C–H Alkylation

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Allylic C–H Alkylation of Unactivated α-Olefins: Serial Ligand Catalysis Resumed**

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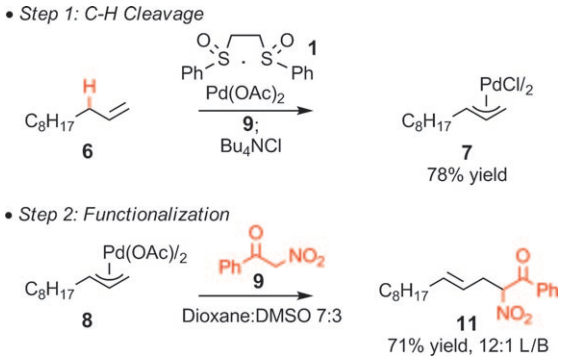
The palladium(0)-catalyzed alkylation reaction of allylic oxygenates has found extensive use in organic synthesis.[1] Recent efforts, however, have focused on the development of catalytic methods to replace allylic C–H bonds directly with C–C bonds.[2] The selective alkylation of normally inert C–H bonds presents exciting opportunities for the development of novel methods and streamlined syntheses of complex molecules.[3] Despite significant advances in C–H alkylation, to date no method has been reported for the intermolecular allylic C–H alkylation of unactivated α-olefins.

Intermolecular palladium(II)-catalyzed allylic C–H alkylation reactions using our $Pd(OAc)_2$/bis(sulfoxide) catalysts **1** and **2**[4] have previously been reported by our research group and others.[2a,b] Despite the use of various reaction conditions (DMSO versus no DMSO) and nucleophiles (methyl nitroacetate versus benzoylacetone **13**) it was observed that both intermolecular reactions had substrate scopes limited to activated, allylarene structures.[5] We were intrigued by the mechanistic underpinnings of this deficiency, particularly in light of the broad α-olefin scope demonstrated for intermolecular and intramolecular allylic C–H esterification and amination reactions catalyzed by **1**.[6,7] Herein we report a mechanistic study that points to competitive ligand binding as the underlying cause for the limited substrate scope observed. Significantly, this mechanistic insight has led to the development of the first intermolecular allylic C–H alkylation reaction of unactivated α-olefins.

We postulated that the allylic C–H alkylation of unactivated α-olefins may be achieved by a serial ligand catalysis[8] mechanism (SLC).[9] Under this scenario, multiple kinetically labile ligands with different electronic properties reversibly coordinate to the metal center and mediate individual steps of the cycle.[10] Specifically, a SLC mechanism for palladium-catalyzed allylic C–H alkylation may proceed as follows: 1) catalytic palladium(II)/bis(sulfoxide)-promoted C–H cleavage to furnish a π-allylPd intermediate, 2) stoichiometric DMSO-promoted functionalization through ionization of the π-allylPd intermediate, and 3) re-oxidation of Pd^0 to Pd^{II} with a quinone. In the previously reported C–H alkylation of allylarenes we found that the complex formed by $Pd(OAc)_2$ and DMSO was sufficiently active to cleave the doubly activated allylic/benzylic C–H bond[11] in the absence of bis(sulfoxide) ligands, thus obviating the requirement for a SLC mechanism.[2a]

In support of the hypothesis that unactivated α-olefins may be alkylated by SLC, stoichiometric studies showed that allylic C–H cleavage of these substrates was effected by palladium(II)/phenyl bis(sulfoxide) catalyst **1** to afford π-allylPd, trapped as chloride dimer **7**, in good yields (78%, Scheme 1). Significantly, although benzoylnitromethane



Scheme 1. Stoichiometric allylic C–H alkylation. L/B = linear/branched product ratio.

nucleophile **9** was present during this C–H cleavage step, no functionalization was observed in the absence of DMSO. Functionalization of π-allylPd **8** proceeded smoothly in the presence of a superstoichiometric amount of DMSO to yield allylic alkylation product **11** (71%, Scheme 1).[12] However, the efficiency of the stoichiometric reactions that comprise the proposed catalytic cycle significantly contrasted with the result of the catalytic reaction. Under optimized conditions where both phenyl bis(sulfoxide) and DMSO ligands were present, the product could only be obtained in 25% yield, leaving substrate, nucleophile, and quinone (Table 1, entry 2). A more detailed analysis of the kinetic profile of the reaction showed that catalyst **1** lost nearly all its activity between 12 and 24 h (Figure 1, red square). Collectively, these results imply that the catalyst becomes prematurely deactivated.[13]

We hypothesized that under a SLC reaction mechanism, an overly competitive ligand may disrupt the ligand-exchange processes necessary for efficient catalysis with challenging unactivated α-olefin substrates. Specifically, DMSO, the ligand required for functionalization, might be interfering at high concentrations with reassociation of the bis(sulfoxide)

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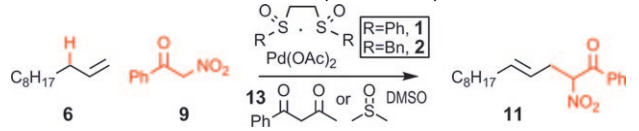
Table 1: Effect of additives on the allylic C–H alkylation reaction.



Entry[a]	Catalyst	Additive	Yield (L + B) [%][b]	L/B[b]
1	R = Ph **1**	–	< 5	–
2	**1**	DMSO (30 vol %)[c]	25	12:1
3	**1**	13 (1 equiv)	< 5	–
4	R = Bn **2**	–	< 5	–
5	**2**	DMSO (30 vol %)	59	12:1
6	**2**	13 (1 equiv)	< 5	–
7	$Pd(OAc)_2$	DMSO (30 vol %)	6	–
8	R = *n*Pr **3**	DMSO (30 vol %)	62	11:1
9	R = Cy **4**	DMSO (30 vol %)	57	12:1
10	R = *t*Bu **5**	DMSO (30 vol %)	40	10:1

[a] **6** (1 equiv), **9** (4 equiv), catalyst (0.10 equiv), 2,6-dimethylbenzoquinone (1.1 equiv), 1,2-dichloroethane (0.67 M), 45 °C, 72 h. [b] Determined by ^{1}H NMR analysis of the crude product. [c] 30 vol % = 6.3 equiv. B = branched, L = linear, Bn = benzyl, Cy = cyclohexyl.

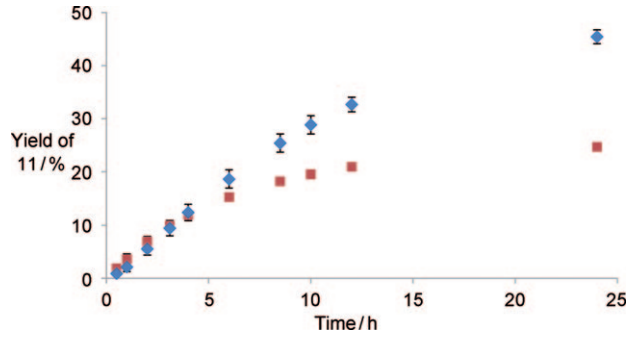
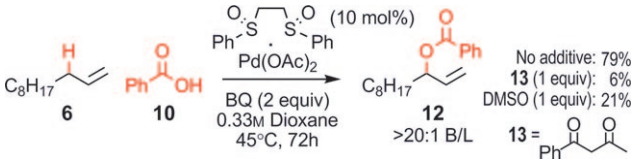


Figure 1. Comparison of the allylic alkylation reaction catalyzed by **1** (red square) or **2** (blue diamond), and DMSO.

ligand (present at only 10 mol %) with palladium to form complex **1**, which is needed for C–H cleavage. In the case of a previously reported allylic C–H alkylation in which no DMSO was used,[2b] analogous inhibition may have resulted from the use of stoichiometric quantities of benzoylacetone nucleophile **13**, a well-known ligand for palladium. Under these conditions, unactivated α-olefins were reported to afford Wacker products;[2b] this reactivity is characteristic of $Pd(OAc)_2$ in the absence of a bis(sulfoxide) ligand.[4]

To investigate the proposed competitive inhibition of **1** by DMSO and benzoylacetone **13** during SLC we evaluated the ability of these ligands to disrupt the allylic C–H esterification reaction. This transformation is known to proceed through a SLC mechanism wherein palladium(II)/bis(sulfoxide) **1** mediates allylic C–H cleavage, and the benzoquinone ligand promotes C–O bond formation.[8] Consistent with these ligands being able to disrupt a SLC catalytic cycle, the addition of just one equivalent of DMSO or **13** to the allylic C–H esterification results in drastically reduced reactivity (DMSO, 79→21 %; **13**, 79→6 %; Scheme 2).

To address the problem of competitive ligand binding effects we investigated alkyl bis(sulfoxide) ligands that would



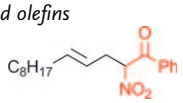
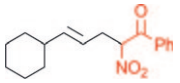
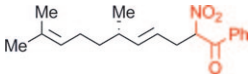
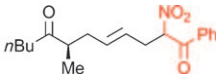
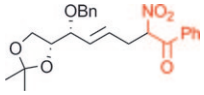
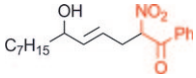
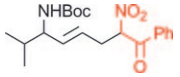
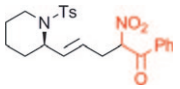
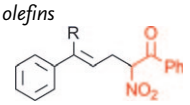
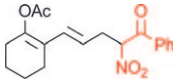
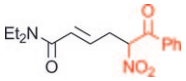
Scheme 2. Effect of additives on the allylic C–H esterification reaction. BQ = benzoquinone.

be stronger σ-donor ligands than aryl bis(sulfoxides). We reasoned that alkyl bis(sulfoxide) ligands may be better able to compete with high concentrations of DMSO for binding to the palladium center. This strategy was inspired by the observation that the sluggish reaction of (phenylsulfonyl)nitromethane nucleophile with allylbenzene required the use of the $Pd(OAc)_2$/benzyl bis(sulfoxide) catalyst **2** to reach full conversion,[2a] which implies that **2** remained active in solution for a longer period of time than **1**. We were gratified to find that alkyl ligands did in fact generate more active catalysts, thereby providing conditions for the first intermolecular alkylation of unactivated α-olefins (Table 1, entries 5, 8–10). While catalyst activity is influenced by steric factors (R = *t*Bu; Table 1, entry 10), it is clear that the electronic effect of replacing aryl with alkyl substituents is primarily responsible for the improved reactivity (compare R = Ph, R = Cy, entries 2 and 9). Notably, catalyst **2** was also relatively insensitive to DMSO in the allylic esterification reaction (see the Supporting Information).

We endeavored to further elucidate the interplay between the two sulfoxide ligands.[14] Consistent with the hypothesis that allylic C–H alkylation of unactivated substrates proceeds through a SLC mechanism, the omission of either sulfoxide ligand dramatically reduces the reactivity (no DMSO, 59→< 5 %; no bis(sulfoxide), 59→6 %; Table 1, entries 4 and 7). Stoichiometric studies demonstrated that catalyst **1** had rates comparable to or faster than **2** for the C–H cleavage and functionalization steps (see the Supporting Information). However, in contrast to **1**, catalyst **2** is active in solution for an extended period of time (Figure 1, blue diamond). These results are consistent with our hypothesis of gradual catalyst deactivation in the presence of DMSO as a result of competitive ligand binding effects, with **2** demonstrating better stability to DMSO than **1**.

Having developed conditions suitable for the allylic alkylation of unactivated α-olefins, we proceeded to examine the substrate scope of the method. In all cases the reaction proceeds with high regioselectivity and excellent *E*/*Z* selectivity (> 20:1). The alkylation is tolerant of a variety of functionality at the homoallylic position, including carbon, oxygen, and nitrogen (Table 2, entries 2, 3, and 5–8). Under these reaction conditions, proximal stereogenic centers are not racemized. Similarly, a potentially epimerizable α-carbonyl stereocenter retains its configuration, thus illustrating how this method is orthogonal to traditional carbanion-based C–C bond-forming reactions (Table 2, entry 4). A trisubstituted olefin is tolerated under the reaction conditions, thus demonstrating the chemoselectivity of the catalyst for terminal olefins (Table 2, entry 3). Notably, even an unprotected secondary alcohol is stable to the oxidative conditions

Table 2: Scope of the allylic C–H alkylation reaction.

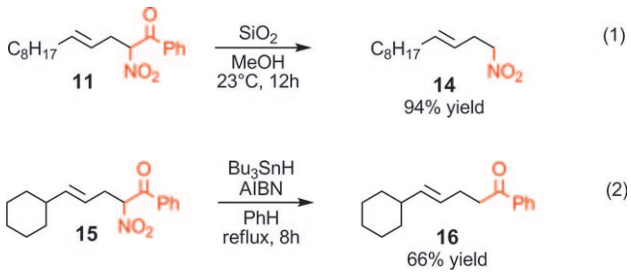
Entry	Major product		L/B[b]	Yield L [%][a]
unactivated olefins				
1			12:1	56
2			>20:1	61
3			>20:1	49[c]
4[d]			>20:1	56[c]
5[d]			>20:1	63[c]
6			>20:1	58[c]
7			>20:1	53[c]
8			>20:1	66[c]
activated olefins				
9		R = H	11:1	73
10		Me	>20:1	54
11			5:1	63
12			>20:1	60

[a] Olefin (1 equiv), **9** (4 equiv), **2** (0.10 equiv), 2,6-dimethylbenzoquinone (1.1 equiv), 1,2-bis(benzylsulfinyl)ethane (0.05 equiv), 1,2-dichloroethane/DMSO (7:3, 0.67 M), 45 °C, 72 h. Average of 2 runs. Product isolated as a single stereo- and constitutional isomer. *E*/*Z* > 20:1. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude product. [c] d.r. = 1:1. [d] Dioxane/DMSO (7:3, 0.67 M). Boc = *tert*-butoxycarbonyl, Ts = 4-toluenesulfonyl.

(Table 2, entry 6). Strategically, the C–H alkylation disconnection provides facile entry to products that are often difficult to access by conventional means (Table 2, entries 5 and 8).[15] Whereas conventional syntheses require tedious manipulation of oxidized functionality, C–H alkylation uses inert α-olefins which may be installed at any stage by using versatile, stereoselective allylation methods.[16]

The C–H alkylation reaction conditions are also suitable for allylbenzene substrates and other classes of activated substrates such as amides and enols, thus providing a general reaction protocol that encompasses both activated and unactivated α-olefin substrates (Table 2, entries 9–12). The alkylation of 1-methylallylbenzene is a unique example of C–H activation of a γ-branched olefin (Table 2, entry 10).

The α-nitro ketone subunit of the products is a versatile synthetic handle for which a variety of methods have been described.[17] As a complement to transformations on the entire subunit, we sought to demonstrate how the motif could be elaborated orthogonally by selectively excising each of the electron-withdrawing moieties. We discovered that the benzoyl group may be cleaved under very mild conditions to furnish homoallylic nitroalkane **14** in excellent yield [Eq. (1)]. Alternatively, the nitro group can be removed by a radical Bu_3SnH/AIBN (AIBN = 2,2′-azobisisobutyronitrile) reaction to provide γ,δ-unsaturated ketone **16** [Eq. (2)].[18]



In summary, this study underscores the delicate balance of ligand-exchange processes required to realize a SLC mechanism, and explores the consequences of competitive ligand binding. By identifying a C–H cleavage ligand that is better able to compete with the functionalization ligand, we have developed the first intermolecular allylic C–H alkylation reaction that encompasses unactivated as well as activated α-olefin substrates. With the further development of general and selective reactions, we anticipate that C–H functionalization will play an increasingly important role in the future of organic synthesis.

Experimental Section

General procedure for the allylic alkylation (Table 2): A one dram vial (4 mL, borosilicate) was charged with Pd[1,2-bis(benzylsulfinyl)ethane](OAc)$_2$ (**2**; 0.10 equiv, 0.030 mmol, 15.9 mg), 2,6-dimethylbenzoquinone (1.1 equiv, 0.33 mmol, 44.9 mg), benzoylnitromethane (**9**; 4.0 equiv, 1.20 mmol, 198 mg), and 1,2-bis(benzylsulfinyl)ethane (0.05 equiv, 0.015 mmol, 4.6 mg). The olefin (1 equiv, 0.30 mmol) was weighed out in a $^1/_2$ dram vial, dissolved in 1,2-dichloroethane (0.315 mL), and transferred to the reaction vial. Dimethylsulfoxide (0.135 mL) and a teflon stir bar were added sequentially to the reaction vial. No precautions were taken to exclude air or moisture. The reaction vial was capped and stirred at 45 °C for 72 h. The vial was cooled to room temperature, and the reaction mixture was diluted with saturated aqueous NH_4Cl (40 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography (SiO_2, EtOAc/hexanes mixtures) provided the pure linear product. In cases where branched product was observed, it could be readily separated and generally possessed a higher R_f value than linear product.

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