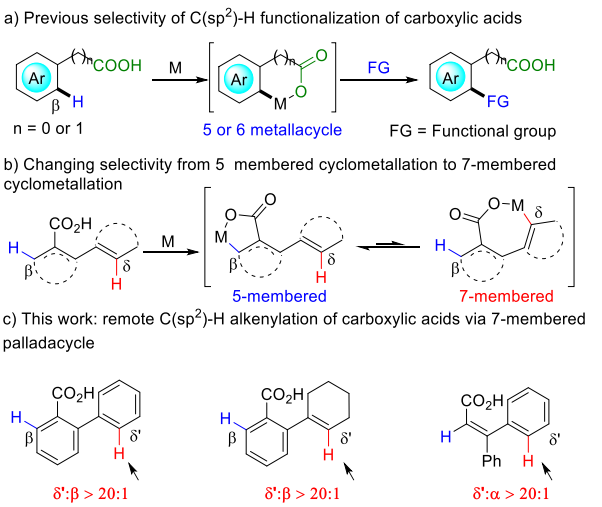


The control of site selectivity is one of the ultimate goals and challenges on the road to synthetic chemistry progress.[1] It is therefore highly desired to track the process and analyze the mechanism for further understanding the source of site selectivity governing the synthetic protocol.[2,3]

To control site selectivity in organic synthesis, introducing directing groups is a common strategy,[4] which has made much progress for substrates with a single reaction site in the vicinity of the directing group.[5] However, it is still hard to control site selectivity when two or more competitive reaction sites exist near the directing group.[6] Consequently, investigating the site-selective methodology, mechanism, and source of multisite competition assisted by the directing group still remains challenging. When it comes to transition metal catalytic directed C−H functionalization, there is a new opportunity for the above challenge[7,8] since cyclometalation reaction relatively facilitates tracking the process and analyzing the mechanism to understand whether kinetics or thermodynamicss controls the reaction.[9]

Among common substrate functional groups, carboxylic acid has proved to be a highly effective directing group to assist the transition metal and position it to break the C(sp^2)−H bond for cyclometalation.[10,11] For aromatic carboxylic acid derivatives with a single activation site, the *ortho*-C−H activation was pioneered by Yu, Ackermann, Gooßen, and other groups (Scheme 1a).[12,13] Yu's group further accounted for the source of selectivity control, resulting from the 5-membered metallacycle intermediate assisted by carboxyl coordination.[12k] However, site-selective C−H bond functionalization for carboxylic acid directed multisite activation is rarely investigated. Recently, Li's group used the carboxylic-acid-assisted κ2 coordination mode to form a U-shaped template to realize *meta*-C(sp^2)−H activation during competition of multiple C−H bonds.[14]

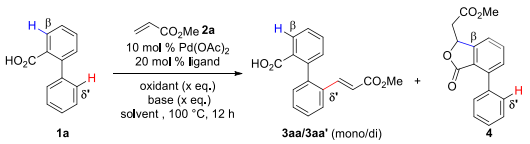
Scheme 1. Remote Functionalization of Carboxylic Acids via Selective C(sp^2)−H Activation



Our group has been working on selective C−H cleavage assisted by carboxylic acids. *ortho*-C−H alkynylation of aromatic acid via a 5-palladacycle[11a] and 6-palladacycle[10c] was included. Then, we found site-selective formation of pyrano[4,3-*b*]indol-1(5*H*)-ones from indole-3-acids, and olefins involve a 7-palladacycle as an intermediate during

Received: April 4, 2020

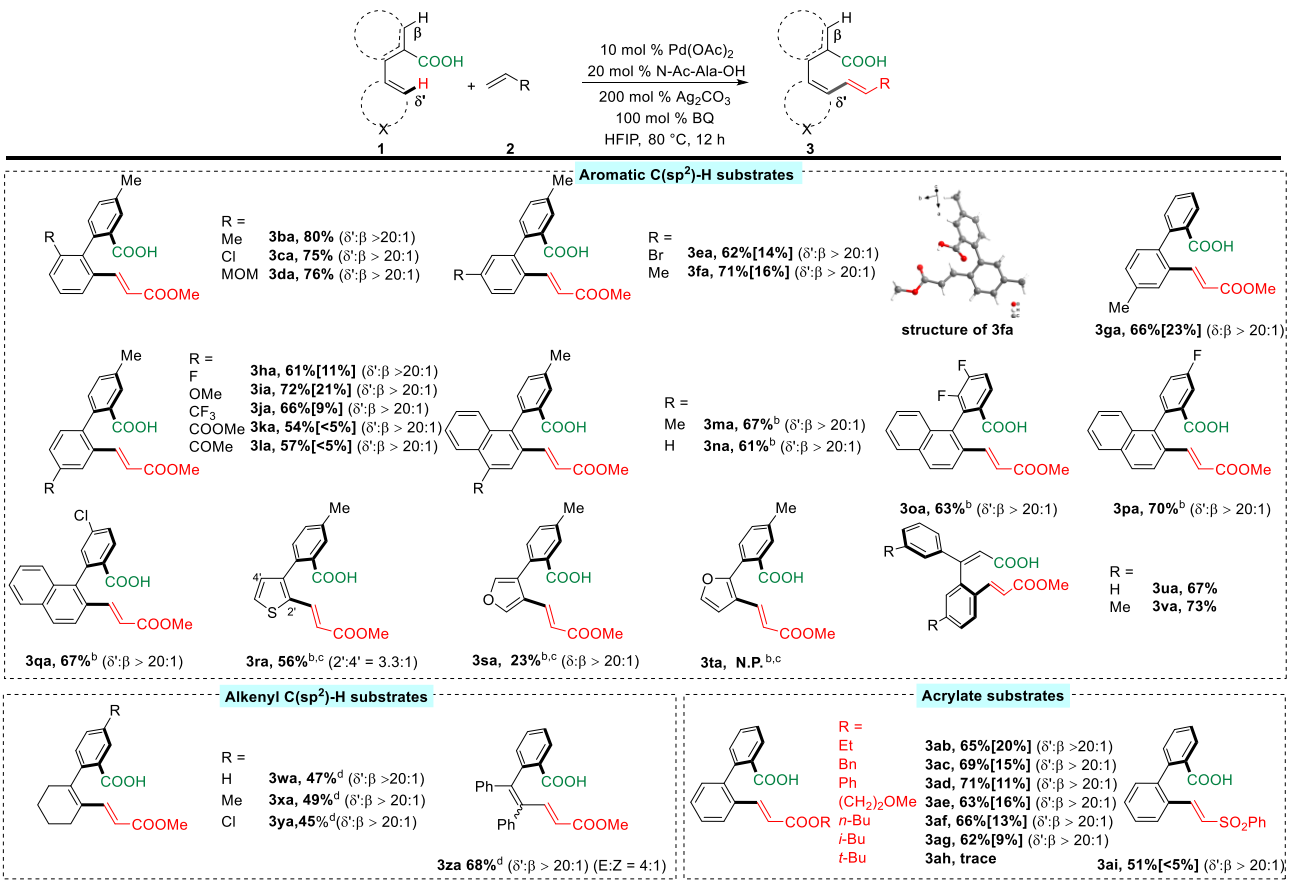
Table 1. Reaction Optimizations[a]



entry	ligand (20 mol %)	oxidant (x equiv)	base (x equiv)	solvent	yield of **3** + **4** [%] (δ': β)
1	---	AgOAc (1.0)	NaOAc (0.5)	DMF	25 (1:1.0)
2	---	AgOAc (1.0)	NaOAc (0.5)	DCE	35 (1:1.2)
3	---	AgOAc (1.0)	NaOAc (0.5)	toluene	37(1:1.6)
5	---	AgOAc (1.0)	NaOAc (0.5)	dioxane	30 (1:1.0)
6	---	AgOAc (1.0)	NaOAc (0.5)	HFIP	41 (4.1:1)
7	---	AgOAc (1.0)	NaOAc (1.5)	HFIP	33 (2.7:1)
8	---	AgOAc (1.0)	---	HFIP	47 (3.7:1)
9	---	BQ(1.0)	---	HFIP	trace
10	---	$Cu(OAc)_2$ (1.0)	---	HFIP	trace
11	---	$AgCO_2CF_3$ (1.0)	---	HFIP	49 (2.5:1)
12	---	Ag_2CO_3 (1.0)	---	HFIP	47 (3.6:1)
13	---	Ag_2CO_3 (2.0)	---	HFIP	48 (5.0:1)
14	---	Ag_2CO_3 (2.0)/BQ (1.0)	---	HFIP	67 (7.4:1)
15[b]	$AdCO_2H$	Ag_2CO_3 (2.0)/BQ (1.0)	---	HFIP	62 (>20:1)
16[b]	*N*-Ac-GIy-OH	Ag_2CO_3 (2.0)/BQ (1.0)	---	HFIP	63 (>20:1)
17[b]	*N*-Ac-AlaOH	Ag_2CO_3 (2.0)/BQ (1.0)	---	HFIP	86 (>20:1)
18[c]	*N*-Ac-Ala-OH	Ag_2CO_3 (2.0)/BQ (1.0)	---	HFIP	46 (1:1.4)

[a]Conditions: **1a** (0.1 mmol), **2a** (5.0 equiv), $Pd(OAc)_2$ (10 mol %), ligand (0.2 equiv), oxidant, base, solvent (0.5 mL), 100 °C, 12 h, air atmosphere. NMR yield analyzed by CH_2Br_2 as an inner standard, δ'/β = (**3aa** + **3aa'**)/**4**. [b]80 °C. [c]140 °C.

Scheme 2. Scope of Selective δ'-C(sp^2)−H Olefination Reaction via Palladacycle 7[a]



[a]Conditions: **1** (0.1 mmol, 1.0 equiv), **2** (5.0 equiv), $Pd(OAc)_2$ (10 mol %), *N*-Ac-Ala-OH (0.2 equiv), Ag_2CO_3 (2.0 equiv), benzoquinone (1.0 equiv), HFIP (0.5 mL), 80 °C, 12 h, air atmosphere; yields of monoalkenylated product; [ ] yields of dialkenylated product. [b]60 °C, 24 h. [c]Without benzoquinone. [d]AgOAc (2.0 equiv), *t*-amylOH (0.5 mL), 60 °C.

https://dx.doi.org/10.1021/acs.orglett.0c01208
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competition between 7-palladacycle and 6-palladacycle.[11b] Based on our past research, we rationally design biaryl carboxylic acids with competing C−H sites in adjacent aromatic rings. Here, we aim to explore the selectivity and origin of carboxylic acid coordination to form a conventional 5-membered metallacycle intermediate or unusual 7-membered metallacycle intermediate for further site selectivity control and theoretical calculation analysis, which offer examples for studying thermodynamics and kinetic control in cyclometalation (Scheme 1b). Considering the remote selectivity achieved, it is convenient to sequentially control the site selectivity for the transformation to phenanthrene[15] through decarboxylative C−H functionalization, namely, that the remote C−H bond could be transformed into the C−C bond under sequential control, which offers a new opportunity for the construction of the valuable aromatic polycyclic compounds (Scheme 1c).

Based on previous studies, we speculate that the selective δ'-C(sp^2)−H functionalization of carboxylic acid will be achieved by rational optimizations of the reaction conditions (Table 1). When the reaction was carried out with **1a** and methyl acrylate **2a** in the presence of 10 mol % of $Pd(OAc)_2$, 1.0 equiv of AgOAc, and 0.5 equiv of NaOAc, at 100 °C under air in DMF (0.5 mL) for 12 h, both remote δ'-C−H olefinic product **3aa** via 7-membered palladacycle and *ortho*-β-C−H olefination and annulation product **4** via 5-membered palladacycle were obtained in 25% yield with low site selectivity (δ'/β = 1:1). To realize the high selectivity of δ'-C−H functionalization, the reaction was extensively investigated. (For details see Supporting Information.) Among the diverse solvents used, the hexafluoroisopropanol (HFIP) exerts a slight improvement in the site selectivity (δ'/β = 4.1:1), which is associated with its acidic nature being favorable for electron-rich δ'-C−H activation via the electrophilic metalation process (entry 6). Next, we investigated the effect of base on the selectivity of the reaction, given that it promotes concerted metalation dehydrogenation during transition-metal-catalyzed C−H activation. As expected, the δ'-olefinated product **3aa** could further increase in the absence of base (entry 8). Considering that oxidants are essential to this oxidative Heck reaction, different oxidants were investigated. The combination of Ag_2CO_3 and 1,4-benzoquinone gave the remote δ'-C(sp^2)−H alkenylated products in 59% yield and the *ortho*-β-C−H-functionalized product **4** in 8% yield (entry 14). To our delight, the δ'-selectivity could be further improved (>20:1) when the reaction was conducted at 80 °C. Lastly, various amino acids as auxiliary ligands were tested and found to improve the yield (entries 15−17). Although most of the acids had a positive effect on the yield, *N*-acetyl-protected alanine was most effective, delivering the high yield (86%) including mono-olefinated product (64%) with diolefinated product (22%) and site selectivity (δ': β > 20:1, entry 17). However, low yield and selectivity were observed when the reaction was conducted at a higher temperature (entry 18).

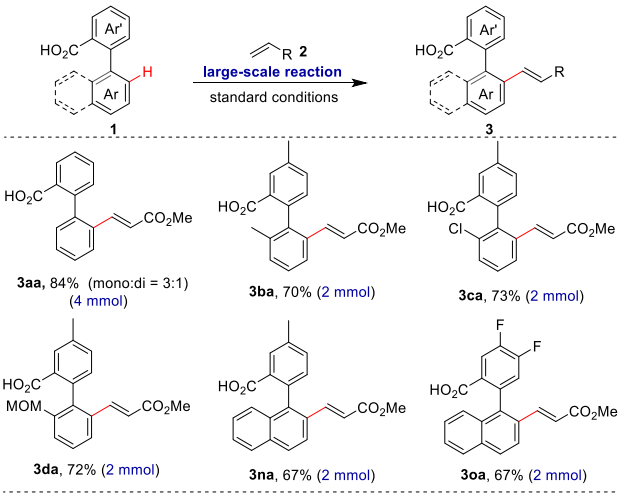
Having identified the optimal conditions, the scope of biaryl-2-carboxylic acids was first investigated (Scheme 2). Aromatic acids with either electron-donating or electron-withdrawing groups were smoothly alkenylated to afford the site-selective δ'-C(sp^2)−H olefinic products with excellent site selectivity (**3ba**−**3la**). The structure of **3fa** was determined by X-ray analyses. Notably, various halogens, even the Br substituent, were tolerated under optimized conditions, generating the remote δ'-C−H alkenylated products in good yields. Moreover, multisubstituted substrates, such as 3,4-disubstituted biaryl carboxylic acids (**3oa**), successfully gave the desired δ'-C(sp^2)−H alkenylated products in moderate yields. Moreover, the biaryl carboxylic acids containing heteroarenes such as thiophene and furan could also give the site-selective δ'-functionalized products but in reduced yields (**3ra** and **3sa**). However, as for 2-(furan-2-yl)biaryl carboxylic acids (**3ta**), there is no desired alkenylated product. We speculate it is a consequence of the more stable palladium complex formation due to palladium ion coordination to the carboxylic group and oxygen of furan. Furthermore, this reaction is also effective for other types of acid substrate such as arylacrylic acid, generating the δ'-C(sp^2)−H-alkenylated product in good yields (**3ua** and **3va**).

After simple optimization of reaction conditions, less acidic solvent (*t*-AmylOH) and AgOAc as oxidant are used. This reaction can also be applied to 2-alkenyl benzoic acid. Cyclic olefin substrates can afford a site-selective conjugated diene product in acceptable yields (**3wa**−**3ya**), and chain olefinic benzoic acid gave the mixture of *Z*- and *E*-type products in good yields (**3za**). Unfortunately, this reaction is not suitable for substrates bearing monosubstituted olefins and disubstituted olefins.

Then, we investigated the scope of olefin reactants. Various acrylates (**2b**−**2i**) underwent a facile reaction with **1a** to afford the corresponding δ'-C(sp^2)−H mono-(**3aa**−**3ae**) in good yields (62%−71% total). However, *tert*-butyl acrylate (**2h**) had no activity under the reaction conditions, possibly due to steric effects of the *tert*-butyl group. In addition to acrylates, phenyl sulfone was suitable for this protocol, giving the corresponding product **3ai** in 51% yield. Unfortunately, styrene and alkyl olefins proved no activities.

To prove the practicability of this reaction, the scale-up reactions were conducted under standard reaction conditions first (Scheme 3). Most of the large-scale reactions (2−4 mmol) of aromatic acids **1** and olefins **2** proceeded smoothly under standard conditions, delivering the desired δ'-C−H olefinated products in moderate to good yields, which provided sufficient feedstock for subsequent diverse conversion of products.

Scheme 3. Large-Scale Reaction[a]



[a]Conditions: **1** (2 or 4 mmol), methyl acrylate **2** (5.0 equiv), $Pd(OAc)_2$ (10 mol %), *N*-Ac-Ala-OH (0.2 equiv), BQ (1.0 equiv), and Ag_2CO_3 (2.0 equiv) at 80 °C in HFIP for 12 h. Isolated yield.

https://dx.doi.org/10.1021/acs.orglett.0c01208
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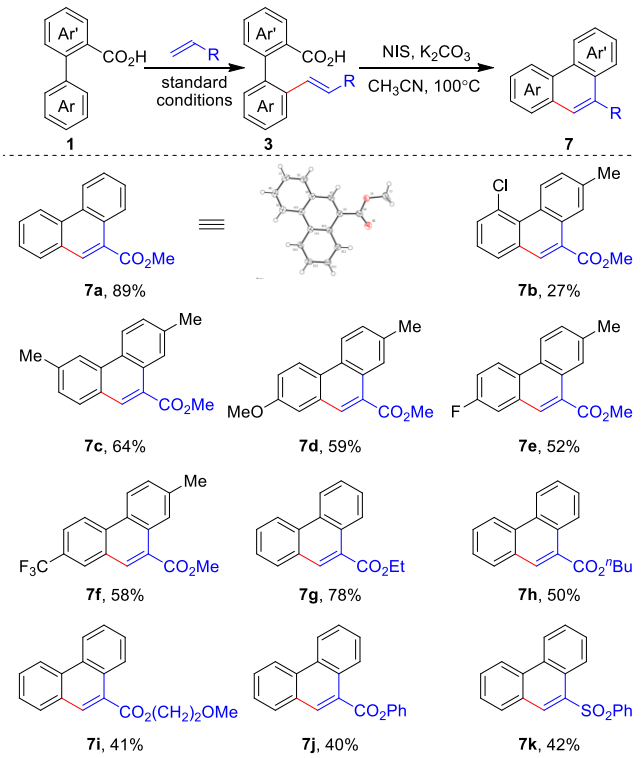
Having the unique δ'-C(sp^2)−H olefinated products in hand, we were inspired by decarboxylative C−H functionalization and utilized them in the syntheses of phenanthrenes which are valuable skeletons found in numerous functional materials and medicinal compounds.[16] A series of substituted methyl phenates were prepared simply and efficiently from olefinated products **3** via decarboxylative C−H functionalization reaction (Scheme 4). It is noteworthy that the δ'-substituent could

Scheme 4. Synthesis of Phenanthrenes from δ'-Olefinated Carboxylic Acids[a]

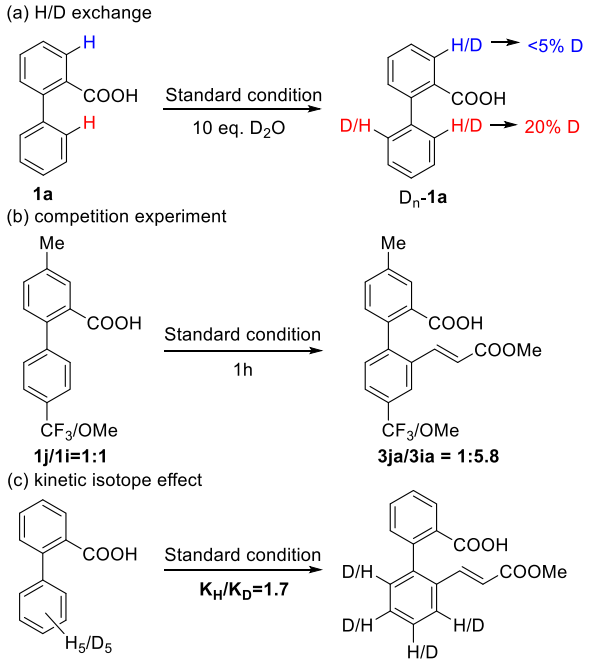


[a]Conditions: **3** (0.1 mmol), NIS (0.4 mmol), and K_2CO_3 (0.1 mmol) at 100 °C in 0.5 mL of CH_3CN for 12 h. Isolated yields.

suppress this transformation, probably due to a strong steric effect of the δ'-substituent, giving the desired methyl phenates (**7b**) in 27% yield. This transformation offers a new protocol for the preparation of multisubstituent phenanthrenes, with much more available aromatic carboxylic acids and olefins as starting materials.

To investigate high site selectivity for the δ'-C(sp^2)−H bond, a combination of different techniques was conducted. First, H/D exchange experiments were performed in heavy water, D_2O. The deuteration reaction of **1a** mainly occurs at the δ'-C(sp^2)−H bond (*D*, 20%), while a trace amount of deuterated product was detected at the β-position (*D*, <5%) (Scheme 5a). This result showed that under our optimized reaction conditions the activation process of the δ'-C(sp^2)−H bond is favorable and faster over that of the β-C(sp^2)−H bond. This is consistent with the selectivity of δ'-C−H metalation and functionalization because of the more electron-rich δ'-C center. Furthermore, an intermolecular competition experiment was conducted to examine the electron-rich substrate **1i** and its electron-deficient counterpart **1j**. The higher yield for **1i** than for **1j** highlights the fact that electron-rich substrates are inherently more reactive, implying that the δ'-C−H

Scheme 5. Mechanistic Studies



activation step proceeds via a facile base-assisted internal substitution-type C−H activation process (Scheme 5b). Moreover, one-pot competitive reaction between **1a** and **d5−1a** proves the significant kinetic isotope effect, which indicates that the δ'-C(sp^2)−H bond cleavage may be the limiting step (Scheme 5c).

Then, density functional theory (DFT) was performed to further understand the unconventional δ'-selectivity. First, two possible pathways were proposed to reveal the origin of selectivity (Figure 1). The activation free energy (AFE) of δ'-C−H bond cleavage assisted by the carboxylic acid is 24.4 kcal/mol, lower than that of the β-C−H metalation pathway (30.7 kcal/mol). This implies that the formation of the 7-membered palladacycle is a kinetic favorable process, which is consistent with the selectivity of experimental results. Second,

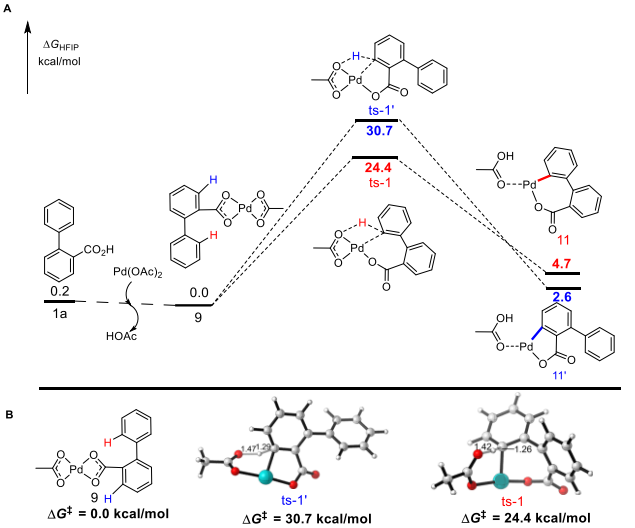


Figure 1. DFT-computed relative Gibbs free energy profiles of C−H functionalization step transition states.

https://dx.doi.org/10.1021/acs.orglett.0c01208
Org. Lett. XXXX, XXX, XXX−XXX

the AFE of the δ'-C−H bond cleavage is the highest, implying the δ'-C−H activation is the rate-determining step in this transformation, which is in agreement with the experimental results (Scheme S6).

In conclusion, we have realized carboxylic acid remote C−H functionalization to obtain δ'-olefinated carboxylic acids by rational design of biphenylcarboxylic acid with two competing C(sp^2)−H sites. Moreover, the reaction has the advantages of broad substrates, good functional group tolerance, and excellent regioselectivity. The principle of using acidic conditions to promote the electrophilicity of palladium catalyst is the key to achieve high regioselectivity of this reaction. Mechanism investigation and DFT calculations clarify the remote site selectivity, originating from a kinetically favorable seven-membered palladacycle. More interestingly, under sequential site selectivity control, it is convenient to transform to phenanthrene through decarboxylative C−H transformation, which offers a new strategy for sequential construction of multisubstituted aromatic polycyclic compounds commonly found in natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01208.

Detailed experimental procedures and compound characterization data (PDF)

Accession Codes

CCDC 1981706 and 1981722 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National NSF of China (Grant 21525101), the NSF of Hubei Province (Grants 2018CFB156 and 2017CFA006), the Program of Ministry of Education Key Laboratory for the Synthesis and Application of Organic Functional Molecules (Grant KLSAOFM1702), and the BAGUI talent program and the NSFGX (Grants 2019AC26001 and 2017GXNSFDA198040) for their financial support. M.K. is funded by the CNRS-France.

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https://dx.doi.org/10.1021/acs.orglett.0c01208
Org. Lett. XXXX, XXX, XXX−XXX