C–H Activation

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Constructing Multiply Substituted Arenes Using Sequential Palladium(II)-Catalyzed C–H Olefination**

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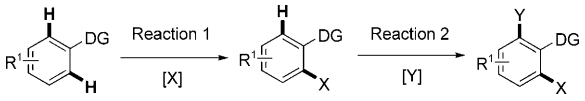
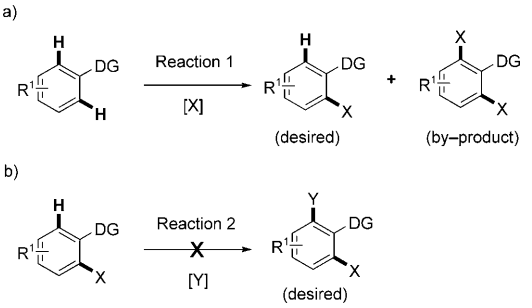
Divinylbenzene derivatives represent an important class of molecular building blocks in organic chemistry and materials science.[1,2] Therefore, their synthesis has been an active area of research.[2] Indeed, shortly after the initial reports describing Pd^0-catalyzed haloarene/olefin coupling (the Mizoroki–Heck reaction),[3] Plevyak and Heck disclosed an example of divinylation of *ortho*-dibromobenzene.[4] Since that time, Heck and co-workers, as well as others, have studied differential olefination of arenes containing two different halides (or pseudohalides) to synthesize unsymmetrical divinylbenzenes.[5,6]

In light of the recent advances in Pd^{II}-catalyzed C(aryl)–H functionalization reactions,[7] including those that directly couple C(aryl)–H bonds and olefins,[8–17] an exciting method for divinylbenzene synthesis would be to use an arene substrate containing a synthetically versatile directing group (DG)[7c] and perform sequential olefination of both *ortho*-C–H bonds (Scheme 1). In this way, two different alkenes could be expediently introduced in a position-selective fashion to form valuable 1,2,3-trisubstituted products,[18] thereby obviating the complications associated with preparing dihaloarene starting materials.



Scheme 1. Sequential directed C–H functionalization. DG = directing group

However, generally speaking, methods for sequential, directed *ortho*-C–H activation with Pd^{II} remain underdeveloped[19,20] owing to problems rooted in both selectivity and reactivity (Scheme 2). In terms of selectivity, a major challenge lies in forming the monofunctionalized product in high yield without functionalizing the second *ortho*-C–H bond to give the difunctionalized by-product. Strategies to avoid this problem include substituting the *ortho* or *meta* positions to block the second C–H insertion, lowering the reaction temperature or time to suboptimal levels, or using reduced equivalents of one of the reactants. However, these maneuvers often lead to limited substrate scope or compromised yields. Similarly, achieving suitable reactivity can also be problematic. For instance, if the first new group is sterically bulky, the substrate's binding affinity for Pd^{II} can be attenuated. Alternatively, if the first new group is electron-withdrawing (e.g., halogen, olefin, or carboxylate), it can deactivate the aromatic ring for the second C–H activation step. Lastly, the original directing group and the newly installed functional group can coordinate to Pd^{II} in a bidentate fashion, preventing the catalyst from accessing the second C–H bond.



Scheme 2. The challenges of sequential directed C–H functionalization. a) Poor selectivity. b) Poor reactivity.

Reflecting on these interrelated challenges, we became aware of a need for complementary catalytic systems in which the selectivity/reactivity balance of Pd^{II} could be modulated through coordination of an external ligand. We report herein the realization of this goal in the case of sequential Pd^{II}-catalyzed C(aryl)–H olefination. Furthermore, as part of our research program to develop expedient and versatile C(aryl)–H functionalization techniques, we describe an example of iterative C–H functionalization, wherein one C–H activation reaction installs a directing group for a subsequent C–H functionalization reaction (Scheme 3).

To this end, we began by revisiting our recently disclosed *ortho*-C–H olefination reaction for phenylacetic acids.[14] The original conditions gave good yields and high levels of monoselectivity with electron-rich and electron-neutral substrates. However, when we took a product from this reaction and resubmitted it to the reaction conditions in the presence of a different olefin, we observed a less than 10% conversion of the desired unsymmetrical diolefinated product. Furthermore, we noted that during our original screening studies to

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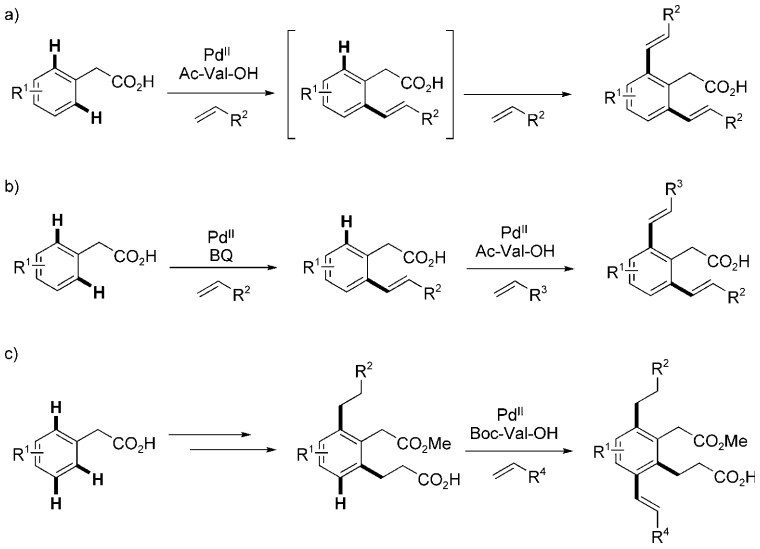


Scheme 3. Outline of this work. a) Improved reactivity: direct diolefination of *ortho*-C–H bonds. b) Combining high selectivity and reactivity: sequential C–H olefination. c) Sequential and iterative C–H olefination to build multiply substituted arenes.

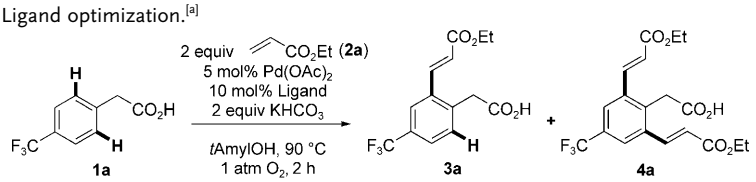
develop the monoselective reaction, we never observed more than 30% of the diolefinated by-product, even as we extensively surveyed different reaction conditions. In light of these findings, we concluded that we faced a problem of low reactivity and needed a more reactive catalyst for the installation of a second olefin.

Encouraged by our recent success in using amino acid ligands[21] to enhance the reactivity of Pd^{II} with electron-deficient substrates,[14] we hypothesized that we could develop a generally applicable diolefination protocol using an optimized amino acid ligand and apply it as the second step in a two-step, sequential olefination procedure. Gratifyingly, we found in our initial screening studies that an array of mono-N-protected amino acid ligands (10 mol%) were highly efficient in promoting diolefination with both electron-poor and electron-rich substrates, such as 4-(trifluoromethyl)phenylacetic acid (**1a**) and 4-methoxyphenylacetic acid (**1b**), fashioning the desired products in quantitative conversion after 48 hours in the presence of ethyl acrylate (**2a**), $Pd(OAc)_2$ (5 mol%), $KHCO_3$ (2 equiv), and *t*AmylOH under O_2 (1 atm) at 90°C.

To determine the optimal ligand, we selected substrate **1a** for screening. Notably, in the absence of amino acid ligands, **1a** was found to give only 13% yield of the mono-olefinated product **3a** after 48 hours. We chose an abridged reaction time of 2 hours to see the comparative kinetic behavior of the ligands. We found that Boc-Val-OH, Ac-Ile-OH, and Ac-Val-OH (Table 1, entries 5, 11, and 12) gave the highest conversion of diolefinated product **4a**. Ac-Ile-OH was found to be the highly active; however, with this ligand the results varied substantially from trial to trial. Ac-Val-OH was found to be the best in terms of activity and reproducibility. Importantly, 1,4-benzoquinone (BQ), which we previously used in our monoselective olefination procedure,[14] was found to decrease the reaction rate. With Ac-Val-OH, increasing the reaction time from 2 hours to 6 hours improved the conversion from 63% to greater than 99% (86% yield of isolated product; entry 18). Importantly, with the reaction time extended to 24 hours, 2 mol% catalyst could also be used to give an 82% yield of **4a** upon isolation.

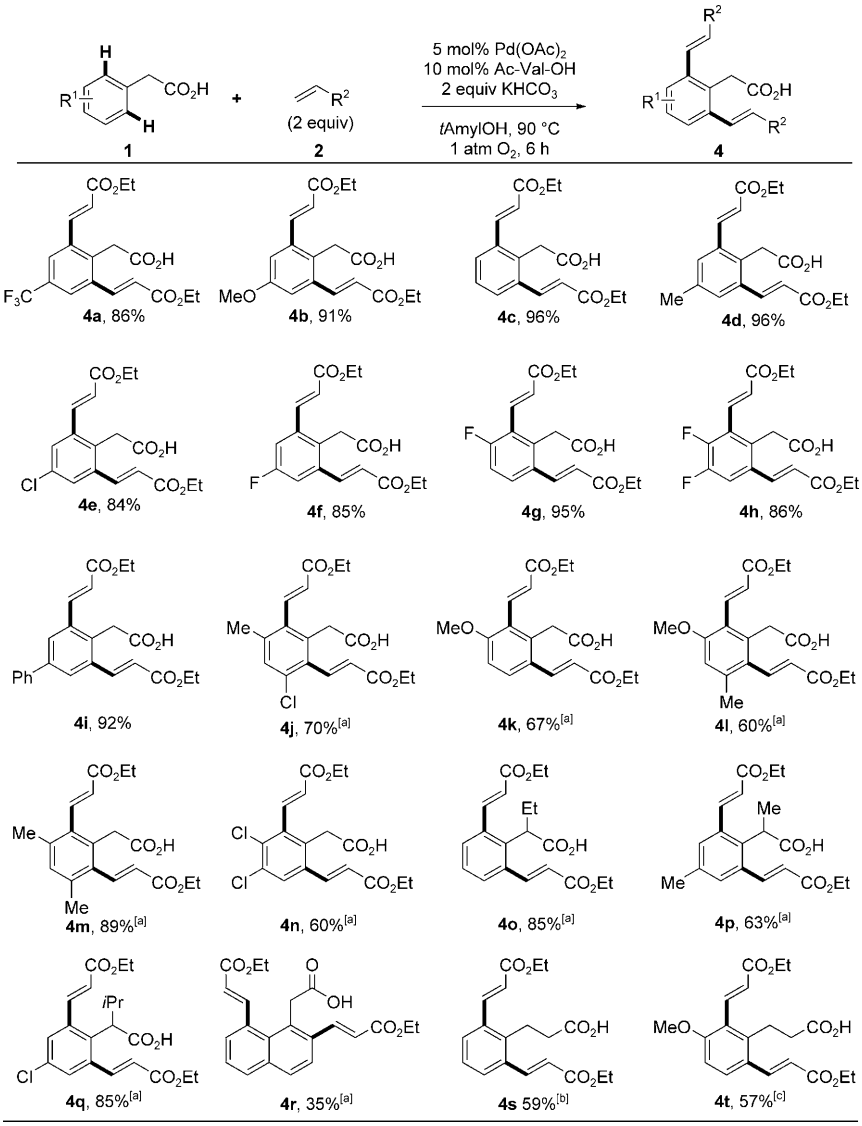
By using these optimized conditions, a wide range of phenylacetic acids (**1**) were converted into the corresponding products (**4**) (Scheme 4). The reaction worked well with electron-rich substrates containing ether and alkyl groups (**4b**, **4d**, **4j**–**4m**, and **4p**) and with electron-poor substrates containing halogen atoms (**4a**, **4e**–**4h**, **4n**, and **4q**). Substrates that contained bulky substitutents at the α position (**4o**–**4q**) or at the position *meta* to the carboxylic acid directing group (**4j**–**4n**) required extended reaction times (48 h), but still generally gave good to excellent yields. 1-Naphthylacetic acid was also found to be a reactive substrate for this reaction (**4r**); although the yield was somewhat low (35%), the second olefination proceeds via an unusual seven-membered cyclopalladated intermediate and represents a unique example of remote C–H activation at the 8-position of a naphthalene ring with a directing group at the 1-position. The reaction was also

Table 1: Ligand optimization.[a]



Entry	Ligand	% 1a	3a	4a	Entry	Ligand	% 1a	3a	4a
1	–	93	7	0	10	Boc-Ser-OH	77	23	0
2[b]	BQ	98	2	0	11[c]	Ac-Val-OH	4	33	63
3[b]	BQ + Boc-Ile-OH	72	27	1	12[c]	Ac-Ile-OH	3	43	54
4	Boc-Ile-OH	24	62	14	13	Ac-Leu-OH	54	43	3
5[c]	Boc-Val-OH	3	62	35	14	formyl-Ile-OH	77	23	0
6	Boc-Leu-OH	11	70	19	15	formyl-Leu-OH	68	31	1
7	Boc-*t*Leu-OH	81	19	0	16	Men-Leu-OH[d]	57	41	2
8	Boc-Ala-OH	25	65	10	17	Men-Val-OH[d]	64	35	1
9	Boc-Phe-OH	47	49	4	18[e]	Ac-Val-OH	0	0	>99 (86)

[a] The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture. [b] 5 mol% BQ used. [c] Average of three trials. [d] Men = (−)-Menthyl(O_2C). [e] Run for 6 h.



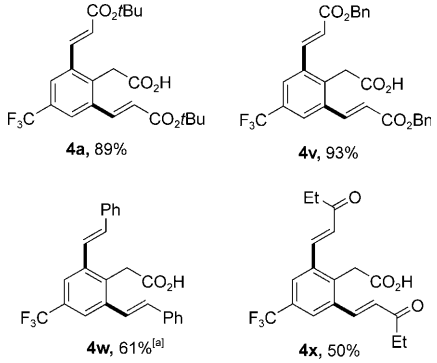
Scheme 4. Substrate scope for Pd^{II}-catalyzed diolefination. The reported yields are of the isolated products. [a] 48 h. [b] 15 mol% $Pd(OAc)_2$, 30 mol% Boc-Val-OH, 96 h. [c] 10 mol% $Pd(OAc)_2$, 20 mol% Boc-Val-OH, 96 h.

4x led to substantial product decomposition. Other olefins, such as vinyl sulfones, vinyl phosphonates, and internal alkenes were unreactive.

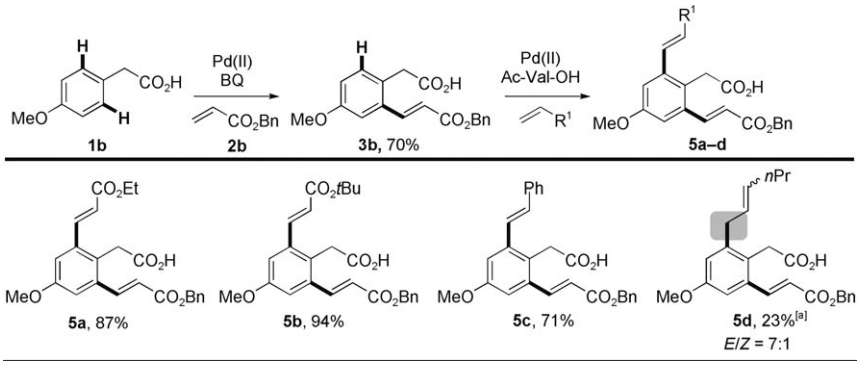
With this robust Pd^{II}-catalyzed diolefination protocol in hand, we returned to our goal of effecting two sequential C–H olefination reactions to install two different alkenes (Scheme 6). We began by using our monoselective C–H olefination reaction,[14] which is compatible with electron-rich and electron-neutral substrates, to couple **1b** and benzyl acrylate (**2b**), giving **3b** in 70% yield (over 2 g prepared). Using this intermediate, we attempted to perform a second olefination reaction with representative alkene coupling partners in the presence of our more active system [Pd^{II}/Ac-Val-OH] catalyst. Gratifyingly, we found that orthogonally protected acrylates could be smoothly coupled to give differentially protected aromatic triacids **5a** and **5b** and that styrene (**2d**) could also be installed in good yield (**5c**). Interestingly, in accordance with our earlier observation,[14] when 1-hexene (**2f**) was used, the unique nonconjugated product **5d** was obtained, thereby representing a formal C–H allylation. The yield of the isolated product was low as a result of the decomposition of the product during the course of the reaction. In principle, virtually all of the substrates used in Scheme 4 could be used for a similar two-step sequence. *meta*-Substituted acids offer another unique element of spatial control because the first olefin selectively reacts away from the substituent.

optimized for hydrocinnamic acids (**4s** and **4t**) (see the Supporting Information). In these cases, Boc-Val-OH was found to be the best ligand. Higher catalyst loadings (10–15 mol%) and extended reaction times (48–96 h) were needed to improve the yield of the products **4s** and **4t**. In nearly all of the cases in Scheme 4 where the yield is below 80%, the remaining starting material had been completely converted into the mono-olefinated product (as evidenced by ^1H NMR analysis of the crude reaction mixture).

Subsequently, different olefin coupling partners were examined (Scheme 5). Several acrylates (**2a–2c**) were found to be highly reactive. Styrene (**2d**) was also found to be a competent coupling partner to give **4w** in 61% yield; however, the reaction required extended time (48 h) and higher Pd loading (10 mol%). Ethyl vinyl ketone (**2e**) was found to be effective, giving 50% yield of **4x** after 6 hours. Attempts to extend the reaction time to improve the yield of



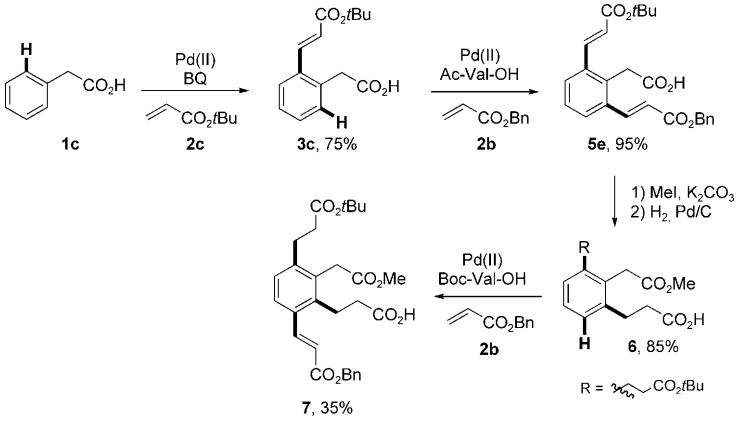
Scheme 5. Olefin scope for Pd^{II}-catalyzed diolefination. Reaction conditions: olefin (2 equiv), $Pd(OAc)_2$ (5 mol%), Ac-Val-OH (10 mol%), $KHCO_3$ (2 equiv), *t*AmylOH, 90°C, 1 atm O_2, 6 h. Reported yields are for the isolated products. [a] 10 mol% $Pd(OAc)_2$, 20 mol% Ac-Val-OH, 48 h.



Scheme 6. Sequential olefination. Reaction conditions (1st step): **2b** (2 equiv), $Pd(OAc)_2$ (5 mol%), BQ (5 mol%), $KHCO_3$ (2 equiv), *t*AmylOH, 90°C, 1 atm O_2, 48 h. Reaction conditions (2nd step): olefin (2 equiv), $Pd(OAc)_2$ (5 mol%), Ac-Val-OH (10 mol%), $KHCO_3$ (2 equiv), *t*AmylOH, 90°C, 1 atm O_2, 6 h. Reported yields are for the isolated products. [a] Used 1-hexene (**2f**; 1 equiv).

The two-step preparation of these advanced unsymmetrical 1,2,3,5-tetrasubstituted arenes demonstrates the power of sequential C(aryl)–H functionalization reactions.

Finally, we sought to explore the possibility of performing iterative C–H functionalization, wherein a newly installed functional group would serve as the directing group for an additional C–H activation (Scheme 7). In particular, we envisioned using sequential olefination to install two different



Scheme 7. Sequential and iterative C–H olefination to synthesize multiply substituted arenes. See the Supporting Information for experimental details.

olefins and then, after functional group manipulations, to use one of the new moieties to direct an additional remote *ortho*-C–H functionalization reaction. To test this idea, we prepared **5e** in good yield using our sequential olefination method (Scheme 7). After methylation and hydrogenation, we obtained highly decorated hydrocinnamic acid **6**. Gratifyingly, we found that treatment of **6** with benzyl acrylate (**2b**; 2 equiv) in the presence of $Pd(OAc)_2$ (10 mol%), Boc-Val-OH (20 mol%), and *t*AmylOH for 12 hours under O_2 (1 atm) effected C–H olefination to give **7** in 35% yield. Attempts to extend the reaction time to improve the yield led to substantial product decomposition, such that only trace quantities of **7** remained in solution after 24 h. Though this yield is low, given the possibility of nonproductive multidentate coordination of the substrate with Pd^{II}, a slow reaction rate can be expected. Moreover, this case represents the most complex setting in which C–H olefination of a hydrocinnamic acid has been attempted. In the absence of Boc-Val-OH, the reaction did not proceed.

In summary, through the discovery and development of complementary catalytic systems that exhibit tunable reactivity and selectivity, we have demonstrated a sequential C–H olefination protocol for synthesizing complex divinylbenzene derivatives from simple starting materials. We first established robust reaction conditions to effect diolefination with a range of different phenylacetic and hydrocinnamic acids. We then applied these conditions as the second step in a two-step sequential C–H olefination to prepare 1,2,3-trisubstitued arenes. Lastly, we used sequential C–H olefination to set the stage for a rare example of iterative C–H functionalization, wherein C–H activation installs a directing group for a subsequent C–H functionalization reaction.

Experimental Section

General procedure for Pd^{II}-catalyzed diolefination of phenylacetic acids: A 50 mL Schlenk-type sealed tube (with a Teflon high-pressure valve and side arm) equipped with a magnetic stir bar was charged with the phenylacetic acid substrate (0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), $KHCO_3$ (100.1 mg, 1.0 mmol), Ac-Val-OH (8.0 mg, 0.05 mmol), the olefin coupling partner (1.0 mmol), and *t*AmylOH (2.5 mL). The reaction tube was capped, then evacuated briefly under high vacuum and charged with O_2 (1 atm, balloon; repeated three times). The reaction mixture was stirred at room temperature for 5 min, then at 90°C for 6 h (or 48 h in the case of less-reactive substrates, see Schemes 4 and 5). Subsequently, the reaction vessel was cooled to 0°C in an ice bath. A 2.0 N HCl solution (5 mL) was added, and the mixture was extracted with EtOAc (3 × 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and then concentrated in vacuo. The resulting residue was purified by silica gel flash column chromatography using hexanes/EtOAc (1:1; with 2–5% HOAc) as the eluent.

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