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Palladium-Catalyzed Enantioselective Addition of Two Distinct Nucleophiles across Alkenes Capable of Quinone Methide Formation

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The formation of two carbon−heteroatom bonds across an alkene is a process which rapidly increases molecular complexity. The osmium-catalyzed Sharpless dihydroxylation[1] is the epitome of enantioselective alkene difunctionalization, though recent research has included other metal catalysts and expanded to the formation of functional groups other than 1,2-diols.[2] Currently, significant focus has been on palladium catalysis, likely due to the efficiency with which palladium activates olefins for nucleophilic attack.[3] However, to achieve the second bond construction, β-hydride elimination from a Pd-alkyl intermediate **A**, which leads to a Wacker-type monofunctionalized alkene product **1**,[4] must be prevented (Scheme 1). The alkene dialkoxylation reaction developed in our laboratory is believed to accomplish this through the formation of a quinone methide intermediate, which allows for attack by a second equivalent of alcohol.[5] Based on this mechanistic proposal, we envisioned an alkene difunctionalization reaction where a sequential intramolecular-intermolecular process would allow for the selective formation of two distinct carbon−heteroatom bonds by employing substrates which contain a nucleophile tethered to the alkene (Scheme 1). We hypothesized initial intramolecular nucleopalladation to form heterocyclic intermediate **B**. Subsequent formation of a quinone methide intermediate **C** allows for attack by an exogenous nucleophile to form the product and release Pd^0, which is reoxidized using molecular oxygen. Herein we report a highly enantioselective addition of two distinct nucleophiles across alkenes capable of quinone methide formation to access oxygen-based heterocycles with contiguous chiral centers.

In exploring the possibility of sequential intraintermolecular alkene functionalization reactions, we examined **2** as a substrate[6] with methanol as the exogenous nucleophile. Under the standard conditions for enantioselective intermolecular alkene dialkoxylation,[5b] using (*S*)-^{i}PrQuinox as the chiral ligand, a low yield of the desired product was observed with promising enantioselectivity, but low diastereoselectivity (Table 1, entry 1).[7] Addition of a catalytic amount of base and removal of molecular sieves led to modest improvements in product yield (entry 2). Reflecting on our intermolecular asymmetric dialkoxylation reaction, where copper improved yield and chemoselectivity but was removed to achieve high enantioselectivity, we revisited the use of copper as an additive to improve the reaction.[5b] We hypothesized that the reason for decreased enantioselectivity with increased copper loading was that Cu sequesters the chiral ligand from Pd via ligand substitution, resulting in an achiral palladium catalyst. Thus we added 20 mol % $CuCl_2$ along with enough chiral ligand to coordinate both metals (32 mol %). A significant improvement in yield was observed without a detrimental effect on the enantiomeric ratio (entry 3). Based on the accelerated rate of the reaction, we were able to decrease the metal and ligand loadings (entry 4). To find conditions that would allow for the use of nucleophiles other than methanol, other solvents were evaluated. We were encouraged to find that both THF and toluene led to increased enantioselectivity, albeit with a decrease in rate and product yield (entries 5 and 6). A 1:1 mixture of THF/toluene was also found to be a viable solvent system (entry 7). Improvements in rate and yield were observed when using CuCl instead of $CuCl_2$, potentially due to a decrease in the [Cl^-] or a change in oxidation potential (entry 9).[8]

Scheme 1. Avoiding β-Hydride Elimination To Develop Pd-Catalyzed Alkene Difunctionalization Reactions

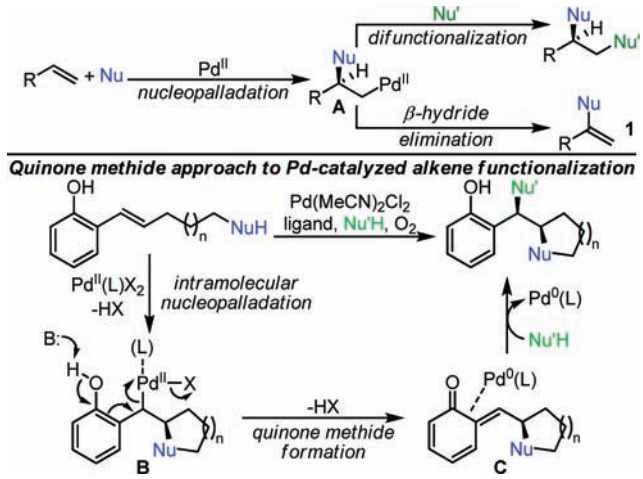
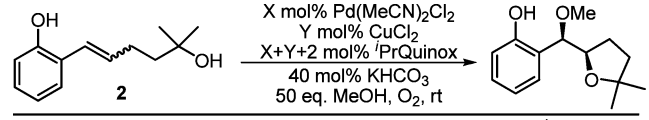
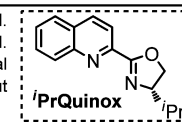


Table 1. Optimization of Reaction Conditions



entry	X	Y	solvent	time	%conv[a]	%yield[a]	er[b]	dr[b]
1[c]	10	--	MeOH	15 h	100	2	88:12	2.4:1
2	10	--	MeOH	15 h	74	8	92:8	2.7:1
3	10	20	MeOH	10 min	100	95	92:8	9.4:1
4	4	8	MeOH	30 min	100	87	92:8	9.6:1
5	4	8	THF	2 h	79	54	98:2	7.8:1
6	4	8	toluene	2 h	96	68	97:3	5.1:1
7	4	8	1:1 THF:toluene	5 h	100	67	97:3	6.7:1
8[d]	4	8	1:1 THF:toluene	2 h	99	80	98:2	8.9:1

Reactions run on 0.1 mmol scale with [**2**]=0.1 M. [a]Determined by GC analysis using an internal standard. [b]Determined by GC with a column equipped with a chiral stationary phase. [c]With 50 mg 3 Å MS and without $KHCO_3$. [d]CuCl was used in place of $CuCl_2$



With these optimized conditions, the scope of the alkene difunctionalization reaction was evaluated. In addition to methanol, *n*-butanol can be used as an exogenous nucleophile (Table 2, **3b**) where the use of toluene as solvent was found to give slightly improved yields.[9] Alcohols containing a functional group are also well tolerated, including 3-butenol, 2-methoxyethanol, and 2-chlo-

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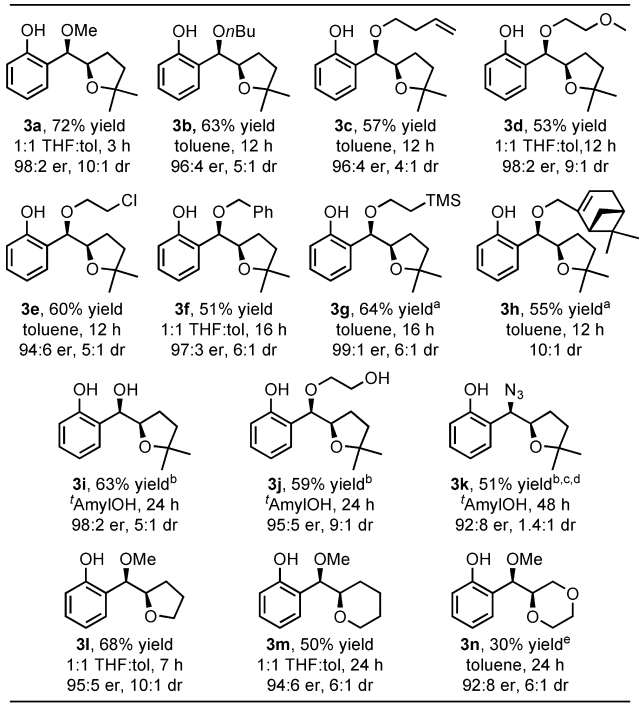
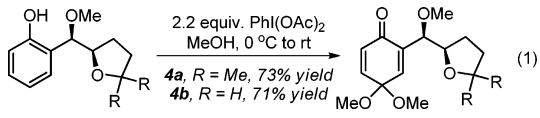
Table 2. Evaluation of Scope



Reaction conditions: 4 mol% $Pd(MeCN)_2Cl_2$, 8 mol% CuCl, 14 mol% (*S*)-^{i}PrQuinox, 40 mol% $KHCO_3$, 50 eq. NuH, balloon O_2, rt, 0.1 M, 0.50 mmol scale. er for major diastereomer determined by GC, HPLC or SFC using a column equipped with a chiral stationary phase. dr determined by GC or ^{1}H NMR. Major diastereomer confirmed by single crystal X-ray analysis of **3a** and absolute configuration determined by Mosher ester analysis of **3i**. [a]25 eq. of NuH. [b]4 mol% Pd[(*S*)-^{i}PrQuinox]Cl_2, 8 mol% Cu[(S)-^{i}PrQuinox]Cl_2, 10 mol% $NaHCO_3$. [c]30 °C, 2 eq. of NaN_3. [d]er of minor diastereomer is 92:8. [e]1 eq. $NaHCO_3$

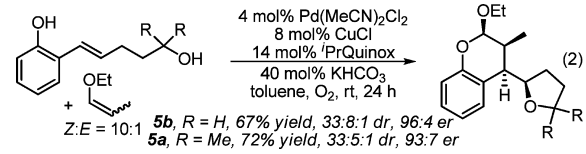
roethanol (entries **3c**−**3e**). Ethers with the potential for deprotection are formed using benzyl alcohol and trimethylsilylethanol, with the latter giving an excellent er of 99:1 (**3f** and **3g**). A relatively complex chiral alcohol, (−)-myrtenol, was employed successfully (**3h**), demonstrating the potential to couple two chiral partners. To enhance miscibility, *tert*-amylalcohol was employed for the addition of water, yielding the free secondary alcohol product with excellent enantioselectivity (**3i**). This solvent was found to be preferred for other polar nucleophiles, such as ethylene glycol (**3j**). Excitingly, the use of sodium azide demonstrates that an exogenous nitrogen nucleophile is viable (**3k**). While low diastereoselectivity is observed, the diastereomers are readily separable. In examining what other ring systems can be accessed, it was found that primary alcohol substrates cyclize to yield tetrahydrofuran (**3l**) and tetrahydropyran (**3m**) containing compounds. A 1,4-dioxane is formed (**3n**) in modest yield and good enantioselectivity.



(1)

While the incorporation of an *o*-phenol in the substrate is a mechanistic necessity at this stage, it can be used as a synthetic handle for further functionalization. To demonstrate this, the phenol was oxidized using $PhI(OAc)_2$ to access *p*-benzoquinone ketals **4a** and **4b** with no loss of diastereomeric purity (eq 1).[10]

To extend the scope of this process to carbon nucleophiles, we submitted an enol ether, a classic inverse electron demand Diels−Alder partner with quinone methides,[11] to the reaction conditions. To our delight, the Diels−Alder products **5a** and **5b** are isolated in good diastereoselectivity and excellent enantioselectivity.[12] This complexity generating reaction sets four contiguous stereocenters and allows access to novel functionalized chroman derivatives, an important pharmacophore.[13]



In conclusion, we have developed a highly enantioselective Pd-catalyzed alkene difunctionalization reaction involving the addition of two distinct nucleophiles, a process which allows for the formation of complex chiral molecules from relatively simple starting materials. Future work will focus on expansion of the scope to include other types of nucleophiles and Diels−Alder partners, improvement of reaction conditions to reduce the required amount of the second nucleophile, and development of a deeper understanding of the mechanistic details of the reaction.

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

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