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Dioxygen-Coupled Oxidative Amination of Styrene

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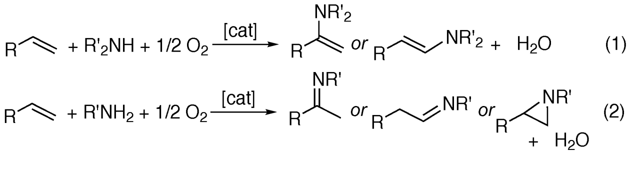
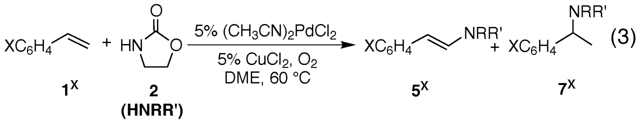
Direct amination of olefins continues to be a major focus of catalysis research,[1] and dioxygen-coupled intermolecular oxidative amination (eqs 1 and 2) is an attractive target.[2] A few examples of this reactivity with electron-deficient olefins, such as methyl acrylate, have been described,[3] but only one example of an "unactivated" olefin has been reported: anti-Markovnikov oxidative coupling of styrene (**1**) and oxazolidinone (**2**) proceeds in low yield with $(CH_3CN)_2PdCl_2$ (**3**) as the catalyst.[3a,4] In the process of investigating this reaction (Scheme 1A), we discovered that $(Et_3N)_2PdCl_2$ (**4**) also catalyzes the reaction, but with a complete switch in regioselectivity (Scheme 1B). This unexpected selectivity reversal results from the presence of a Brønsted base in the reaction (NEt_3), as revealed by the fact that simple anionic bases (e.g., acetate), used in combination with **3**, also induce formation of the Markovnikov product (Scheme 1C). In the presence of base, palladium-catalyzed aerobic oxidative amination proceeds successfully with several different aryl olefins and nitrogen nucleophiles.



We initiated our study by evaluating a series of *para*-substituted styrene derivatives, $p\text{-}XC_6H_4CH{=}CH_2$ (X = H, CF_3, Cl, F, CH_3), in the $(CH_3CN)_2PdCl_2$-catalyzed oxidative amination reaction with oxazolidinone. Anti-Markovnikov enecarbamate ($\mathbf{5^X}$) is the primary product, but small quantities (<10%) of the Markovnikov hydroamination product ($\mathbf{7^X}$) are observed with $\mathbf{1^F}$ and $\mathbf{1^{CH3}}$ (eq 3, Table S1). Speculating that adventitious acid might promote hydroamination,[5] we conducted the reactions in the presence of triethylamine (10 mol %)[6] as an acid scavenger.[7] Under these conditions, no hydroamination products form, but, more significantly, the reactions display >5-fold increase in rate, and the Markovnikov enecarbamates are produced (**6**; Table 1, entries 1−6). The major oxidative amination products of dihydronaphthalene (Table 1, entry 7) and indene (Supporting Information) reflect addition of oxazolidinone to the benzylic alkene position followed by olefin isomerization.[8]



Control experiments confirm that both **5** and **6** result from direct metal-mediated amination of the olefin, not from condensation of oxazolidinone with the corresponding aldehyde or ketone. No olefin amination occurs in the absence of palladium, and the copper cocatalyst does not affect the reaction selectivity. In the absence of $CuCl_2$ under anaerobic conditions, stoichiometric oxidation products display the same product selectivity.

Scheme 1. Regioselective Oxidative Amination of Styrene

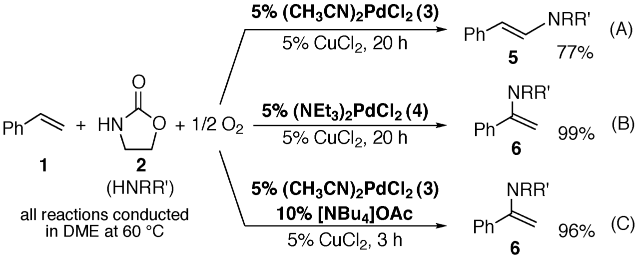
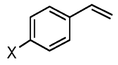
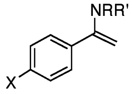
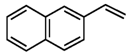
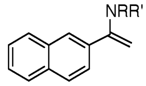
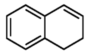
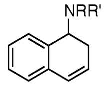


Table 1. $(NEt_3)_2PdCl_2$-Catalyzed Oxidative Amination of Aryl Olefins by Oxazolidinone (**2**, HNRR′)[a]

	Substrate	Product	% Yield[c]
			
1	X = H		99
2	CF_3		39
3	Cl		70
4	F		77
5	CH_3		73
6[b]			98
7[b]			72

[a] Reaction conditions: olefin (3 mmol), **2** (0.5 mmol), $(CH_3CN)_2PdCl_2$ (0.025 mmol), NEt_3 (0.05 mmol), $CuCl_2$ (0.025 mmol), 1 atm of O_2, 2 mL of DME, 60 °C, 24 h. [b] Olefin (2 mmol). [c] Isolated yields, based on **2**.

^1H NMR spectroscopic studies ($CDCl_3$, THF-d_8) reveal that triethylamine coordinates readily to palladium in solution, and $(Et_3N)_2PdCl_2$ (**4**) was prepared independently and characterized by single-crystal X-ray crystallography. This complex exhibits the same activity and product selectivity as catalyst generated in situ.

The catalyst-dependent switch in regioselectivity is a remarkable feature of these reactions, and the coordinating ability of triethylamine initially suggested that ligand steric effects might influence product selectivity (NEt_3 cone angle = 158°).[9,10] Subsequent experimental observations, however, failed to support this model as simple anionic bases exert the same effect as triethylamine.[11] In the presence of 10 mol % $[NBu_4]OAc$, $(CH_3CN)_2PdCl_2$ catalyzes nearly quantitative formation of the Markovnikov enecarbamate (**6**, Scheme 1C), and the reaction exhibits a rapid catalytic rate nearly identical to that observed with $(NEt_3)_2PdCl_2$ as the catalyst. This observation leads us to postulate that the increased rate and altered regioselectivity arises from a Brønsted base effect. Indeed, the use of deprotonated oxazolidinone (lithium salt) results in the formation of **6** with $(CH_3CN)_2PdCl_2$ as the catalyst, even if no external base is added. Studies of stoichiometric palladium-mediated amination of olefins by saturated secondary amines reveal that external base deprotonates the adduct arising from nucleophilic attack on the

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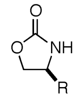
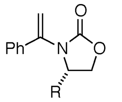
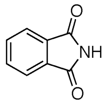
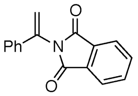
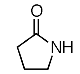
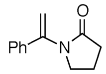
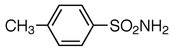
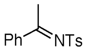
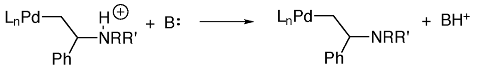
Table 2. Variation of Nitrogen Nucleophiles in the Aerobic Oxidative Amination of Styrene[a]

	RR'NH/RNH$_2$	Product	% Yield[b]
			
1[c]	R = Benzyl		90
2[c]	R = Isopropyl		56
3[d]			86
4[e]			93
5[c]			79

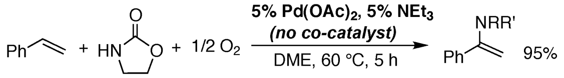
[a] Reaction conditions: styrene (3 mmol), nucleophile (0.5 mmol), $(CH_3CN)_2PdCl_2$ (0.025 mmol), $CuCl_2$ (0.025 mmol), base (0.05 mmol), 1 atm of O_2, 2 mL of DME, 60 °C, 24 h. [b] Isolated yield, based on nucleophile. [c] Base = NEt_3. [d] Base = $[NBu_4]OAc$. [e] Base = NaOAc.

coordinated olefin (eq 4).[12,13] Further studies will be necessary to identify mechanistic details of the catalytic reactions, in particular to determine the origin of base-induced rate enhancement and the unusual switch in product regioselectivity. Nucleophilic attack on a coordinated olefin represents one reasonable mechanism, but the data cannot exclude a pathway involving N−H activation followed by olefin insertion into the palladium−nitrogen bond.[14]


(4)

The beneficial effect of base in the catalytic reaction permits several other nitrogen nucleophiles to be used (Table 2). Successful examples include chiral oxazolidinones, a cyclic imide and amide, and *p*-toluenesulfonamide. With the primary sulfonamide, an initially formed enamide product presumably tautomerizes under the reaction conditions to form the imine. Further exploration of the substrate scope is ongoing, but we note that each of the successful nucleophiles possesses a relatively acidic N−H group. Less acidic nucleophiles, including morpholine, piperidine, and anilines, were unsuccessful under the present conditions. The ineffectiveness of the latter class of substrates probably reflects their coordinating ability and is related to the observation that catalytic turnover is inhibited at elevated $[NEt_3]$ (>15 mol %). ^{1}H NMR spectroscopic studies (THF-d_8) reveal that triethylamine readily displaces olefins coordinated to palladium(II).[15]

In each of the reactions above, the copper cocatalyst is required for efficient catalytic turnover. Nevertheless, preliminary observations suggest it will be possible to identify alternative catalytic conditions compatible with direct dioxygen-coupled turnover.[16] Palladium acetate (**8**) is less effective than **3** under standard reaction conditions. The combination of **8** with catalytic quantities of NEt_3 (5 mol %), however, promotes efficient catalytic turnover in the absence of copper cocatalyst under otherwise identical conditions (eq 5). This catalyst system bears significant resemblance to recently reported methods for alcohol oxidation[13,16b−d] and intramolecular oxidative amination of olefins.[2d] The versatility demonstrated by such a simple catalyst composition holds significant promise for the development of new dioxygen-coupled oxidation reactions.



(5)

1 **2** **6**

On the basis of the reactivity described herein, we envision many new opportunities for the intermolecular oxidative functionalization of alkenes with molecular oxygen. Studies directed toward this end are ongoing.

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Supporting Information Available: Experimental procedures, product characterization, and crystallographic data (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Preliminary studies indicate that with **4** as the catalyst, one equivalent of NEt_3 remains coordinated throughout the reaction, and the other serves as a Brønsted base. The first equivalent of NEt_3 can be successfully replaced by other donor ligands, such as the *N*-heterocyclic carbene, 1,3-bis-(2,6-diisopropylphenyl)-imidazol-2-ylidene) (IPr).

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