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Palladium-Catalyzed Proaromatic C(Alkenyl)−H Olefination: Synthesis of Densely Functionalized 1,3-Dienes

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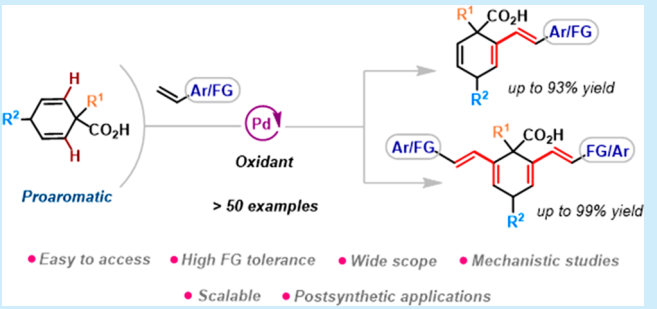
ABSTRACT: An example of proaromatic C(alkenyl)−H olefination is reported. This protocol utilized a free carboxylic acid as a directing group for C(alkenyl)−H activation of 1,4-cyclohexadiene and coupled with various alkenes. Direct and sequential bisolefinations of proaromatic acids were achieved. The synthetic applicability has been exhibited by [4 + 2] cycloaddition and decarboxylative aromatization of the resulting proaromatic 1,3-dienes. Additionally, several kinetic studies also have been carried out to elucidate the reaction mechanism.



Direct C(sp^2)−H functionalization has the advantage of providing access to a complex scaffold from simple building blocks.[1] Although the past decade has seen many achievements in aromatic and alkene C−H activation, C−H activation of the proaromatic system remains elusive. Proaromatics are found in high-value material science.[2] The C−H activation of proaromatics is highly desirable but remains undeveloped. Major pitfalls in the proaromatic system, such as 1,4-cyclohexadiene, are ring strain, tendency to aromatize, and an allylic C−H bond cleavage.[3] Therefore, the C(sp^2)−H functionalization of 1,4-cyclohexadiene has rarely been realized (Scheme 1a). The reaction design of the 1,4-cyclohexadiene ring by introducing a directing group and two additional substituents at the 1,4-position is of benefit to C(sp^2)−H functionalization and prevention of side reactions (Scheme 1b), allowing synthesis of synthetically valuable conjugated 1,3-dienes which can serve as a promising scaffold in biomedical and material sciences.[4]

The realization of C(alkenyl)−H functionalization to access molecular complexity and diversity has been attributed to a significant strategy of introducing an exogenous directing group.[5] However, this method is complex with its multiple steps in prefabrication of the directing group and extirpation of it after functionalization. By contrast, utilization of free carboxylic acid without an exogenous directing group for C−H functionalization is a straightforward method to facilitate C−H activation in a step-economical manner.[6] Numerous studies have demonstrated that free carboxylic acid can be efficiently used as a directing group for C(aryl)−H and C(alkyl)−H functionalization.[7,6h] However, the development of C(alkenyl)−H functionalization using free carboxylic acid as a directing group, particularly in proaromatics, still under investigation.

Scheme 1. Overview, Reaction Design, and Proaromatic C(Alkenyl)−H Olefination

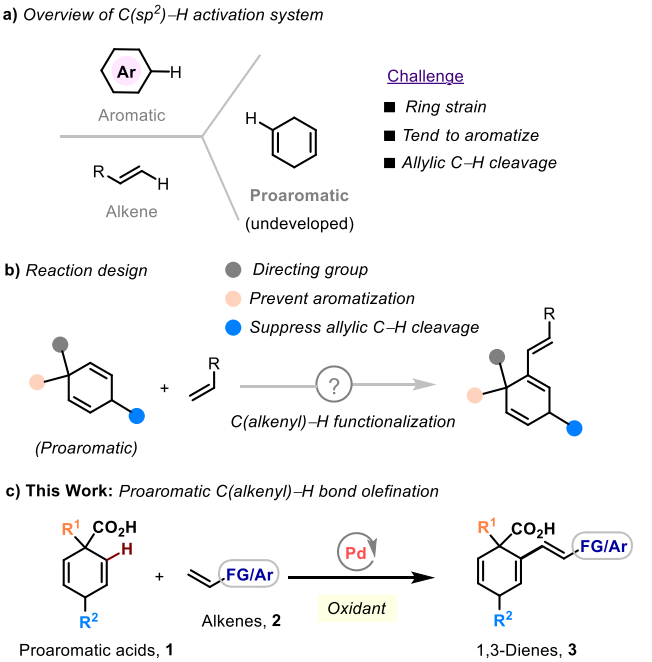


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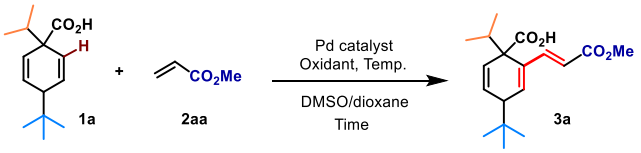
Table 1. Optimization of the Pd-Catalyzed C(Alkenyl)−H Olefination of Proaromatic Acids[a]



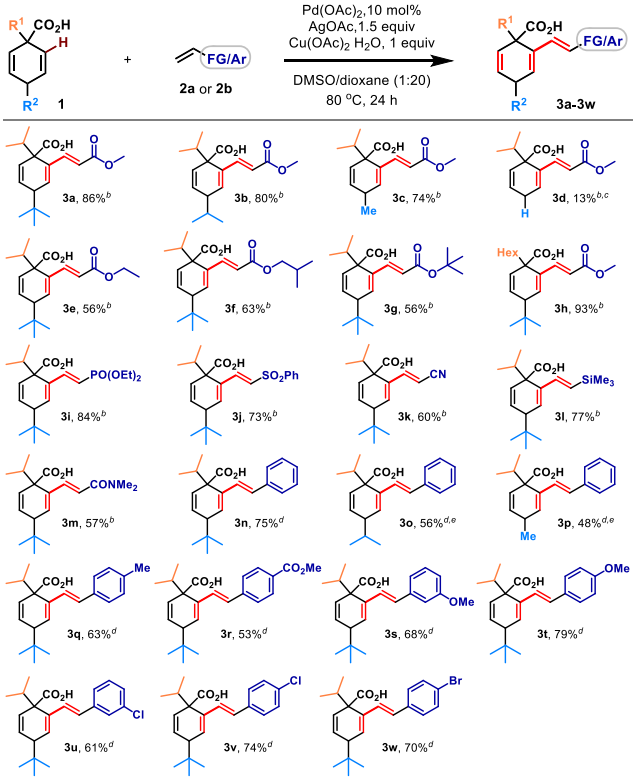
entry	Pd (mol %)	oxidant (equiv)	t (h)	T (°C)	3a (%)[b]
1	$Pd(OAc)_2$ (10)	AgOAc (3)	48	50	75
2	$Pd(OAc)_2$ (10)	AgOAc (1.5)	48	50	74
3	$Pd(OAc)_2$ (5)	AgOAc (1.5)	48	50	52[c]
4	$Pd(OAc)_2$ (10)	AgOAc (1)	48	50	40[c]
5	$Pd(OAc)_2$ (10)	AgOAc (1.5), $Cu(OAc)_2 \cdot H_2O$ (1)	48	80	51[d]
6	$Pd(OAc)_2$ (10)	AgOAc (1.5), $Cu(OAc)_2 \cdot H_2O$ (1)	24	80	86
7	$Pd(OAc)_2$ (10)	AgOAc (1.5), $Cu(OAc)_2 \cdot H_2O$ (1)	24	50	35[c]
8	$Pd(OAc)_2$ (5)	AgOAc (1.5), $Cu(OAc)_2 \cdot H_2O$ (1)	24	80	66[c]
9	$Pd(TFA)_2$ (10)	Ag_2CO_3 (1.5), $Cu(OAc)_2 \cdot H_2O$ (1)	1	120	75[e]

[a]Reaction conditions: **1a** (0.12 mmol), **2aa** (0.1 mmol) in 2 mL of solvent (DMSO/dioxane = 1:20). [b]Isolated yield. [c]Recovery of **1a**. [d]Decarboxylative aromatization of **3a** was observed. [e]Trace amount of bisolefination was observed.

Previously, we and Studer's group have individually reported that proaromatic acids **1** initially underwent Pd-catalyzed carboxylate-directed C(alkenyl)−H olefination with alkenes **2** using Ag(I) or TEMPO as an oxidant followed by tandem decarboxylative aromatization. As a result, the in situ generated C−H olefinated 1,3-dienes **3** experienced complete loss of its proaromaticity leading to the formation of *ortho*-alkylated vinylarenes.[8] We envisioned that it would be more attractive if a complementary approach could be established to inhibit the decarboxylative aromatization enabling synthetically more valuable 1,3-dienes. Weak coordination of the carboxylate group, deactivation by transition metals and oxidants, reactive alkene π-chelation, ring instability, regain of aromaticity, and unbidden reactions of the π-bond with oxidants are crucial in C(alkenyl)−H activation of proaromatic carboxylic acids **1**. Herein, we report a palladium-catalyzed unprecedented proaromatic C(alkenyl)−H activation for direct C(alkenyl)−H olefination. In addition, this protocol can also be used for the bis- and sequential C(alkenyl)−H olefination process. Notably, our protocol also prevents the deterioration of functionalized carboxylic acid through an intramolecular cyclization[9] and maintains the proaromatic 1,3-diene scaffold for further synthetic transformations.

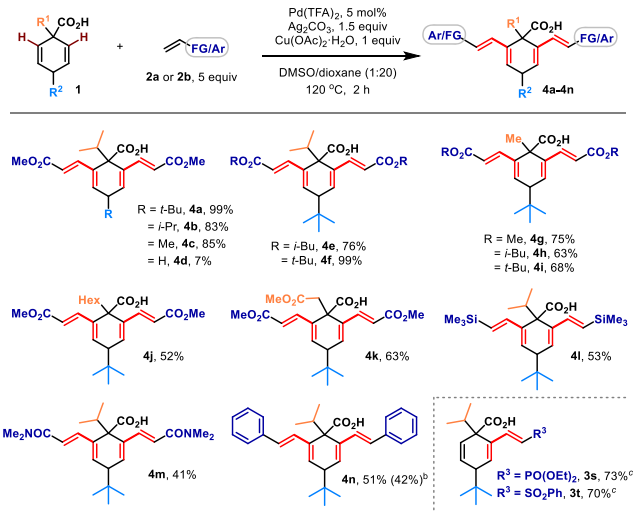
In our previous work, we have found olefinated 1,3-diene **3** underwent decarboxylative aromatization in the conditions of 10 mol % of $Pd(TFA)_2$ and 3 equiv of Ag_2CO_3 at 120 °C.[8a] A mild catalytic system needed to be established to suppress decarboxylative aromatization. Initial studies on the reaction of 4-(*tert*-butyl)-1-isopropylcyclohexa-2,5-diene-1-carboxylic acid (**1a**) with methyl acrylate (**2aa**) were investigated, and reaction parameters were optimized under various conditions (Table 1). After extensive screening, 10 mol % of $Pd(OAc)_2$, 1.5 equiv of AgOAc, and 1 equiv of $Cu(OAc)_2 \cdot H_2O$ at 80 °C in DMSO/dioxane for 24 h was found to have the highest yield of the olefinated product **3a** at 86% (entry 6).

Scheme 2. Palladium-Catalyzed C(Alkenyl)−H Olefination of Proaromatic Acids[a]



[a]Reaction was conducted with **1** and functionalized alkenes **2a** or styrene derivatives **2b**. [b]**1** (1.2 equiv), **2a** (1.0 equiv). [c]$Pd(OAc)_2$ (10 mol %), AgOAc (1.5 equiv) at 50 °C, 48 h. [d]**1** (1.0 equiv), **2b** (1.5 equiv), AgOAc (1.5 equiv), $Pd(OAc)_2$ (20 mol %), DMSO/dioxane (1:20) at 120 °C for 48 h. [e]The reaction was performed at 60 °C.

Scheme 3. Palladium-Catalyzed C(Alkenyl)−H Bisolefination of Proaromatic Acids[a]



[a]Reaction was conducted with **1** and functionalized alkenes **2a** or styrene derivatives **2b**. [b]Yield of mono-olefinated product. [c]Only mono-olefinated product was observed.

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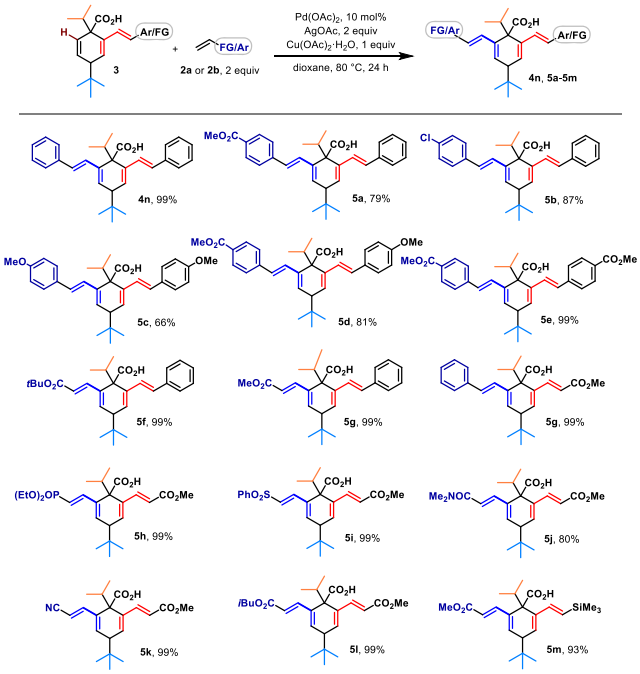
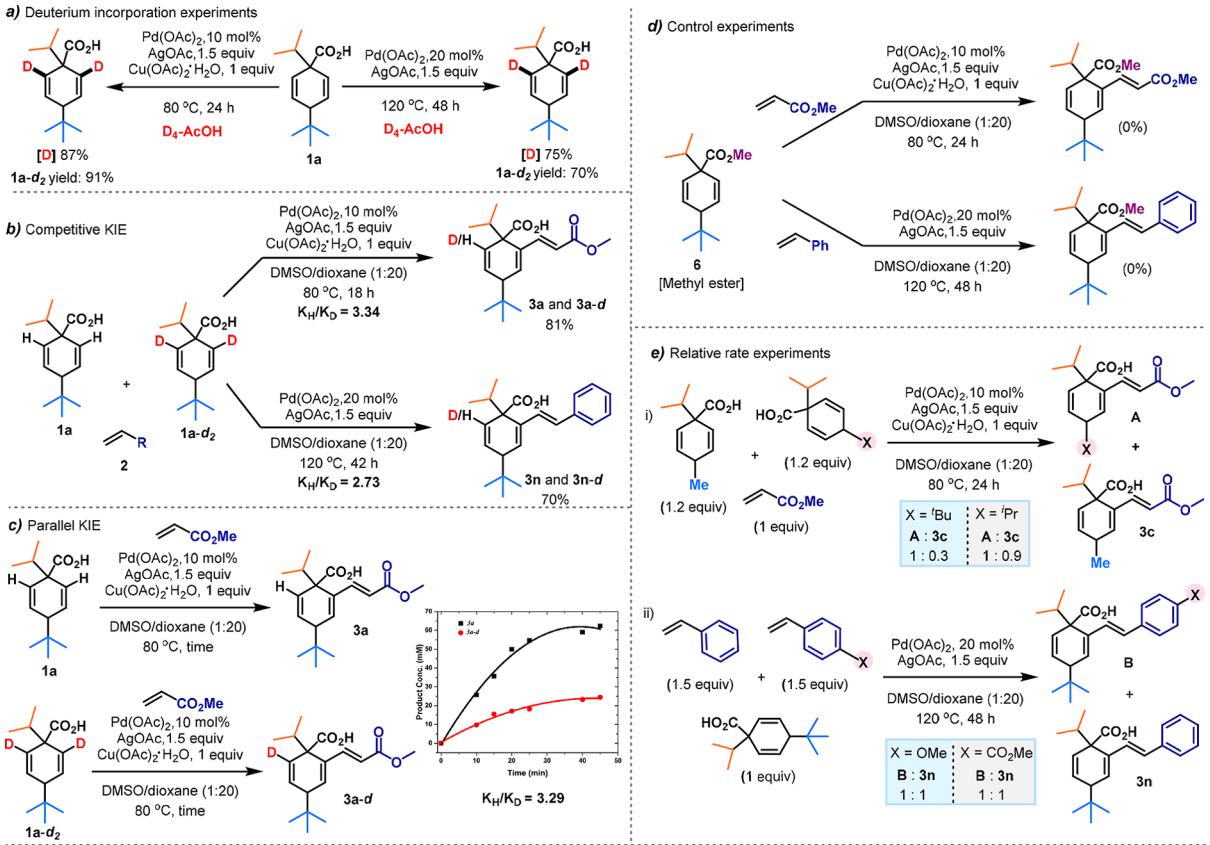
Scheme 4. Palladium-Catalyzed Sequential C(Alkenyl)−H Bisolefination of Proaromatic Acids[a]



[a]Reaction was conducted with mono-olefination products **3** and alkenes **2a** or **2b**.

With the optimized conditions in hand, we investigated the scope of various proaromatic acids with methyl acrylate **2aa** (Scheme 2). Proaromatic acids containing 4-*tert*-butyl, 4-isopropyl, and 4-methyl reacted well with acrylate to afford olefinated products in 74−86% yields (**3a**−**3d**). The efficiency of the interior methylene proaromatic acid was limited (**3d**, 13%), even at low temperature. We found that the poor efficiency of C(alkenyl)−H olefination was due to the rapid decarboxylative aromatization of the proaromatic acid. Ethyl, isopropyl, and *tert*-butyl acrylates were well-tolerated under the present reaction conditions to give moderate yields (**3e**−**3g**). The α-long chain produced a high yield (**3h**). Diethyl vinyl phosphonate, phenyl vinyl sulfone, and acrylonitrile reacted smoothly and produced desired olefinated products in good yields (**3i**−**3k**). Trimethyl vinyl silane and *N*,*N*-dimethyl acrylamide were also compatible with the reaction conditions, providing the resultant products in moderate yields (**3l** and **3m**). We next investigated the scope by varying the alkene derivatives to styrenes. The optimal reaction conditions for styrene derivatives (**2b**) were also studied, and we found that using 20 mol % of $Pd(OAc)_2$, 1.5 equiv of Ag(OAc) at 50 °C for 48 h gave the satisfactory result (see Table S1 in Supporting Information for details). Scope of various styrene derivatives with proaromatic acids **1** were then examined (Scheme 2). 4-Substituted proaromatic acids **1** generated olefinated products with styrene in moderate to good yields (**3n**−**3p**). *Para*-methyl or -methylester styrenes had reasonable yields (**3q** and **3r**). *Meta*- or *para*-methoxy-substituted styrenes

Scheme 5. Mechanistic Studies[a]



[a](a) Deuterium incorporation experiments. (b) Competitive KIE experiments. (c) Parallel KIE Experiments. (d) Control experiments. (e) Relative rate experiments.

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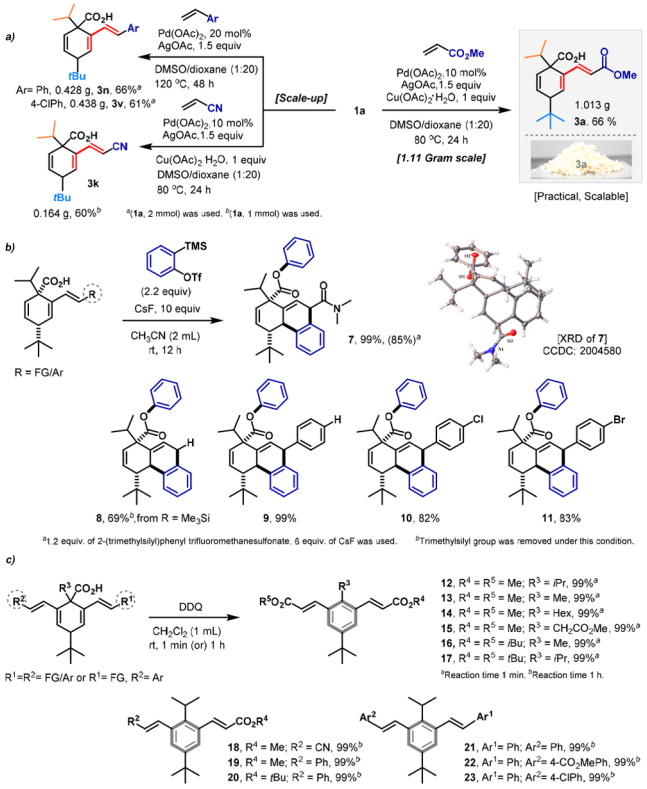
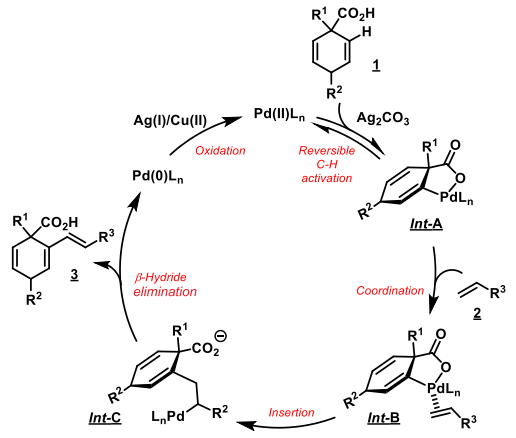
Scheme 6. Synthetic Utilities



[a]Scale-up and practical gram-scale. Postsynthetic transformations. [b][4 + 2] cyclization. [c]Decarboxylative aromatization.

Scheme 7. Proposed Mechanism



led to good yields (**3s** and **3t**). It is worth mentioning that halide-containing styrenes such as chloro and bromo also performed well under the reaction conditions (**3u**−**3w**).

C(alkenyl)−H bisolefination was also achieved with slight modification of optimum reaction conditions (see Table S2 in Supporting Information for details). Bisolefination of proaromatic acids was investigated with a range of proaromatic acids and functionalized alkenes (Scheme 3). Different proaromatic acids with methyl acrylate produced bisolefinated products in good yields (**4a**−**4c**). Again, methylene proaromatic acid was ineffective (**4d**).

Isopropyl and *tert*-butyl acrylates generated products in good yields (**4e** and **4f**). *α*-Methyl, *α*-hexyl, and *α*-methylene ester-bearing acids proceeded well with various functionalized alkenes (**4g**−**4k**). Trimethyl vinyl silane and *N*,*N*-dimethyl acrylamide were well tolerated (**4l** and **4m**). However, styrene afforded both mono- and bisolefinated products, whereas diethyl vinylphosphonate and phenylvinylsulfone yielded only mono-olefinated products under the present reaction conditions.

We have investigated the efficiency of the carboxylate directing group of sterically crowded mono-olefination products in the sequential bisolefination process (Scheme 4). The optimal reaction conditions were also studied, and it was found that using 10 mol % of $Pd(OAc)_2$, 2 equiv of Ag(OAc), and 1 equiv of $Cu(OAc)_2{\cdot}H_2O$ at 80 °C in dioxane for 24 h gave the quantitative yield (see Table S3 in Supporting Information for details). From mono-olefinated styrene, both symmetrical and unsymmetrical bisolefinated products were afforded in good to excellent yields (**4n**, **5a**−**5e**). Similarly, with acrylates, desired products were obtained in excellent yields (**5f** and **5g**).

Mono-olefinated ester was well compatible with styrene (**5g**), diethyl vinyl phosphonate (**5h**), phenyl vinyl sulfone (**5i**), *N*,*N*-dimethyl acrylamide (**5j**), acrylonitrile (**5k**), and isobutyl acrylate (**5l**) resulting in excellent yields. Mono-olefinated silane was also compatible with methyl acrylate and delivered the product **5m** in excellent yield.

Mechanistic studies were performed to gain insights into the proaromatic C(alkenyl)−H olefination (Scheme 5). The reversibility experiment was conducted in the presence of D_4-AcOH, and a higher level of deuterium incorporation was found at both proximal positions (**1a**-d_2), suggesting that the C(alkenyl)−H activation is a reversible process (Scheme 5a). Kinetic isotope effect experiments revealed that C(alkenyl)−H activation of the proaromatic acid is the rate-determining step (Scheme 5b, c). Moreover, **6** was subjected to standard conditions; an ester did not confer to carboxylate palladacycle and failed to deliver the product. This highlights the crucial involvement of carboxylic acid in the palladacycle for proaromatic C(alkenyl)−H activation (Scheme 5d). Relative rate experiments were conducted for carboxylic acids and alkenes (Scheme 5e). In the reaction event of different steric hindrance substituents at the 4-position of acids, the *β*-H elimination was analogous and the competition of C(alkenyl)−H bond activation and decarboxylative aromatization was solely influenced by electronic and steric properties. The results implied that C(alkenyl)−H activation highly favored *tert*-butyl substituents. Similarly, the C(alkenyl)−H bond activation was identical in several electronically varied styrenes, but *β*-H elimination was influenced by electronic properties. Results demonstrated that electronic bias on the styrene ring could not influence *β*-H elimination.

The proaromatic C(alkenyl)−H olefination is practically applicable and amenable to scale up and use for gram-scale synthesis without any modification of reaction conditions (Scheme 6a). We also demonstrated the postsynthetic applications of olefinated cyclic carboxylic acids. Mono-olefinated acids reacted well with *o*-silyl aryl triflates through *O*-arylation of the acid followed by [4 + 2] cycloaddition, which directly provides multiple rings of cyclic aryl ester products **7**−**11** in good yields. The trimethylsilyl group was detached, and the product **8** was obtained with a 69% yield. Moreover, in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, bisolefinated acids underwent decarboxylative aromatization quantitatively and readily converted into alkylated divinylbenzene derivatives **12**−**23**, which also

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represents an important class of compounds in organic chemistry and materials science[10] (Scheme 6b, c).

Scheme 7 illustrates a proposed catalytic cycle for this Pd-catalyzed proaromatic C(alkenyl)−H olefination. Initially, proaromatic acid **1** weakly coordinates with Pd(II), followed by a reversible C(alkenyl)−H bond activation, leading to formation of a proaromatic five-membered *exo*-palladacycle *Int*-**A**. Subsequent alkene coordination to ***Int*-B** occurs, which is followed by a 1,2-migratory insertion to give *Int*-**C**. β-H elimination provides an olefinated product **3** and Pd(0) species. Pd(II) is regenerated by the oxidant from Pd(0), thus completing the catalytic cycle.

In summary, we have developed an efficient method of proaromatic C(alkenyl)−H olefination that allows the synthesis of highly substituted 1,3-dienes. This method is compatible with a wide range of electron-rich, -neutral, and -deficient alkenes. This approach is straightforward, convenient, scalable, practical, and atom-economical and has high functional group tolerance. Direct and sequential bisolefinations of proaromatic acids were also achieved. Functionalized proaromatic acids were employed to expand synthetic diversifications. This study advances the C−H activation to a new arena of the proaromatic system, which may govern wide synthetic applications in the near future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02241.

Experimental procedures, characterization data, NMR spectra, crystallographic data (PDF)

Accession Codes

CCDC 2004580 contains 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.

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