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Palladium(II)-Catalyzed Enantioselective Aerobic Dialkoxylation of 2-Propenyl Phenols: A Pronounced Effect of Copper Additives on Enantioselectivity

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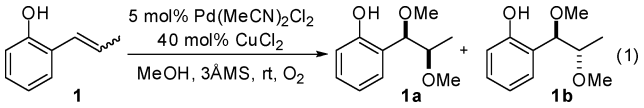
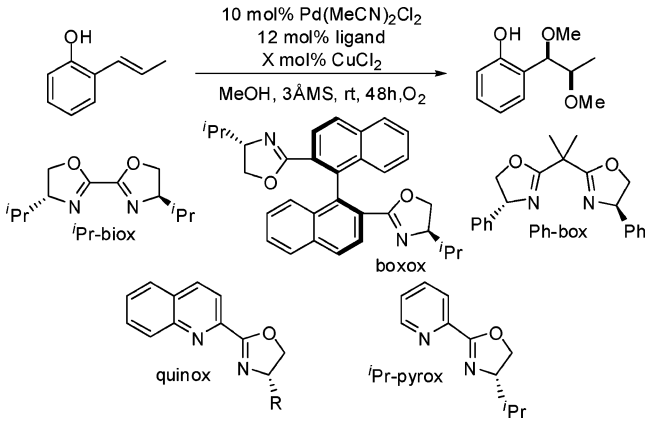
Despite the potential synthetic utility, very few enantioselective intermolecular olefin functionalization reactions have been reported using Pd(II)-catalyzed oxidation reactions, especially those which involve nucleopalladation.[1,2] To achieve enantioselective nucleopalladation, not only must a suitable ligand be identified in order to differentiate the enantiotopic faces of the coordinated olefin, but also reversible β-hydride elimination must be inhibited to avoid erosion of the initial asymmetric induction. Recently, as part of our program aimed at the development of Pd(II)-catalyzed olefin functionalization reactions, we discovered a dialkoxylation reaction of styrenes containing an *o*-phenol (eq 1).[3] A key finding based on isotopic labeling experiments was that β-hydride elimination is avoided in the dialkoxylation process, making the development of an enantioselective variant possible. Additionally, an enantioselective dialkoxylation reaction would allow rapid generation of a common structural motif found in a number of biologically active compounds.[4] Herein, we present the discovery of an enantioselective dialkoxylation reaction where removal of copper from the reaction, a standard additive in Pd(II)-catalyzed oxidation reactions, proved essential for effective asymmetric catalysis.



Previous mechanistic studies suggested that the dialkoxylation reaction proceeded through a regioselective nucleopalladation of **A** via methanol addition to the β-carbon of the styrene **B**, followed by formation of a quinone methide intermediate **C** with concomitant reduction of Pd(II) (Scheme 1).[3] Dialkoxylation is achieved by the addition of a second equivalent of methanol to **C** where modest diastereoselection is observed and attributed to the influence of the chiral center of **C**. We therefore proposed that the initial alcohol addition to the coordinated olefin would set the absolute stereochemistry with identification of a suitable chiral ligand. To test this hypothesis, Pd[(−)-sparteine]Cl_2 was used in the dialkoxylation reaction of 2-propenylphenol in MeOH using the previously optimized conditions (Table 1, entry 1). To our surprise, a racemic dialkoxylation product was observed. It was difficult to envision why no enantioselective catalysis is observed using (−)-sparteine even if it is not the optimal ligand. A plausible explanation for the absence of asymmetric induction is that copper could displace the chiral ligand from Pd, leading to the formation of a copper−ligand complex. To test this possibility, copper was removed from the reaction and, indeed, a modest enantiomeric excess of 17% was observed albeit with a reduction in yield (entry 2, Table 1).[5] It should be noted that in the initial optimization phase of this reaction, copper was found to be crucial for catalyst turnover.

On the basis of the low enantiomeric excess found using (−)-sparteine and that this ligand is very difficult to systematically modify, oxidatively stable C_2- and C_1-symmetric oxazoline based ligands were evaluated (entries 3−10, Table 1). C_2-symmetric oxazolines were found to be poor ligands in this reaction; however, in the absence of copper, excellent asymmetric catalysis is observed using quinoline derived oxazolines (entries 7−10).[6] These quinoline oxazoline derivatives are readily synthesized in two steps from the corresponding carboxylic acid and enantiopure β-amino alcohol making this ligand class highly modular.[7] Use of the (*R*)-benzyl derivative leads to an 85% ee and an 84% GC yield of 2-(1*S*,2*S*)-

Table 1. Evaluation of Chiral Ligands



entry	ligand	$CuCl_2$ (mol %)	yield (%)[a]	ee (%)[b]
1	(−)-sparteine	20	70	0
2	(−)-sparteine	0	24	17
3	^{i}Pr-biox	0	11	5
4	boxox	0	3	0
5	Ph-box	0	NR	NR
6	^{i}Pr-pyrox	0	10	60
7	Ph-quinox	0	14	37
8	^{t}Bu-quinox	0	10	83
9	Bn-quinox	0	85	84
10	^{i}Pr-quinox	0	67	82
		With $CuCl_2$		
11	^{i}Pr-quinox	2.5	80	72
12	^{i}Pr-quinox	5	78	59
13	^{i}Pr-quinox	10	81	26
14	^{i}Pr-quinox	20	88	10

[a] GC yields using 5-nonanone as the internal standard; NR = no reaction. [b] Determined by GC equipped with a chiral stationary phase.

Scheme 1. Proposed Mechanism

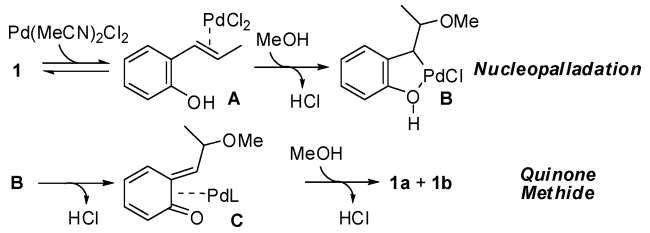


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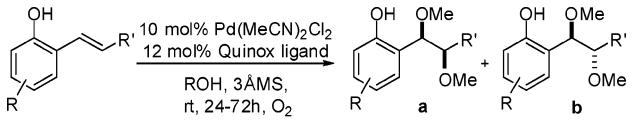
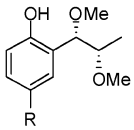
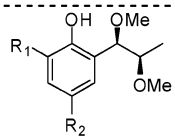
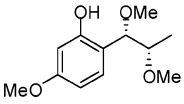
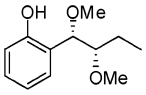
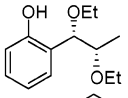
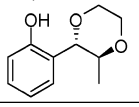
Table 2. Scope of Pd(II)-Catalyzed Enantioselective Dialkoxylation



entry	ligand	product		yield[a] (%)	ee[b] (%)	a : b[c]
1	(*R*)-Bn-quinox		R = H **1a**	63	85	5 : 1
2[d]	(*R*)-Bn-quinox		R = OMe **2a**	74	92	7.5 : 1
3[d]	(*R*)-Bn-quinox		R = Me **3a**	70	91	8 : 1
4	(*R*)-Bn-quinox		R = Cl **4a**	60	86	5 : 1
5	(*S*)-^{i}Pr-quinox		R_1 = Me, R_2 = H **5a**	68	83	9 : 1
6	(*S*)-^{i}Pr-quinox		R_1 = ^{t}Bu, R_2 = ^{t}Bu **6a**	56	63	7 : 1
7	(*R*)-Bn-quinox		**7a**	69	84	5 : 1
8	(*R*)-Bn-quinox		**8a**	64	82	6 : 1
9	(*R*)-Bn-quinox		**9a**	58	83	3: 1
10	(*R*)-Bn-quinox		**10a**	46	81	7 : 1

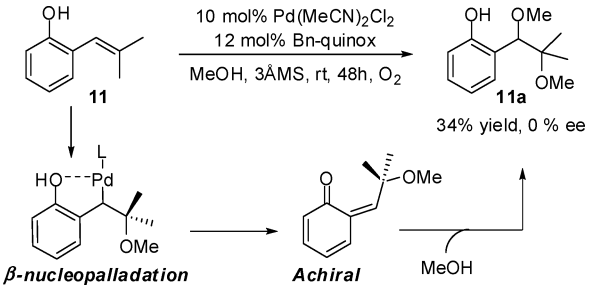
[a] Yield is reported as a mixture of **a** and **b** and is an average of two experiments. [b] Determined by GC or HPLC equipped with chiral stationary phase. [c] Determined by ^{1}H NMR and GC. [d] The reaction was carried out at 0 °C.

1,2-dimethoxypropyl)phenol (entry 9).[8] Additionally, as the [copper] is increased under these conditions, a significant reduction in the ee is observed, consistent with a ligand exchange process (entries 10−14). This result may explain why there are very few examples of enantioselective Pd(II)-catalyzed oxidation reactions in the presence of copper salts.

With the optimized ligand and reaction conditions established, the scope of the enantioselective dialkoxylation reaction was examined for a number of 2-propenylphenols (Table 2). Modest to good yields are observed for both electron rich and electron poor substrates with enantiomeric excesses up to 92%. Of note, for substrates with an additional substituent ortho to the phenol (entries 5 & 6), the ^{i}Pr-quinox ligand proves to be more effective for this substrate class. Ethanol and ethylene glycol were also examined to probe whether other alcohols could act as the nucleophile in this reaction (entries 9 & 10). Both solvents led to successful dialkoxylation with good enantiomeric excesses albeit in modest yields. An exciting aspect of developing these direct-O_2 coupled reactions is that the scope of the process has been extended to substrates which did not undergo the dialkoxylation reaction previously (entries 2 and 6−8).

Our next goal was to probe if the absolute configuration is set by β-nucleopalladation. To explore this, trisubstituted olefin **11** was subjected to the dialkoxylation reaction (Scheme 2). If the reaction involves an α-nucleopalladation, an enantiomeric excess comparable to other examples above in product **11a** was predicted. In contrast, if β-nucleopalladation occurs, a racemic product was expected. In

Scheme 2. Evidence for β-Nucleopalladation



the experiment, the product **11a** was found to be racemic supporting β-nucleopalladation as the enantio-determining step. Additionally, the minor product diastereomer for all substrates in Table 2 has a very similar enantiomeric excess as the major diastereomer which is consistent with the absolute configuration set by initial nucleopalladation.

In conclusion, we have successfully developed a direct O_2-coupled Pd(II)-catalyzed enantioselective dialkoxylation of 2-propenylphenols by utilizing chiral quinoline oxazoline ligands. In this process, evidence for enantioselective β-nucleopalladation has been garnered. Of most significance, without removing the Cu salts, it is unlikely that this enantioselective catalytic process would have been discovered. Considering that copper is a standard cooxidant in Pd(II) oxidation chemistry, this finding should provide the foundation for the development of other Pd(II)-catalyzed asymmetric oxidative transformations. Future efforts are directed toward this goal.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The absolute configuration of the product was determined by comparison to an independently prepared authentic sample. See Supporting Information for details.

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