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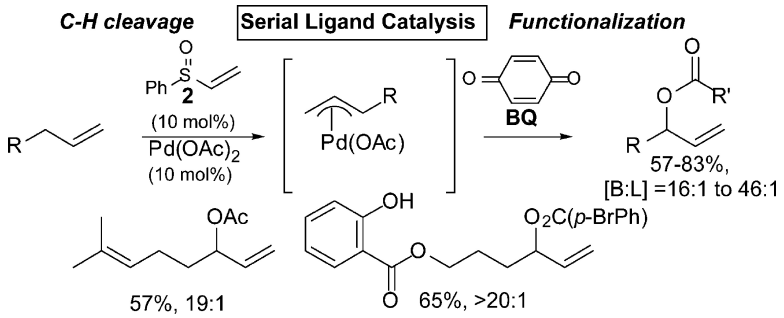
J. Am. Chem. Soc., **2005**, 127 (19), 6970-6971• DOI: 10.1021/ja0500198 • Publication Date (Web): 21 April 2005



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Serial Ligand Catalysis: A Highly Selective Allylic C−H Oxidation

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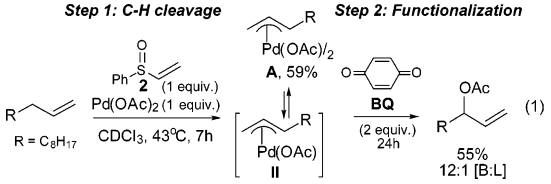
Conventional homogeneous catalysis relies on one transition metal/ligand combination to promote all steps within a catalytic cycle. This approach is suboptimal when different steps within the cycle place different demands on the catalyst. Herein we report for the first time a serial ligand catalysis mechanism in which two different ligands interact sequentially with the metal to promote different product-forming steps of the same catalytic cycle.

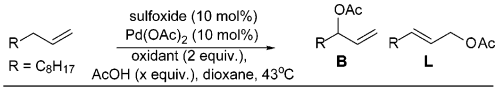
We recently reported sulfoxide-promoted, catalytic $Pd(OAc)_2$/benzoquinone (BQ)/AcOH α-olefin allylic oxidation systems[1] that have the interesting feature of furnishing either predominantly linear or branched allylic acetates depending on whether DMSO or bis-sulfoxide ligands are used, respectively.[1a] While investigating the bis-sulfoxide-promoted system, we discovered that **1** partially decomposes[2] under the reaction conditions to generate vinyl sulfoxide **2** (Table 1). We tested commercially available **2** and found that 10 mol % **2**/$Pd(OAc)_2$ effectively promotes the oxidation reaction to furnish branched products with no decomposition.[1b,3] Reducing the equivalents of AcOH significantly improves regioselectivities (Table 1, entries 3a,b) by suppressing a background Pd(II)-mediated isomerization.[4] We now report a vinyl sulfoxide-promoted catalytic system for the mild, chemo- (α- versus internal olefins), and highly regioselective C−H oxidation of α-olefins to furnish allylic alkyl and aryl esters that proceeds via a mechanism in which two different ligands are responsible for promoting different steps in the catalytic cycle (Table 3).

Mechanistic studies were carried out to establish the fundamental steps of this catalytic cycle and the role of vinyl sulfoxide **2** and BQ therein. When stoichiometric mixtures of 1-undecene, $Pd(OAc)_2$, and **2** were heated and monitored by ^{1}H NMR, dimeric π-allylpalladium acetate complex **A** was observed in ca. 59% yield (eq 1).[5a−c] When BQ was then added to this reaction mixture, formation of allylic acetate product was observed with yields and regioselectivities similar to those observed for the stoichiometric reaction run in the presence of BQ (eq 1, Table 1, entry 3h). In the absence of **2**, with and without BQ, formation of complex **A** was not observed. These data are consistent with **2**, and not BQ, acting as a ligand to effect Pd-mediated allylic C−H cleavage to likely form a monomeric π-allylpalladium intermediate that is detected in the form of dimeric complex **A**.



A combination of **A** (10 mol % Pd) and **2** (10 mol %) catalyzed the allylic oxidation reaction with similar yields and the same regioselectivities as those observed with $Pd(OAc)_2$/**2** (10 mol %) but with lower rates of product formation (Table 1, entries 3b,c). Significantly, **A** is not observed by ^{1}H NMR under the catalytic reaction conditions, consistent with **II** being formed only at low concentration disfavoring dimerization.[5d] Moreover, no olefin exchange was observed upon exposure of **A** to 1-benzyloxy-4-pentene (10 equiv) in the presence of AcOH (40 equiv) and **2** after 48 h at 43 °C in dioxane. This indicates that formation of the π-allylpalladium moiety is not reversible and that a reaction by a pathway separate from this intermediate is unlikely. Thus, while **A** does not lie within the catalytic cycle, it can re-enter the cycle, albeit slowly, upon exposure to the reaction conditions presumably as its monomeric version **II** or **III** (Scheme 1).

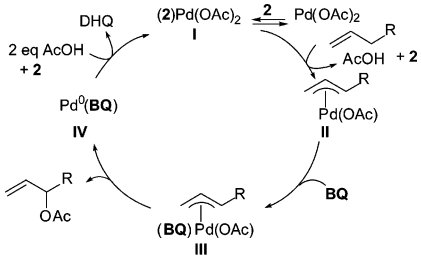
Table 1



entry	sulfoxide		AcOH (equiv.)	oxidant	% yield GC[a], 48h, **B**	[B:L]
1	none		52	BQ	3%	3:1
2	**1**		52	BQ	73%	11:1
3	**2**	a.	52	BQ	66%	12:1
		b.	**4**	**BQ**	**64%**	**31:1**
		c.	4[b]	BQ	60%	31:1
		d.	4	$Cu(OAc)_2$	1%	1:1
		e.	4	BQ(Me)[c]	59%	32:1
		f.	4	$BQ(Me)_2$[d]	15%	21:1
		g.	4	DQ[e]	1%	1:1
		h.[f]	4	BQ	58%	9:1
4	**3**		52	BQ	3%	2:1
5	**4**		52	BQ	4%	3:1

[a] Average of 2−3 runs. Yields are corrected for response factor variations. [b] Complex **A** (10 mol % based on Pd), 72 h. [c] Methyl-1,4-benzoquinone. [d] 2,6-Dimethyl-benzoquinone. [e] Duroquinone. [f] 1 equiv of Pd(OAc)2/**2**, 24 h.

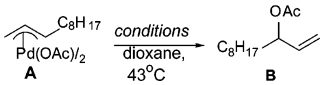
Scheme 1. Serial Ligand Catalysis



We examined the effect of individual reaction components on the functionalization of synthetic **A**[5b,c] under conditions that mimic the reaction of a monomeric Pd−π-allyl intermediate during one catalytic reaction cycle (ca. 3.3 mM Pd, 20 equiv of BQ, 40 equiv of AcOH, 1 equiv of **2**, Table 2). BQ was uniquely effective at promoting product formation with similar yields and the same regioselectivities as those observed under standard catalytic conditions (Table 2, entry 3). Importantly, the addition of both vinyl sulfoxide **2** and BQ did not significantly impact yields or regioselectivities (Table 2, entry 4). These data are consistent with BQ, and not vinyl sulfoxide **2**, acting as a ligand to effect functionalization from a monomeric Pd−π-allyl intermediate.[6]

10.1021/ja0500198 CCC: $30.25

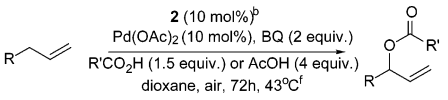
Table 2 [a]

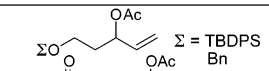
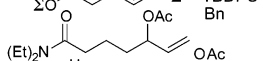
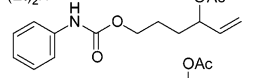
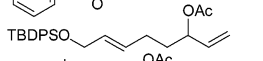
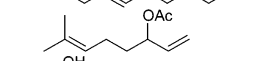
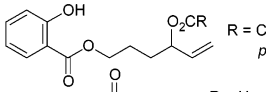
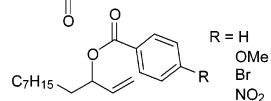
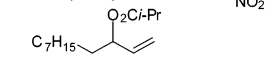


entry	conditions	GC yield, B $t = 6$ h	[B:L]
1	AcOH (40 equiv)	<1%	–
2	**2** (1 equiv)	<1%	–
3	BQ (20 equiv)	58%	32:1
4	**2** (1 equiv) BQ (20 equiv)	62%	34:1
5	PPh3 (20 equiv)	42%	1:1[b]
6	dppe[c] (10 equiv)	44%	1:1[d]

[a] Average of 3 runs. [b] **L**, 46%. [c] 1,2-Bis(diphenylphosphino)ethane. [d] **L**, 47%.

Table 3 [a]



entry	major product	isolated yield	branched:linear[c]
1	 Σ = TBDPS	72%	16:1
2	 Bn	59%	18:1
3[e]		56%	18:1
4		64%	26:1
5		56%	>20:1[d]
6		57%	19:1[d]
7	 R = CH_3	64%	22:1
8	*p*-BrPh	65%	>20:1[d]
9	 R = H	71%[g]	37:1
10	OMe	70%	41:1
11	Br	74%[g]	46:1
12	NO_2	83%[g]	>20:1[d]
13		64%[g]	32:1

[a] Data based on an average of 3−4 runs. [b] **2** and $Pd(OAc)_2$ must be mixed neat. [c] Ratio based on GC analysis of crude. [d] Ratio based on ^{1}H NMR analysis of crude. [e] 20 mol % **2**. [f] Temperatures below 40 °C (e.g., 38 °C) result in decreased yields. [g] 48 h.

A catalytic cycle consistent with these data is outlined in Scheme 1. The first step involves electrophilic allylic C−H cleavage of the α-olefin via a **2**/$Pd(OAc)_2$ complex (**I**) to afford Pd−π-allyl intermediate **II**.[7] Both the sulfoxide and vinyl moieties of **2** are necessary for effecting Pd-mediated C−H cleavage; ethyl **3** and ketone **4** analogues do not promote this reaction (Table 1, entries 4 and 5). In the absence of BQ, monomer **II** dimerizes to give the observed complex **A**. Under the reaction conditions, **II** reacts directly with BQ (present in high concentrations)[5e] to give **III** that is activated toward nucleophilic functionalization.[8] In further support of the well-precedented role of BQ as a functionalization-promoting ligand,[8b−f] no reaction was observed with other standard Pd(0)/Pd(II) oxidants and decreasing yields and regioselectivities were observed with increasing steric hindrance of BQ (Table 1, entries 3d−g).[6] Moreover, the branched regioselectivity of these reactions is consistent with functionalization of an electronically dissymmetric π-allyl intermediate that may be generated from ligands with differential trans effects such as BQ and carboxylate.[9] In support of this, when complex **A** was treated with either PPh_3 or dppe, ligands capable of both breaking up dimeric **A** and displacing anionic ligands to generate electronically symmetric Pd−π-allyl intermediates, high yields of product formation with no regioselectivity were observed (Table 2, entries 5 and 6).

The high functional group compatibility of this mild method is demonstrated in Table 3. Incorporation of benzylic, acidic, and basic functionality is possible without a loss in yields or regiocontrol (Table 3, entries 2−4, 7, and 8). Significantly, with diolefin substrates, chemoselectivity is observed for the α-olefin (Table 3, entries 5 and 6). Variation in the steric and electronic properties of the carboxylic acid component is also well-tolerated (Table 3, entries 8−13).

In conclusion, this report describes a mild, chemo-, and highly regioselective Pd-catalyzed allylic oxidation reaction that proceeds via a novel mechanism where two different ligands interact serially with Pd to promote different steps of the catalytic cycle. Further studies are targeted toward elucidating the role of **2** in promoting C−H cleavage, developing asymmetric versions of this reaction, and exploring the generality of serial ligand catalysis for effecting other challenging transition metal-mediated transformations.

Acknowledgment. M.C.W. gratefully acknowledges the Henry Dreyfus Foundation and Harvard University for financial support. We are grateful to Dr. G. Dudek and Ms. Q. Liao for HRMS and to a reviewer for suggesting the experiment in Table 2, entry 6.

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

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(4) (a) Isomerization is suppressed in the presence of α-olefin (SI). (b) Overman, L. E.; Knoll, F. M. *Tetrahedron Lett.* **1979**, *4*, 321. (c) Lowering AcOH equivalent in the $Pd(OAc)_2$/DMSO system leads to significantly decreased product yields.

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(6) Preliminary data suggest that the $Pd(OAc)_2$/DMSO system proceeds via a different mechanism than **2**/$Pd(OAc)_2$, which may account for the different regioisomeric outcomes observed.[1b,4c] For example, the $Pd(OAc)_2$/DMSO system is significantly less sensitive to the steric hindrance of BQ, suggesting that BQ may not be necessary for functionalization. This is consistent with previous observations that DMSO promotes formation of linear allylic acetates from α-olefins in stoichiometric $Pd(OAc)_2$ reactions: Kitching, W.; Rappoport, Z.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1966**, *88*, 2054. Additionally, structural changes to the DMSO ligand result in different regioselectivities, but changes to **2** do not (SI). A complete reversal in regioisomeric outcomes as a result of a change in mechanism (i.e., S_N2' on σ-allyl Pd vs S_N2 on a π-allyl Pd) in the amination of π-allyl PdCl complexes has been reported: Åkermark, B.; Åkermark, G.; Hegedus, L.; Zetterberg, K. *J. Am. Chem. Soc.* **1981**, *103*, 3037.

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JA0500198