C–H Activation

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Palladium-Catalyzed Alkylation of 1,4-Dienes by C–H Activation**

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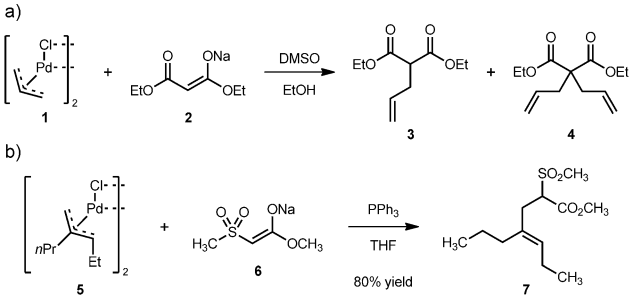
Transition-metal-catalyzed direct functionalization of C–H bonds is an area of widespread and active research, because of the potential to dramatically affect the ways in which molecules are synthesized.[1] Because of such new chemical methods the need to prepare substrates that bear functional groups with which transition-metal catalysts engage can be avoided, thus increasing the efficiency of a synthetic sequence by rendering prefunctionalization steps unnecessary.[2] Synthesis plans that rely upon direct C–H bond functionalization may also benefit significantly in terms of chemoselectivity, because C–H bonds can often be carried through a series of reactions until they are converted into the functional group of interest. Despite the relative inertness of C–H bonds and the challenges associated with the development of catalysts that can discriminate between many C–H bonds in a given substrate, this strategy for molecular construction has made and will continue to make important contributions to the design and execution of chemical synthesis.[3]

Given the myriad ways in which palladium-catalyzed allylic substitutions have enabled the synthesis of a broad range of complex molecules,[4] our and other research groups have been motivated to evaluate whether the value of this methodology could be further enhanced by performing these reactions by allylic C-H activation rather than allylic leaving group ionization, because the latter approach requires prefunctionalization of the electrophile.[5] Stoichiometric palladium-mediated allylic alkylations that proceed by C–H activation are well known,[6] and the first disclosure of a nucleophilic addition to a stoichiometrically prepared π-allylpalladium complex was made in 1965 by Tsuji and coworkers, who demonstrated that sodium diethyl malonate (**2**) could be allylated with $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (**1**) in the presence of DMSO (Scheme 1 a).[7] Despite nearly half a century of advances in organometallic chemistry, only recently[8] have there been reports of methods that reduce this two-step procedure to a single, palladium-catalyzed process, and all have similarly employed sulfoxides as ligands.[9]

In our early work, we found that such conditions failed with more substituted allylic substrates. In the course of studying the alkylation of π-allylpalladium species, we found



Scheme 1. a) DMSO-promoted allylation of sodium diethyl malonate with $[(\eta^3\text{-}C_3H_5)PdCl]_2$. b) PPh_3-promoted allylation of sodium methyl 2-(methylsulfonyl)acetate with a π-allylpalladium complex. DMSO = dimethyl sulfoxide.

that phosphorus-based ligands proved advantageous for promoting the attack by stabilized nucleophiles on such complexes (Scheme 1 b),[10] a discovery that has provided the basis for chemo-, regio-, and stereocontrol in palladium-catalyzed allylic alkylation chemistry ever since. Although these ligands have been reported to be unsuitable under the oxidative conditions necessary for C–H activation,[11] we hypothesized that if phosphorus-based ligands could promote palladium-catalyzed allylic C–H alkylations, there would be a similarly great opportunity to expand both the scope and selectivity of this process.

We began our investigation by studying the ability of palladium to catalyze the alkylation of *tert*-butyl 2-cyano-2-phenylacetate (**8**) with 1,4-pentadiene (**9**). We were motivated to evaluate 1,4-pentadiene in particular as an electrophile for such a transformation, because palladium activation of a bis-allylic C–H bond might prove more facile than the analogous activation of a mono-allylic C–H bond, and because unconjugated 1,4-dienes are a class of substrates that have never been reported to undergo any transition-metal-catalyzed C–H alkylation. Furthermore, such a transformation would generate the corresponding 1,3-diene, a functional group with diverse applications in synthetic chemistry.[12] We were delighted to discover that in the presence of 1.1 equivalents Et_3N, 1.0 equivalent 2,6-dimethylbenzoquinone (2,6-DMBQ), 5.0 mol% $Pd(OAc)_2$, and 10 mol% PPh_3, the desired allylic C–H alkylation product (**10**) can be isolated in 73% yield as a single regio- and stereoisomer (Scheme 2). Control experiments establish that 2,6-DMBQ, $Pd(OAc)_2$, and PPh_3 are each essential to the success of the reaction.[13]

These reaction conditions can be used for a broad range of nucleophiles (Scheme 3). Many substituted α-cyano-*tert*-butyl esters undergo allylic C–H alkylation with 1,4-pentadiene (**9**), including those that bear α-phenyl, α-methyl, α-ethyl, α-*iso*-propyl, α-benzyl, and α-*n*-hexyl substituents (**10**–**15**). Many

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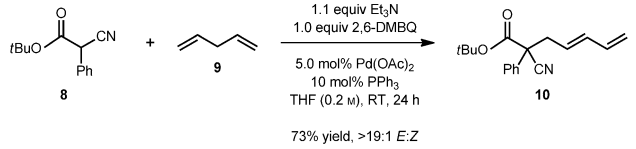
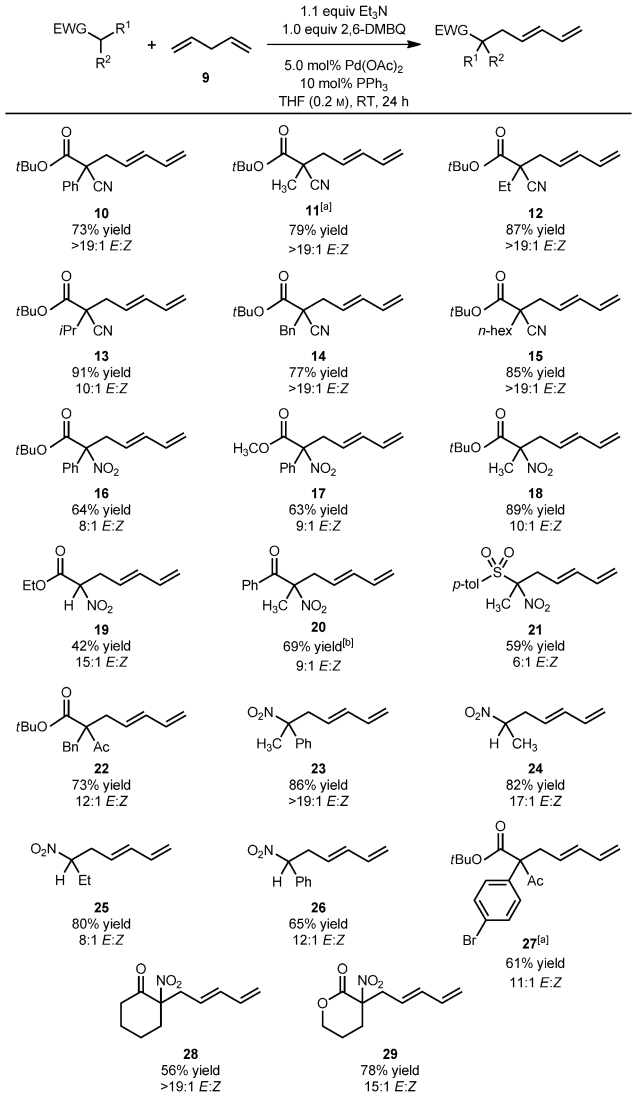


Scheme 2. Palladium-catalyzed allylic C–H alkylation of cyano ester **8** with 1,4-pentadiene. 2,6-DMBQ = 2,6-dimethylbenzoquinone.

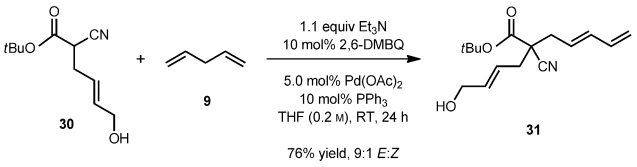


Scheme 3. Palladium-catalyzed allylic C–H alkylations of nucleophiles with 1,4-pentadiene. Reactions were performed on a 0.2 mmol scale in THF (0.2 M) for 24 h at RT with nucleophile (1.0 equiv), 1,4-pentadiene (1.1 equiv), Et_3N (1.1 equiv), 2,6-DMBQ (1.0 equiv), $Pd(OAc)_2$ (5.0 mol%), and PPh_3 (10 mol%). All yields are of isolated products; *E*:*Z* ratios were obtained by ^1H NMR spectroscopy. [a] Reaction performed on a 0.1 mmol scale. [b] Isolated as mixture with (*E*)-6-nitrohepta-1,3-diene; see the Supporting Information for details.

corresponding α-nitro esters also undergo allylic C–H alkylation (**16**–**18**), even when they are otherwise unsubstituted, as in the case of ethyl 2-nitroacetate (**19**). Similarly, α-nitro ketones (**20**) and α-nitro sulfones (**21**) also provide the desired allylated products, as do β-keto esters (**22**).

Nitro-substituted substrates are sufficiently acidic that they do not require a second α-electron-withdrawing group to activate them for nucleophilic attack. For example, (1-nitroethyl)benzene gives the desired C–H alkylation product (**23**) in 86% yield with complete stereoselectivity. Primary alkyl nitro nucleophiles, such as nitroethane, 1-nitropropane, and (nitromethyl)benzene, also undergo C–H alkylation (**24**–**26**). This catalyst system shows reactivity that is orthogonal to cross-coupling chemistry. For example, *tert*-butyl 2-(4-bromophenyl)-3-oxobutanoate can be allylated (**27**) without the significant production of side products that result from oxidative addition into the C(aryl)–Br bond by the palladium(0) species, which is presumably generated in the reaction. The method is not limited to acyclic nucleophiles either; cyclic substrates, such as 2-nitrocyclohexanone and 3-nitrotetrahydro-2*H*-pyran-2-one, react to give the desired products (**28** and **29**).

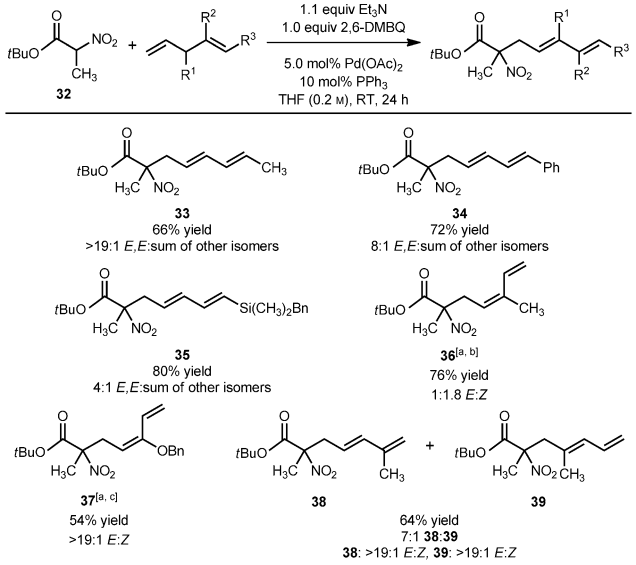
Notably, allylic C–H alkylation proceeds smoothly with (*E*)-*tert*-butyl 2-cyano-6-hydroxyhex-4-enoate (**30**) to give **31** (Scheme 4), thus demonstrating that an unprotected reactive functionality, such as a primary alcohol, is well tolerated by the catalyst, and that allylic C–H activation is chemoselectively effected only at 1,4-dienes. The mono-allylic C–H bonds, even those on a carbon atom that also bears a heteroatom, are inert to these reaction conditions.



Scheme 4. Palladium-catalyzed allylic C–H alkylation of *tert*-butyl 2-cyano-6-hydroxyhex-4-enoate with 1,4-pentadiene.

This palladium-catalyzed allylic C–H alkylation is also general for many differently substituted 1,4-dienes (Scheme 5). When *tert*-butyl 2-nitropropanoate (**32**) is treated with *trans*-1,4-hexadiene under the optimized conditions, alkylated product **33**, which results from nucleophilic attack at the less sterically-hindered terminus of the electrophile, can be isolated in 66% yield as a single stereoisomer. Significantly, if a mixture of *cis*- and *trans*-1,4-hexadiene is employed instead, **33** can still be obtained in 62% yield as a single stereoisomer, evidence that the catalyst is able to isomerize the alkene geometry of the electrophile to the thermodynamically favored *E*,*E* configuration observed in the product. Replacing the methyl substituent of 1,4-hexadiene with either a phenyl or benzyldimethylsilyl group gives the corresponding products (**34** and **35**) as sole regioisomers and with predominantly *E*,*E* configurations.

It is not necessary for the bis-allylic C–H bond that undergoes activation to be a methylene C–H bond; reaction of **32** with 3-methylpenta-1,4-diene, an electrophile for which a methine C–H bond must be activated, gives alkylation

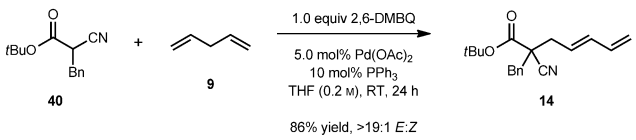


Scheme 5. Palladium-catalyzed allylic C–H alkylation of *tert*-butyl 2-nitropropanoate with 1,4-dienes. Reactions were performed on a 0.2 mmol scale in THF (0.2 M) for 24 h at RT with *tert*-butyl 2-nitropropanoate (1.0 equiv), 1,4-diene (1.1 equiv), Et_3N (1.1 equiv), 2,6-DMBQ (1.0 equiv), $Pd(OAc)_2$ (5.0 mol%), and PPh_3 (10 mol%). All yields are of isolated products; *E*:*Z* ratios were obtained by ^1H NMR spectroscopy. [a] Alkene geometry was determined by NOE measurements; see the Supporting Information for details. [b] Reaction performed at 35 °C. [c] Reaction performed on a 0.1 mmol scale at 50 °C.

product **36**. The reaction with the corresponding 3-benzyloxypenta-1,4-diene provides **37**, and thus constitutes the stereoselective formation of a benzyl enol ether. Finally, reaction with 2-methylpenta-1,4-diene gives predominantly **38**, the product of nucleophilic attack on the less sterically hindered terminus of the diene.

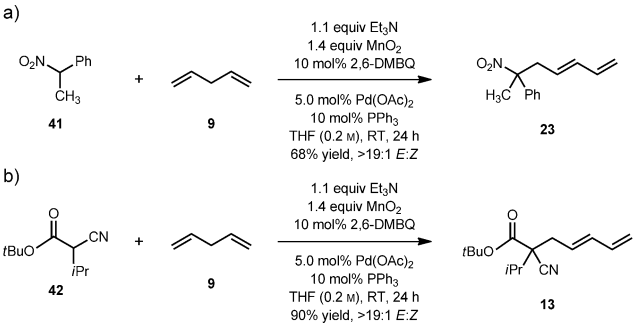
The addition of a base, such as Et_3N, is not always required, thus indicating that it is not necessary in the C–H activation event. For example, when *tert*-butyl 2-cyano-3-phenylpropanoate (**40**), a nucleophile that readily undergoes keto/enol tautomerization, is reacted with 1,4-pentadiene (**9**) in the absence of Et_3N,[14] the desired product **14** is obtained in 86% yield (Scheme 6). Remarkably, this yield is significantly higher than the yield of **14** obtained in the presence of Et_3N (Scheme 3), thus indicating that for certain activated substrates it may be beneficial to conduct the reaction under base-free conditions.

The palladium-catalyzed allylic C–H alkylation of 1,4-pentadiene can be performed with less than one equivalent of 2,6-DMBQ. No desired reaction is observed in the absence of a quinone, an observation that suggests that the quinone plays



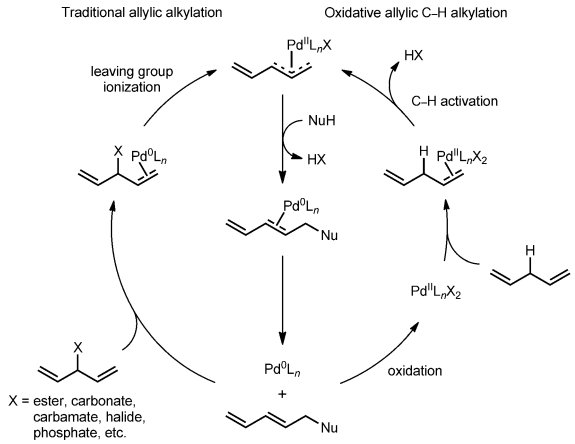
Scheme 6. Palladium-catalyzed allylic C–H alkylation under neutral conditions.

a crucial role as a ligand for the metal in addition to regenerating the palladium(II) species that is responsible for C–H activation. In the presence of manganese(II) oxide, a reagent known to oxidize hydroquinones to the corresponding quinones,[15] the quantity of 2,6-DMBQ employed can be dramatically reduced. As an example, when the amount of 2,6-DMBQ is reduced from 1.0 equivalent to only 10 mol% in the reaction of (1-nitroethyl)benzene (**41**) with 1,4-pentadiene (**9**), the addition of 1.4 equivalents of manganese(II) oxide is sufficient for the desired product **23** to be obtained in 68% yield (Scheme 7a). Similarly, when *tert*-butyl 2-cyano-3-methylbutanoate (**42**) is reacted with 1,4-pentadiene (**9**), C–H alkylation product **13** is isolated in 90% yield (Scheme 7b).



Scheme 7. Palladium-catalyzed allylic C–H alkylations with MnO_2 as the terminal oxidant.

We propose that this allylic C–H alkylation proceeds through a catalytic cycle that is mechanistically distinct from that of a traditional palladium-catalyzed allylic alkylation (Scheme 8). Rather than beginning with a palladium(0)-mediated ionization of an allylic leaving group, this process starts with a palladium(II)-mediated allylic C–H activation to generate an electrophilic π-allylpalladium intermediate. Nucleophilic attack reduces the catalyst and decomplexation of the alkene releases the allylic alkylation product. Finally,



Scheme 8. Mechanistic comparison of palladium-catalyzed traditional allylic alkylation and oxidative allylic C–H alkylation.

oxidation by 2,6-DMBQ regenerates the palladium(II) species necessary for the next catalytic turnover.

By demonstrating that PPh_3 promotes palladium-catalyzed allylic C–H alkylations, this study contains the first examples of such catalytic transformations that proceed in the absence of a sulfoxide ligand, an advance that augurs well for further developments in allylic C–H alkylation chemistry, given the chemo-, regio-, and stereocontrol in traditional palladium-catalyzed allylic substitution processes that have been enabled by the discovery and development of phosphorus-based ligands. We have also demonstrated that a broad range of nucleophiles undergo reaction with variously substituted 1,4-dienes under mild conditions, providing direct access to the corresponding 1,3-diene-containing alkylation products with high regio- and stereocontrol. Investigations into other palladium-catalyzed allylic C–H alkylation reactions with phosphorus-based ligands are ongoing.

Experimental Section

General procedure for the palladium-catalyzed allylic C–H alkylation of 1,4-dienes: An oven-dried reaction vial equipped with an oven-dried stirrer bar was charged with 2,6-DMBQ (27.2 mg, 0.200 mmol), $Pd(OAc)_2$ (2.20 mg, 0.010 mmol), and PPh_3 (5.20 mg, 0.020 mmol). The vial was sealed with a septum, and then evacuated and filled with Ar three times. THF (0.6 mL) was added and the mixture was stirred for ca. 1 min until a yellow solution was obtained. 1,4-pentadiene (23.0 μL, 0.220 mmol) was then added by syringe, followed by *tert*-butyl 2-cyano-2-phenylacetate (43.5 mg, 0.200 mmol), Et_3N (30.5 μL, 0.220 mmol), and THF (0.4 mL). The reaction was stirred for 24 h at room temperature, over which time the solution changed color from yellow to red. After concentration under reduced pressure, the crude material was purified by column chromatography on silica gel (hexanes:EtOAc = 95:5) to give the (*E*)-tert-butyl 2-cyano-2-phenylhepta-4,6-dienoate (41.4 mg, 73 % yield, > 19:1 *E*:*Z*) as a colorless oil.

General procedure for the palladium-catalyzed allylic C–H alkylation of 1,4-dienes with MnO_2 as the terminal oxidant: As per the general procedure for the palladium-catalyzed allylic C–H alkylation of 1,4-dienes, except for the initial addition of MnO_2 (24.3 mg, 0.280 mmol) and the reduced amount of 2,6-DMBQ (3.00 mg, 0.020 mmol) that was used.

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