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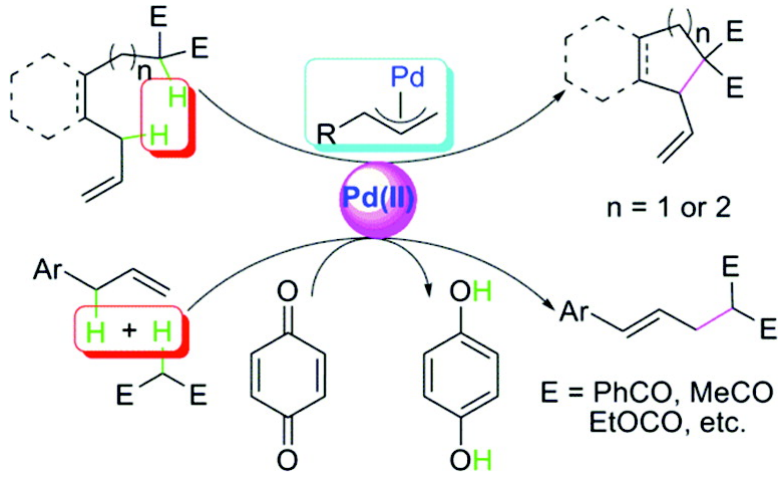

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Intra/Intermolecular Direct Allylic Alkylation via Pd(II)-Catalyzed Allylic C−H Activation

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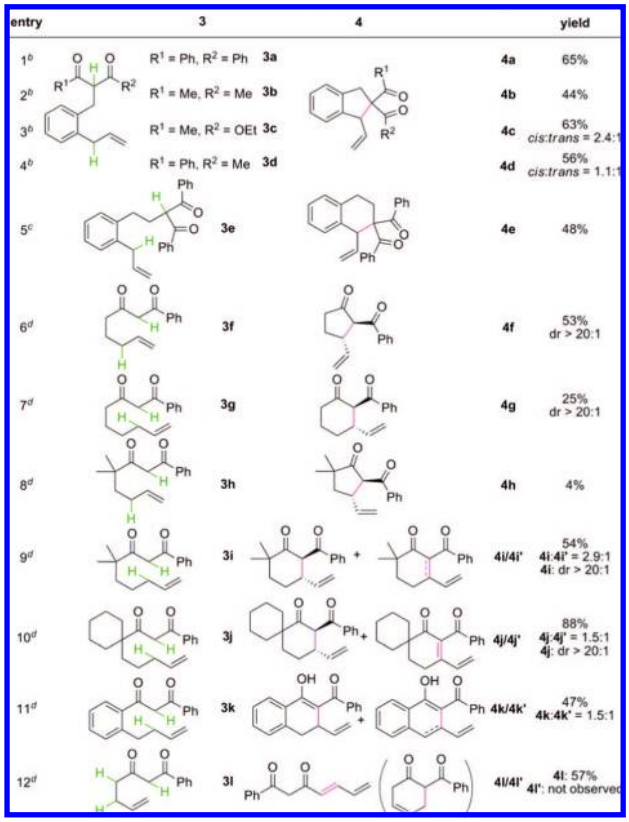
Tsuji−Trost reaction (Pd-catalyzed allylic alkylation) is an important transformation to construct C−C bonds in organic synthesis.[1] Many efforts have been devoted to this methodology to improve its efficiency and selectivity, which made it more powerful and applicable.[2] Generally, a functional group at the allylic position is required in Tsuji−Trost alkylation to serve as a reacting and leaving group.[3] Many trials have already been made to eliminate the allylic substituents for this chemistry, but failed (Scheme 1).[4] Trost and co-workers observed that allylic alkylation could proceed via C−H activation in two steps in the presence of stoichiometric Pd species, mostly because the in situ reoxidation of Pd(0) into Pd(II) is difficult.[5] This challenge was also depicted by Li and co-workers, who have made a significant contribution to address this issue through a different pathway.[6a]

Very recently, White and co-workers made significant progresses in the allylic C−O/N formation via Pd(II)-catalyzed C−H activation.[7] Liu and co-workers also reported a Pd(II)-catalyzed oxidative amination of allylic C−H bond.[8] During these processes, allylpalladium species **1** was proposed as the key intermediate. We envisioned that allylpalladium species **1** may also serve as an intermediate in direct allylic alkylation. To the best of our knowledge, direct alkylation of allylic C−H via Pd-catalysis is still unknown. Herein, we demonstrated the first example of the intra/intermolecular direct allylic alkylation of alkenes.

Our attention was initially paid to the annulation via intramolecular allylic C−H activation. After systematically screening, we gratifyingly found that, in the presence of the prepared 1,2-bis(benzylsulfinyl)-ethane palladium acetate (**2**) as the catalyst and benzoquinone as the oxidant, **3a** was transformed into the desired product **4a** in a good yield. Encouraged by this result, we further designed various substrates to construct fused, mono, and spiro rings (Table 1). Polysubstituted indane and 1,2,3,4-tetrahydronaphthalene (**4a**−**e**) with quaternary carbons were easily obtained in good efficiencies. When a prochiral substrate was used, two diastereoisomers were isolated (**4c** and **4d**). To our delight, when the aliphatic allylic substrates (**3f**−**k**) were submitted to the similar conditions, the annulations occurred smoothly with moderate to good yields (entry 6−11). For **4f**−**j**, high diastereoselectivities were achieved and only trans adducts were detected, which was clearly elucidated by X-ray structure of **4j** (Figure 1). We also discovered that (1) without the γ-substituents of the dione, a five-membered ring was more efficiently formed than a six-membered one (**4f** vs **4g**); however, (2) when steric hindrance was introduced at the γ-position, results were reversed, wherein the five-membered ring was hardly constructed (**4h** vs **4i**,**j**). The reason for these intriguing results may arise from the tuned configuration by introducing the steric hindrance at the γ-position (Thorpe−Ingold effect).[9] In some cases, the coupling products were partially dehydrogenated to form highly conjugated compounds (**4i′**−**k′**). Unexpectedly, when we attempted to afford the *endo* adduct **4l′**, only **4l** was isolated instead, which may be generated via allylic C−H activation followed by β-H elimination (entry 9).

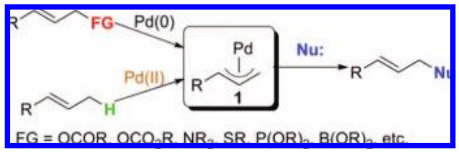
On the basis of these results, we started tackling a more ambitious proposal, wherein intermolecular allylic alkylation would be facilitated

Table 1. Intramolecular Direct Allylic Alkylation *via* Palladium-Catalyzed sp^3 C−H Activation[a]



[a] The reactions were carried out with **3** (0.3 mmol) in the presence of **2**, BQ (1.3 equiv), toluene (2.1 mL) under a balloon pressure of O_2 for 60 h unless otherwise noted, and isolated yields were reported. [b] With 10 mol% of **2**. [c] With 20 mol% of **2**. [d] With 15 mol% of **2**.

Scheme 1. Traditional Tsuji–Trost Alkylation and Our Proposed Allylic C−H Alkylation



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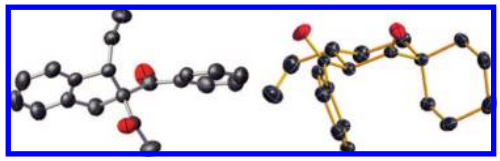
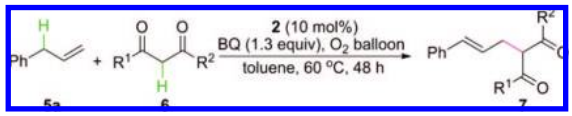


Figure 1. ORTEP diagram of **4d** and **4j** showing the 40% probability thermal ellipsoids for all non-hydrogen atoms.

Table 2. Intermolecular Direct Allylic Alkylation with Different Nucleophiles[a]



entry	R^1	R^2	7	yield (%)[b]
1	Ph	Me	**7aa**	82
2	Ph	Ph	**7ab**	69
3	Et	Et	**7ac**	64
4	Me	Me	**7ad**	55
5	Me	Oet	**7ae**	25
6[c]	Oet	Oet	**7af**	<5

[a] The reactions were carried out with **5** (0.5 mmol) and **6** (0.7 mmol) in the presence of **2** (10 mol%), BQ (1.3 equiv.), toluene (2.5 mL) and an O_2 balloon, unless otherwise noted. [b] Isolated yield. [c] GC yield.

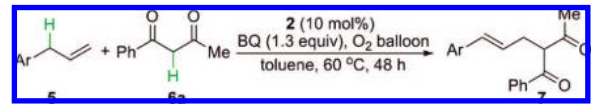
directly from an allylic C−H bond and external nucleophiles. Using the same reaction conditions, the alkylation of allylbenzene (**5a**) was satisfyingly achieved with benzoylacetone (**6a**) and the desired product **7aa** was observed by GC in 68% yield. We further optimized the conditions and found that the efficiency could be highly improved to 82% isolated yield by simply increasing the concentration to 0.2 M (Table 2, entry 1). Different from intramolecular alkylations, these intermolecular transformations had dominant terminal regioselectivities, which may arise from the steric discrimination between 1 and 3 positions of the π-allyl-Pd intermediate **1** when attacked by the carbanions.

Different nucleophiles were surveyed (Table 2). Compared with benzoylacetone, other linear 1,3-diketones **6b**−**d** also served well (entry 1−4). However, unlike the corresponding intramolecular reaction, ethyl acetoacetate (**6e**) was not suitable for this alkylation (entry 5). Since the competitive byproduct cinnamyl acetate **8** was isolated (12%), we supposed that the poor yield of using **6e** arose from its relatively lower nucleophilicity. It is noteworthy that in all studied cases, no branched or *cis*-product was observed by GC, which demonstrated that this transformation was highly regio- and stereo-selective.

This coupling occurred to produce the desired products **7** in moderate to excellent yields with various allyl arenes, regardless of whether an electron-withdrawing or electron-donating group was introduced on the phenyl ring (Table 3). It is noteworthy that steric hindrance obviously influenced the efficiency. Ortho- and meta-methyl allyl benzenes were not as reactive as para-substituted substrate (entries 3−4 vs entry 2). More sterically hindered 2,4,6-trimethyl allylbenzene (**5f**) furnished the product **7fa** in a much lower efficiency (entry 5). Furthermore, substrates with electron-withdrawing groups had lower reactivities, and relatively high catalyst loading was required to reach higher yields (entries 7−9). Moreover, aryl C−Cl and C−Br bonds were compatible with this system, which could be further transformed into different functionalities (entry 7 and 8). However, simple olefins such as *n*-dodecene led to the formation of ketones through Wacker process, instead of the alkylation product in the same reaction condition.

For this direct allylic alkylation, four different pathways have been proposed in Scheme 2. Many efforts were made to clarify the mechanism. First, Widenhoefer and co-workers have reported a protocol for the intramolecular oxidative alkylation of alkenes with

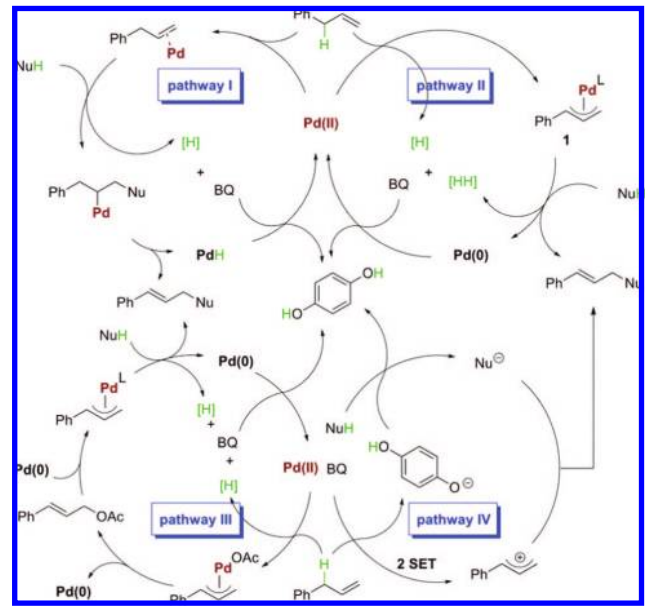
Table 3. Intermolecular Direct Allylic Alkylation with Different Allylarenes[a]



entry	Ar	7	yield (%)[b]
1	p-$CH_3OC_6H_4$	**7ba**	64
2[c]	p-$CH_3C_6H_4$	**7ca**	75
3[c]	m-$CH_3C_6H_4$	**7da**	42
4[c]	o-$CH_3C_6H_4$	**7ea**	34
5	2,4,6-$(CH_3)_3C_6H_2$	**7fa**	16
6	p-C_6H_5−C_6H_4	**7ga**	77
7[d]	p-ClC_6H_4	**7ha**	59
8[d]	p-BrC_6H_4	**7ia**	63
9[d]	C_6F_5	**7ja**	63
10	1-$C_{10}H_7$	**7ka**	67

[a] The reactions were carried out with **5** (0.5 mmol) and **6** (0.7 mmol) in the presence of **2** (10 mol%), BQ (1.3 equiv), toluene (2.5 mL), and an O_2 balloon, unless otherwise noted. [b] Isolated yield. [c] Reaction completed in 72 h. [d] Run using 15 mol% of **2**.

Scheme 2. Proposed Mechanisms for Direct Allylic Alkylation

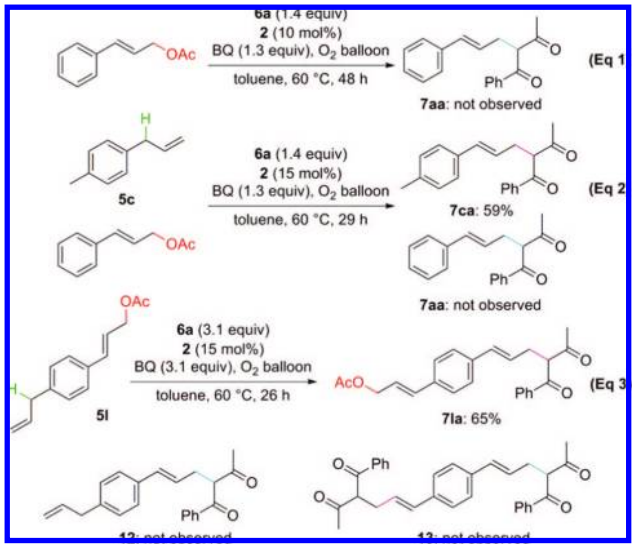


nucleophiles, including the Wacker-type process as the key step.[10a] However, our further studies showed that the intramolecular reactions only constructed the exo-type five/six-membered rings. Moreover, during the intermolecular reaction, the isomerization of **5a** to produce 1-aryl-1-propene was not observed in the in situ monitoring by GC. Besides, 1-aryl-1-propene did not transform into the desired product **7aa** in the model reaction condition. Thus, this transformation was not likely to go through the nucleophilic attack followed by β-H elimination as the Wacker-type process (pathway I).[10]

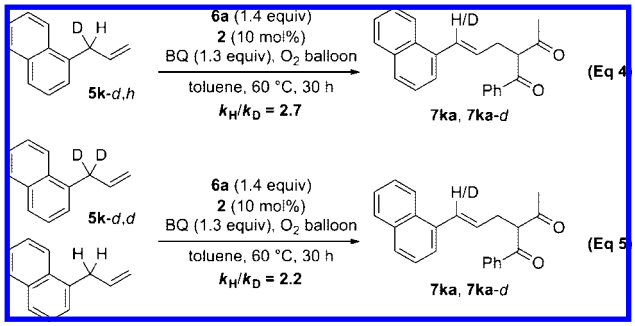
On the other hand, a small amount of cinnamyl acetate was also isolated in some cases, which could possibly serve as the key intermediate (pathway III). The acetate formed through allylic C−H activation and acyloxylation,[7g] and then underwent Tsuji−Trost reaction to furnish the final product. Nevertheless, in our work, the traditional allylic alkylation originating from cinnamyl acetate under the described condition failed to produce **7aa** (eq 1). Besides, inter/intramolecular studies with both allyl acetate and bare allyl groups as the competitive reacting partners exhibited a highly selective alkylation from the allylic C−H bond, leaving the C-OAc bond untouched (eq

2−3). Therefore, this transformation was not mediated by allyl acetate as shown in pathway III.

Recently, Bao and co-workers also reported a DDQ-mediated oxidative coupling between diarylallylic C−H bond and active methylenic C−H bond.[11] This result suggested that the mechanism of our transformation might involve oxidation of the olefin to an allyl cation by the quinone (pathway IV). In our studies, however, neither BQ nor DDQ could fulfill the allylic alkylation in the absence of $Pd(OAc)_2$. Accordingly, a similar pathway as described by Bao et al. was excluded.



On the basis of these preliminary results, we hypothesized a reasonable mechanism for this direct allylic alkylation as shown in pathway II. π-Allylpalladium species **1** was assumed as the key intermediate formed via an electrophilic allylic C−H bond cleavage by Pd(II) catalyst. Nucleophilic attack by 1,3-dicarbonyl compounds or their enolate forms occurred subsequently to afford the final product **4** or **7**. Pd(0) was then reoxidized by BQ to fulfill the catalytic cycle. It is of importance to note that no base was required for both inter/intramolecular reactions. The quinone was shown to play a vital role as a proton acceptor as well as the oxidant.[6e,11] The intra/intermolecular isotopic effect studies further strongly supported the assumed catalytic pathway (eq 4−5). The observation of different allylpalladium species by ESI mass spectroscopy at different stages of this transformation also partially supported our hypothesis (Please refer to Supporting Information).



In summary, we have reported a novel method toward direct intrta/intermolecular allylic alkylation between allylic sp^3 C−H bond and methylenic sp^3 C−H bond via Pd(II)-catalysis. This methodology not only broadened the application of traditional Tsuji−Trost alkylation, but also offered an opportunity to study its stereoselectivity with chiral ligands.[13−15]

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Supporting Information Available: Brief experimental details, spectral data for products and some substrates. This material is available free of charge via the Internet at http://pubs.acs.org.

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