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Catalytic Intermolecular Allylic C—H Alkylation

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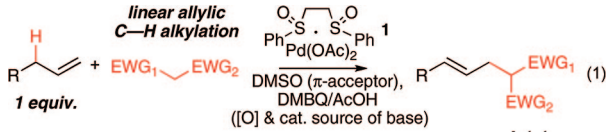
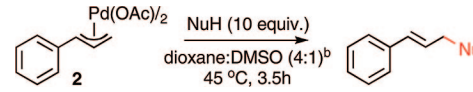
Reactions that form carbon−carbon bonds lie at the heart of organic synthesis. The general approach for effecting this bond formation involves the union of preoxidized fragments via either acid/base-promoted processes or metal-catalyzed cross-coupling reactions. An orthogonal approach that is emerging is the direct conversion of C—H to C—C bonds. By unveiling C—H as a "functional group," novel disconnections can be envisioned that will streamline the synthesis of complex molecules. Despite significant advances in directed C—H arylations and alkylations,[1] nondirected C—H to C—C bond forming processes are more scarce.[2] Herein, we report the first electrophilic, Pd(II)-catalyzed intermolecular allylic C—H alkylation reaction (eq 1).[2a,b,d]



Stoichiometric Pd(II)-mediated, two-step allylic C—H alkylation, amination, and oxidation reaction sequences have been known since the 1960s.[3] A significant challenge in developing catalytic versions of these reactions has been the discovery of conditions that support both Pd(II)-mediated electrophilic C—H cleavage and nucleophilic π-allylPd functionalization. Allylic alkylations catalyzed by Pd(0) avoid the requirement for electrophilic C—H cleavage and oxidant (generally[2a] by utilizing preoxidized substrates), thus permitting the use of phosphine ligands to stabilize electrophilic π-allylPd intermediates and stoichiometric base to activate the nucleophile.[3b] Alternatively, we have shown that allylic C—H esterification and amination reactions can be rendered catalytic using sulfoxide/Pd(OAc)$_2$/benzoquinone (BQ) systems in which sulfoxide ligands stabilize electrophilic Pd(II) and BQ promotes functionalization.[4] In addition to serving as an oxidant for Pd(0), BQ acts as a π-acidic ligand to activate π-allylPd toward reductive elimination[4b] and generates catalytic carboxylate base to activate acidic nucleophiles *in situ*.[4c,5] These conditions were unsuccessful for effecting alkylations because BQ has a propensity for irreversible conjugate addition reactions with many soft carbon nucleophiles. Dimethylsulfoxide (DMSO) is known to activate π-allylPd complexes toward alkylation with malonates,[6] leading us to hypothesize that, in the absence of BQ, sulfoxide might facilitate functionalization. Herein we report that bis-sulfoxide/Pd(OAc)$_2$ catalyst **1** in combination with DMSO and 2,6-dimethylbenzoquinone (DMBQ)/AcOH effects the first catalytic allylic C—H alkylation reaction. A wide range of aromatic and heteroaromatic allyl compounds are alkylated with methyl nitroacetate to furnish linear (*E*)-α-nitroarylpentenoates. The products of this reaction can serve as nucleophiles in asymmetric conjugate addition reactions to generate optically enriched, unnatural α,α-disubstituted amino acid precursors.

We began our study by investigating the product forming steps of a putative catalytic cycle under stoichiometric conditions (Table 1). Complex **1** effected rapid allylic C—H cleavage of allylbenzene **7** to afford good yields of π-allylPd dimer **2** (see Supporting Information, SI). We investigated a range of carbon nucleophiles in the presence of solvent quantities of DMSO and found that those with the lowest pK_a, benzoylnitromethane **4**, methyl nitroacetate **5**, and (phenylsulfonyl)nitromethane **6** (pK_a < 6), furnished alkylated products in excellent yields and useful regioselectivities (entries 1−4). Significantly, alkylation does not occur in the absence of the π-acceptor ligand DMSO

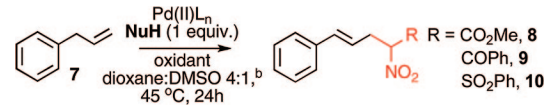
Table 1. Development of the Allylic C—H Alkylation Reaction



entry	NuH	yield (L + B)[a]	L:B[a]
1	$PhO_2SCH_2CO_2Me$, **3**	9%	–
2	NO_2CH_2COPh, **4**	82%	8:1
3	$NO_2CH_2CO_2Me$, **5**	86%	4:1
4	$NO_2CH_2SO_2Ph$, **6**	89%	16:1
5	**5** (no DMSO)[c]	–	–

[a] Determined by ^{1}H NMR analysis of the crude. [b] 0.033 M. [c] Dioxane (0.033 M).

Table 2.



entry	Pd(II)L_n (equiv)	NuH (equiv)	oxidant	yield (L + B)[a]	L:B[a]
1[c]	**1** (1.0)	**5** (1.0)	–	50%	5:1
2	**1** (0.1)	**5** (1.0)	O_2 (1 atm)	27%	4:1
3	**1** (0.1)	**5** (1.0)	DMBQ/AcOH[d]	72%	4:1
4	**1** (0.1)	**5** (1.0)	DMBQ/AcOH[d,e]	–	–
5	**11** (0.1)[f]	**5** (1.0)	DMBQ	4%	–
6	$Pd(OAc)_2$ (0.1)	**5** (1.0)	DMBQ/AcOH[d]	63%	4:1
7	**1** (0.1)	**5** (3.0)	DMBQ/AcOH[d]	83%	4:1
8	**1** (0.1)	**4** (3.0)	DMBQ/AcOH[d]	74%	7:1
9	**12** (0.1)[g]	**6** (3.0)	DMBQ/AcOH[d]	71%	13:1

[a] ^{1}HNMR analysis of crude. [b] 0.33 M. [c] 8 h [d] DMBQ (1.5 equiv), AcOH (0.5 equiv). [e] Bu_4NOAc (1 equiv). [f] 1,2-Bis(phenylsulfinyl)-ethane/Pd(TFA)$_2$. [g] 1,2-Bis(benzylsulfinyl)ethane/Pd(OAc)$_2$.[4a]

(entry 5). As anticipated, a sulfoxide environment is compatible with allylic C—H cleavage. Product was generated when olefin and nucleophile were exposed to **1** and DMSO (Table 2, entry 1).

With a uniform set of conditions for effecting both product forming steps, we began to investigate oxidants to render this process catalytic. Of the oxidants that may be compatible with our carbon nucleophile, we found that sterically hindered DMBQ with AcOH was most effective (Table 2, entries 2−3). Reactivity was significantly diminished when either adding stoichiometric Bu_4NOAc or omitting all sources of catalytic acetate (entries 4−5). These results underscore the importance of quinone/AcOH as a source of catalytic acetate base[4c] and suggest a mechanism that involves Pd(II)/sulfoxide-mediated C—H cleavage followed by DMSO/acetate promoted functionalization. The use of Pd(OAc)$_2$/DMSO gave allylic alkylation product in only moderately diminished yields relative to reaction with **1** (entry 6). Nucleophiles containing ester **5**, ketone **4**, and sulfonyl **6** moieties all gave excellent yields of alkylated products **8**−**10** under optimized conditions (entries 7−9). Interestingly, aliphatic substrates gave ca. 10% yield of product under these conditions.

Experiments to probe the scope of the olefin substrate are summarized in Table 3. A wide variety of both electron-donating (entries 1−3) and -withdrawing (entries 5−11) substituents are well-tolerated on the aryl moiety. Alkylated products are furnished in high yields with good regioselectivities and outstanding *E*/*Z* selectivities (>20:1). Significantly, pure linear compound is readily obtained in good

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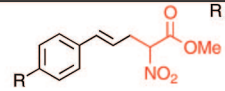
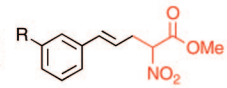
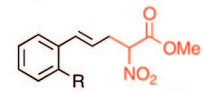
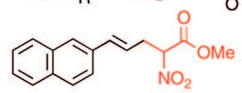
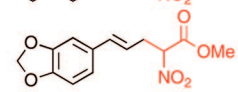
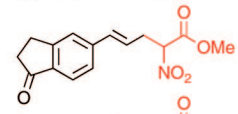
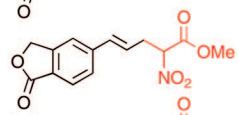
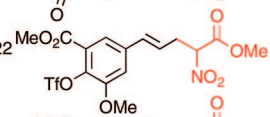
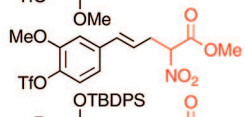
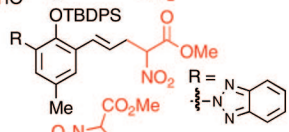
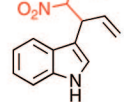
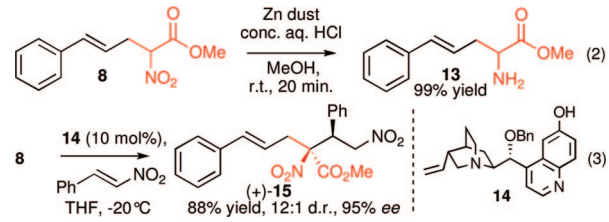
Table 3. Scope of the Allylic C—H Alkylation Reaction

entry	major product		L:B[b]	isolated yield L[a] *E:Z >20:1*
1		R = OMe	1.7:1	50%
2		Me	3:1	61%
3		CH_2=CH_2	3:1	63%
4		H	4:1	62%
5		Br	4:1	60%
6		NTsMe	4:1	63%
7		F	4:1	65%
8		CO_2Me	10:1	61%
9		C(O)Me	10:1	66%
10		CF_3	10:1	56%
11		CN	12:1	65%
12		OMe	5:1	58%
13		N=CPh$_2$	9:1	58%
14		Me	5:1	62%
15		CF_3	>20:1	59%
16		OTBS	3:1	58%
17		OTf	15:1	57%
18			4:1	65%
19			3:1	56%
20			12:1	62%
21			15:1	70%
22			7:1	63%
23			5:1	64%
24		R =	5:1	68%
25			1:5	42% 1.2:1 d.r.

[a] Olefin (1 equiv), **5** (3 equiv), DMBQ (1.5 equiv), AcOH (0.5 equiv), **1** (10 mol%), dioxane/DMSO (4:1, 0.33 M). Average of two runs at 0.5 mmol. Products isolated as one regioisomer and olefin isomer [b] Determined by ^{1}H NMR analysis of the crude.

yields (50−70%) *via* standard column chromatography. We have noted a strong correlation between the electronic properties of the aryl ring and the regioselectivity of alkylation. Electron-withdrawing moieties significantly increase linear isomer ratios (entries 8−11, 20−21), whereas electron-donating moieties erode linear selectivity (e.g., entries 1−2). In the case of electron-rich 3-allylindole a complete reversal of selectivity is observed furnishing the branched isomer as the major product (entry 25). A steric influence on regioselectivity is also observed with *ortho* substitution leading to significant increases in linear product (entries 14, 15 vs 2, 10). The electronic and steric influence upon selectivity may derive from modulation of the stability of a Pd benzyl allyl intermediate that favors alkylation at the internal carbon (e.g., electron-donating groups increase its stability favoring branched isomers).[7]

Functionalities that are unstable to traditional palladium(0)-catalyzed allylic alkylations, such as aryl halides and triflates, are inert to these oxidative conditions (entries 5, 17, 22−23). A variety of pharmacophoric functionalities such as catecol, indanone, benzotriazole, and unprotected indole are also well-tolerated (entries 19−20, 23−25). This functional group tolerance is unexpected given that heteroaromatics are often reactive with and/or attenuate the electrophilicity of Pd(II) catalysts.



To demonstrate the synthetic utility of these alkylation products we investigated further transformations. The nitro moiety can be selectively reduced by the action of zinc dust to furnish the amine **13** in excellent yield (eq 2). This product may be classically resolved to furnish optically enriched unnatural α-amino acid precursors. Alternatively, taking advantage of the nucleophilicity retained by the methine carbon of **8**, a second alkylation can be effected with *trans*-*β*-nitrostyrene (eq 3). This asymmetric conjugate addition, catalyzed by a modified cinchona alkaloid **14**,[8] proceeded in high yield with excellent diastereo- and enantioselectivities, to afford an optically enriched, structurally complex α,α-disubstituted amino acid precursor (+)-**15**.

In summary, the first Pd(II)-catalyzed allylic C—H alkylation is disclosed, providing a novel method for formation of sp^3−sp^3 C—C bonds directly from C—H bonds. We anticipate that this reaction and others like it that provide direct disconnections for rapidly building carbon frameworks will play an important role in advancing synthesis. Further investigations to expand the scope of both substrate and nucleophile are ongoing.

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Supporting Information Available: Experimental procedures, full characterization, and additional experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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