Letter

Synthesis of Highly Substituted Arenes via Cyclohexadiene–Alkene C–H Cross Coupling and Aromatization

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Synthesis of Highly Substituted Arenes via Cyclohexadiene–Alkene C–H Cross Coupling and Aromatization

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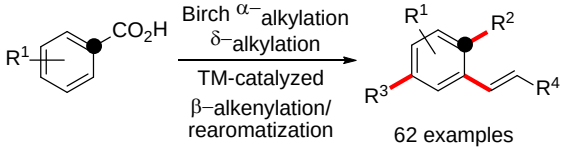
Supporting Information Placeholder

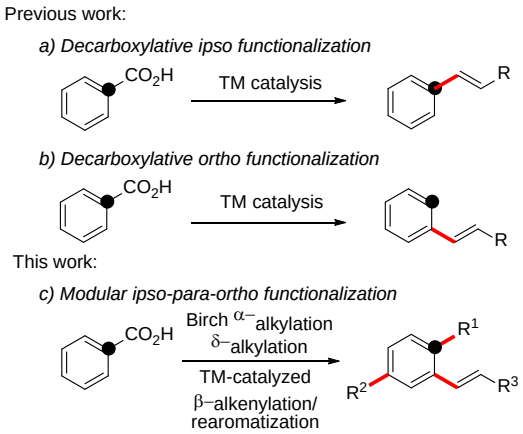
ABSTRACT: The development of a cross-coupling method for the regioselective β-alkenylation of 2,5-cyclohexadiene carboxylic acid derivatives to form ortho-alkenylarenes through in situ decarboxylation and aromatization is described. The carboxylic acid functionality is used as a traceless directing group for efficient and mild β-alkenylation. The modular sequence comprises a reductive Birch α-alkylation, ionic δ-alkylation followed by a Pd-catalyzed decarboxylative β-alkenylation with subsequent aromatization resulting in an overall threefold ipso-para-ortho functionalization of readily accessed benzoic acid derivatives. Efficient synthesis of various alkyl-alkenylarenes under mild conditions in moderate to excellent yields is presented.



KEYWORDS: *palladium catalysis, C–H activation, decarboxylation, aromatic substitution, synthetic methods*

Highly substituted arenes are versatile reagents and valuable targets in synthetic chemistry.[1] Transition-metal-catalyzed C–H functionalization of aromatic rings has been intensively studied to access multi-substituted arenes[2] and direct arene C–H alkenylation to provide styrene derivatives has been in focus.[3] Considering transition-metal catalysis, arene alkenylation is generally conducted by the Heck reaction,[4] where a stoichiometric amount of an organometallic reagent, organohalide or pseudohalide is required. Alternatively, the direct Pd(II)-catalyzed Fujiwara-Moritani coupling of arenes with activated alkenes offers an atom economical route to styrenes.[5] However, by applying a direct arene C–H functionalization strategy the regioselectivity problem arises.

As a solution, the use of a directing group assisting selective cleavage of the proximal arene C–H bond allows for highly selective *ortho* functionalization.[6a-d] Directing groups leading to selective *meta* or *para* functionalization have also been introduced.[6e-h] However, installation and detachment of the directing group require extra steps. In this context, the carboxylic acid functionality has proved to be an efficient directing group.[7] The acid functionality can be traceless removed by protodecarboxylation[8] or alternatively be used for generation of aryl metal intermediates resulting in *ipso*-substitutions. In 2002, Myers disclosed Pd-catalyzed decarboxylative Heck-type olefination of aromatic acids (Scheme 1a).[9a] This seminal work has fostered further studies and Gooβen reported Cu-catalyzed decarboxylative coupling between aromatic acids and aryl halides or triflates to form biaryls.[9b] Daugulis disclosed Pd-catalyzed *ortho* C–H arylation of aromatic acids using the carboxylic acid functionality as a traceless directing group.[10a] *Ortho* arylation of aromatic acids have also been investigated by Gooβen,[10b] Zhang,[10c] Larrosa,[10d] Su[10e] and Miura developed an efficient Rh-catalyzed *ortho* alkenylation of aromatic acids (Scheme 1b).[11] However, in all these processes protodecarboxylation is not achieved during C–H functionalization. Decarboxylation requires high temperature, a stoichiometric amount of Cu(II) or Ag(I) salt as an oxidant and undesired side products such as *ortho,ortho'* bisfunctionalized carboxylic acids are formed prior to decarboxylation. Therefore, the development of an efficient method for regioselective *ortho* alkenylation directed by the acid functionality that is efficiently removed *in situ* after C–H functionalization under mild conditions is still highly desirable.



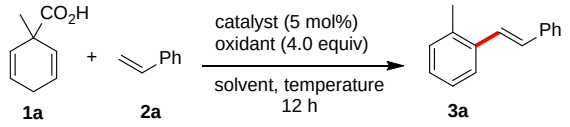
Scheme 1. Transition-metal catalysed decarboxylative alkenylation.

Our recent efforts revealed that 2,5-cyclohexadiene carboxylic acids undergo Pd-catalyzed decarboxylative γ-arylation with aryl iodides.[12a-b] The same reactivity was found for acyclic analogs[12c] and was applied to the total synthesis of resveratrol-

based natural products, macheriols, and THC.[12d-e] We envisaged that the carboxylate group in 2,5-cyclohexadien-1-carboxylic acids can act as a traceless directing group for Pd-catalyzed β-alkenylation with subsequent decarboxylative oxidative aromatization to afford *ortho*-alkenylarenes (Scheme 1c). Notably, the starting 2,5-cyclohexadiene carboxylic acids are easily prepared through alkylative Birch reduction which allows to introduce the *ipso* R¹-substituent into the starting benzoic acid core.[13] Moreover, such acids are readily alkylated at the δ-position to access 1,4-dialkylcyclohexa-2,5-diene-1-carboxylic acids,[12b] addressing the *para* position (R²-substituent) of the initial benzoic acid core structure and the decarboxylative cross coupling eventually installs the third substituent, thereby also regenerating the parent arene structure. We show herein that this modular sequence offers an efficient route to the regioselective threefold *ipso-para-ortho* substitution of various aromatic acids.

We first focused on the *ipso-ortho* disubstitution of benzoic acid. The acid **1a** was readily prepared by reductive Birch methylation of benzoic acid with NH_3, Li, and iodomethane.[13] For *ortho* alkenylation, **1a** was treated with styrene in the presence of 5 mol% $Pd(TFA)_2$ and Ag_2CO_3 (4.0 equiv) in a DMSO/DMF solvent mixture at 110 °C for 12 h and the targeted **3a** was formed in 31% yield (Table 1, entry 1). A similar yield resulted in DMF (Table 1, entry 2), but in DMSO or in toluene **3a** was formed only in traces (Table 1, entries 3 and 4). Oxidant screening in DMF revealed that $Cu(OAc)_2$ and $Cu(OTf)_2$ provide slightly improved yields but O_2 and TEMPO are not suitable oxidants in this solvent (Table 1, entries 5-8). An improved result was achieved with AgOAc affording **3a** in 55% yield (Table 1, entry 9). Replacing $Pd(TFA)_2$ by $Pd(OAc)_2$ led to a significantly reduced yield (Table 1, entry 10).

Table 1. Reaction optimization: alkenylation of 1a with styrene to give 3a[a]

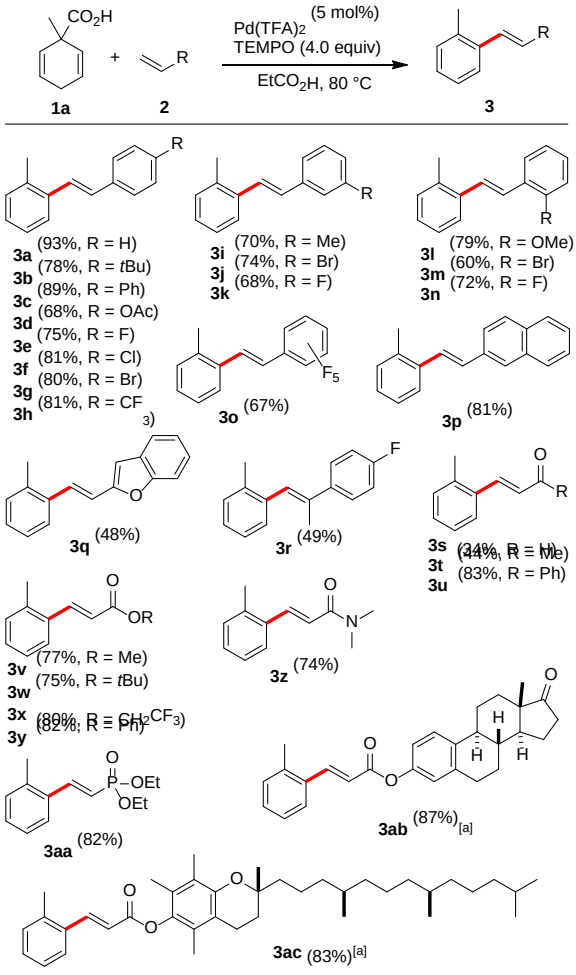


Entry	Catalyst	Solvent	T [°C]	Oxidant	Yield (%)
1	$Pd(TFA)_2$	5% DMSO/DMF	110	Ag_2CO_3	31
2	$Pd(TFA)_2$	DMF	110	Ag_2CO_3	30
3	$Pd(TFA)_2$	DMSO	110	Ag_2CO_3	<5[b]
4	$Pd(TFA)_2$	Toluene	110	Ag_2CO_3	<5[b]
5	$Pd(TFA)_2$	DMF	110	$Cu(OAc)_2$	39
6	$Pd(TFA)_2$	DMF	110	$Cu(OTf)_2$	46
7	$Pd(TFA)_2$	DMF	110	O_2	<5[b]
8	$Pd(TFA)_2$	DMF	110	TEMPO	<5[b]
9	$Pd(TFA)_2$	DMF	110	AgOAc	55
10	$Pd(OAc)_2$	DMF	110	Ag_2CO_3	23
11	$Pd(TFA)_2$	$EtCO_2H$	110	TEMPO	90
12	$Pd(TFA)_2$	$MeCO_2H$	110	TEMPO	80
13	$Pd(OAc)_2$	$EtCO_2H$	110	TEMPO	85
14	*$Pd(TFA)_2$*	*$EtCO_2H$*	*80*	*TEMPO*	*93[c]*
15	$Pd(TFA)_2$	$EtCO_2H$	80	TEMPO	60[d]
16	$Pd(TFA)_2$	$EtCO_2H$	50	TEMPO	12[b]
17	$Pd(TFA)_2$	$EtCO_2H$	80	O_2	<5[b]

[a]Reactions were carried out with **1a** (0.2 mmol), **2a** (0.4 mmol), Cs_2CO_3 (0.22 mmol) in 0.5 mL solvent under argon, Yield of isolated **3a** is given. [b]Yield determined by GC. [c]Reaction performed without Cs_2CO_3. [d]2 mol% $Pd(TFA)_2$ used.

Solvent change to propionic acid in combination with TEMPO as an oxidant increased the yield to 90% (Table 1, entry 11) and a good result was also obtained in acetic acid (Table 1, entry 12).[14] In acidic media, $Pd(OAc)_2$ was again inferior to $Pd(TFA)_2$ (Table 1, entry 13) and the highest yield was obtained upon lowering the reaction temperature to 80 °C to afford **3a** in excellent 93% yield (Table 1, entry 14). These conditions were regarded as optimal since lowering of the catalyst loading, lowering temperature or replacing TEMPO by O_2 led to worse results (Table 1, entries 15-17). Importantly, this process provides selectively mono-alkenylation product **3a** without formation of any detectable amount of the corresponding bis-styrenylated arene. Reaction performed at 5 mmol scale afforded **3a** in 84% yield, documenting the robustness of the novel sequence.

Table 2. Variation of the alkene component



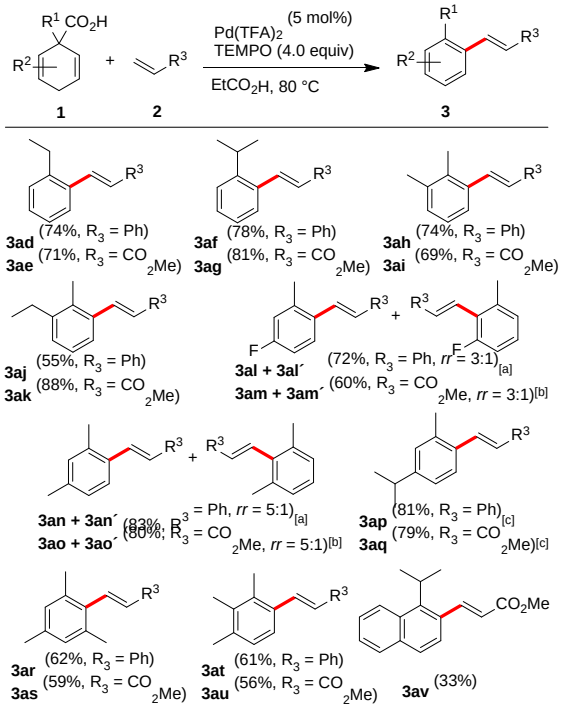
Reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), $Pd(TFA)_2$ (0.025 mmol), propanoic acid (1.5 mL), TEMPO (2.0 mmol), 80 °C, 12 h. [a]**1a** (0.6 mmol) and **2** (0.5 mmol) used.

We next investigated the scope by varying the alkene component (Table 2). Styrene derivatives bearing an electron–donating or withdrawing group at the *ortho*, *meta* or *para* position

of the aromatic ring are tolerated to afford **3a–3n** with complete *E*-selectivity in good to excellent yields. Pentafluorovinylbenzene and 2-vinylnaphthalene gave **3o** and **3p** in reasonable yields and also 2-vinylbenzofuran could be employed (see **3q**). 1,1-Disubstituted styrenes are tolerated (see **3r**). Acrolein, methyl vinyl ketone and phenyl vinyl ketone reacted with **1a** to the alkenylated products **3s–3u** in moderate to good yields. Various acrylates, *N,N*-dimethyl acrylamide and diethyl vinyl phosphonate underwent smooth cross coupling to afford **3v–3aa**. Late stage functionalization of more complex acrylates derived from cholesterol and vitamin E gave **3ab** and **3ac**. Non-activated alkenes, such as 1-decene, did not engage in this sequence.

We next varied the acid component (for acid preparation, see SI). Cross coupling and aromatization worked well on 1-ethyl and 1-isopropyl substituted acids (Table 3, see **3ad–3ag**). The reaction of 1,2-disubstituted acids with styrene and methyl acrylate afforded 1,2,3-trisubstituded arenes **3ah–3ak** in good yields. In case of 1-methyl-3-fluoro-2,5-cyclohexadiene carboxylic acid, two regioisomers were formed with styrene (**3al** and **3al'**) and also with methyl acrylate (**3am** and **3am'**). The sterically less encumbered 1,3,4-trisubstituted regioisomers were formed as major compounds in moderate 3:1 regioselectivity. Selectivity improved to 5:1 upon switching to the 3-methyl-substituted congener (**3an**, **3ao**) and with the bulkier 3-isopropyl-substituted acid, C–H alkenylation occurred with complete regiocontrol (**3ap**, **3aq**). Our method allows preparing tetrasubstituted arenes **3ar–3au** and also a naphthalene carboxylic acid was successfully used as a substrate (**3av**).

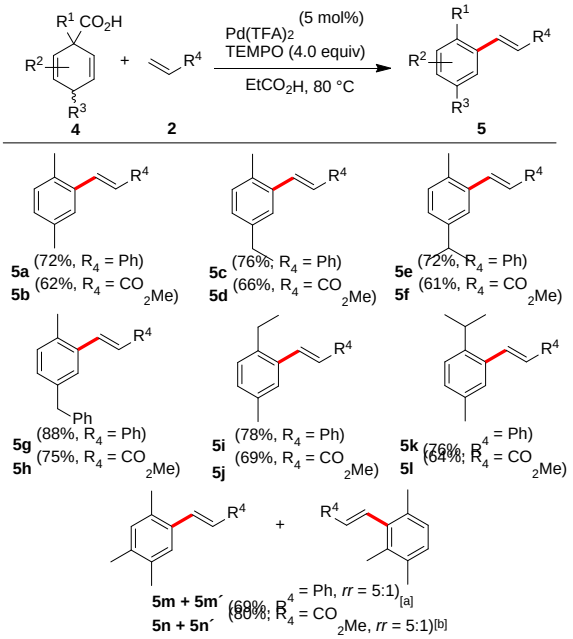
Table 3. Variation of the acids



Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), $Pd(TFA)_2$ (0.025 mmol), $EtCO_2H$ (1.5 mL), TEMPO (2.0 mmol), 80 °C, 12 h. [a]Isolated as mixture of isomers. [b]Major isomer isolated. [c]rr = 20:1.

To achieve threefold *ipso-para-ortho* substitution of benzoic acid derivatives, acids **1** were alkylated at the δ-position to form 1,4-dialkylcyclohexa-2,5-diene-1-carboxylic acid derivatives **4** with moderate to good yields with variable diastereoselectivity by double deprotonation of the acid **1** with *n*-BuLi and TMEDA in THF at -78°C and C-alkylation upon warming to room temperature (see SI).[12b] Importantly, the diastereoselectivity of the δ-alkylation is not of importance since both isomers undergo the rearomatizing *ortho*-alkenylation with similar efficiency. Hence, separation of the two diastereoisomers was not necessary substantially improving practicability of the overall transformation. Reaction with styrene and methyl acrylate worked well on 1,4-dimethyl-2,5-cyclohexadiene carboxylic acid to provide **5a** and **5b** in 72% and 62% yield, respectively (Table 4). Similar yields were noted for the 4-ethyl substituted acid (**5c**, **5d**) and steric effects at the 4-position are not important since the isopropyl-derivatives **5e** and **5f** were isolated in good yields. The modularity of our approach readily allowed varying the R^1 and R^3-substituents (see **5g–5l**). The tetrasubstituted arenes **5m** and **5n** were isolated along with their regioisomers **5m'** and **5n'** with 5:1 selectivity.

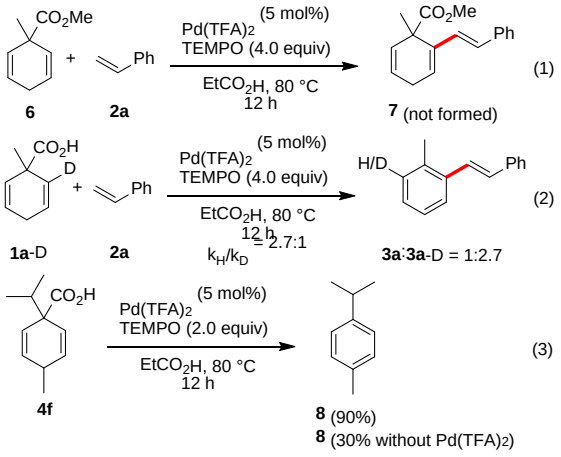
Table 4. Preparation of highly substituted arenes



Reaction conditions: **4** (0.5 mmol), **2** (1.0 mmol), $Pd(TFA)_2$ (0.025 mmol), $EtCO_2H$ (1.5 mL), TEMPO (2.0 mmol), 80 °C, 12 h. [a]Isolated as a mixture of isomers. [b]Major isomer isolated.

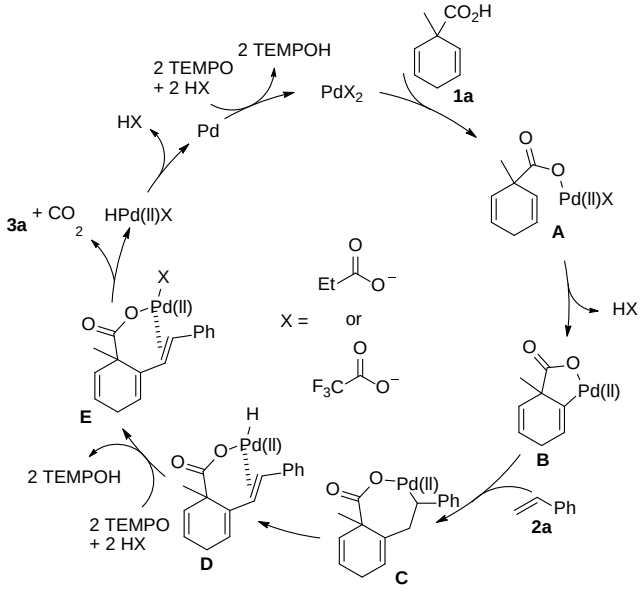
To shed light on the mechanism of this decarboxylative functionalization, additional experiments were conducted (Scheme 2). Oxidative cross coupling of the methyl ester **6** with styrene to give **7** did not work, revealing that the directing acid is crucial for the C–H alkenylation (Scheme 2, eq. 1). The intramolecular kinetic isotope effect in the reaction of **1a-D** with styrene was 2.7:1 indicating that the C–H activation likely occurs via a concerted metalation deprotonation (CMD) mechanism (Scheme 2, eq. 2).[15] To address the decarboxylation rearomatization steps, we reacted **4f** in the absence of styrene and obtained **8** in 90% yield (Scheme 2, eq. 3). Repeating the experiment in the absence of the Pd-catalyst afforded only 30% of **8**, indicating that the Pd salt is likely involved in the

decarboxylation.[16] If the reaction of **1a** with styrene is conducted with only 2 equivalents of TEMPO, **3a** was isolated in 40% showing that C–H alkenylation is slower than the downstream decarboxylation aromatization steps. This is also in line with the fact that we did not identify any double styrenylated arene as a final product.



Scheme 2. Mechanistic studies.

Based on these studies we propose the following mechanism (Scheme 3).[17] The cycle starts with the formation of complex **A**. C–H activation by CMD generates the carbopalladium(II) intermediate **B** followed by insertion of styrene to form **C**, which undergoes β-hydride elimination to afford **D**. Due to the fact that 4 equivalents of TEMPO are required (see above), we assume that TEMPO abstracts a H-atom from the weak Pd–H bond in **D** and the thus generated Pd(I)-complex gets trapped by the second equivalent of TEMPO to generate **E** after ligand exchange with HX. Pd-mediated decarboxylation and aromatization[18] give **3a** and HPd(II)X. HPd(II)X further reacts via α-elimination to Pd(0) that is oxidized by 2 equivalents of TEMPO to give after ligand exchange PdX_2 and 2 TEMPOH.[14]



Scheme 3. Postulated mechanism.

In summary, we have developed a method for highly regioselective *ortho* alkenylation of cyclohexadiene carboxylic acids. The process uses Pd-catalysis and proceeds via selective and rare[19] alkenyl/alkenyl C–H cross coupling followed by oxidative decarboxylation. The starting carboxylic acids are readily prepared by reductive Birch alkylation. The 4-position in these cyclohexadiene acids is easily alkylated using classical ionic chemistry. *Ortho* alkenylation followed by oxidative decarboxylation provide multi-substituted arenes with moderate to excellent yields. This sequential multi-functionalization allows for efficient preparation of highly substituted arenes that are difficult to access by other methods.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

Supporting Information

The supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental procedures and spectral data for all new compounds (PDF).

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