

Formation of Enamides via Palladium(II)-Catalyzed Vinyl Transfer from Vinyl Ethers to Nitrogen Nucleophiles

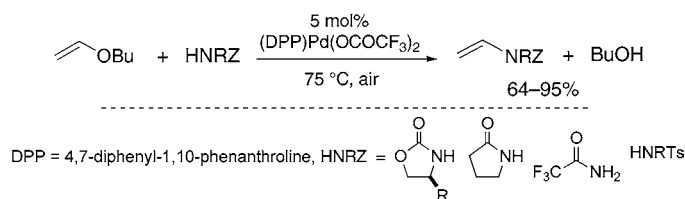
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ABSTRACT



Palladium(II) complexes catalyze the formation of enamides via the formal cross-coupling reaction between nitrogen nucleophiles and vinyl ethers. These vinyl transfer reactions proceed in good yields with amide, carbamate, and sulfonamide nucleophiles, and the optimal catalyst is (DPP)Pd(OCOCF₃)₂ (DPP = 4,7-diphenyl-1,10-phenanthroline).

Recent developments in palladium(0)-catalyzed carbon–nitrogen bond formation have led to numerous useful synthetic methodologies, particularly for the cross-coupling of allyl,¹ aryl,² and vinyl^{3,4} halides and related electrophiles

with amine and amide nucleophiles. These reactions are initiated by oxidative addition of a C–X bond (X = halide, acetate, triflate) at a palladium(0) center. Palladium(II)-catalyzed transformations have also been developed for C–N bond formation, and both oxidative and nonoxidative reactions are known.⁵ Examples include allylic substitution,⁶ rearrangement of allylic imidates,⁷ and hydroamination⁸ and oxidative amination^{8–10} of alkenes. This report describes a new method for carbon–nitrogen bond formation involving

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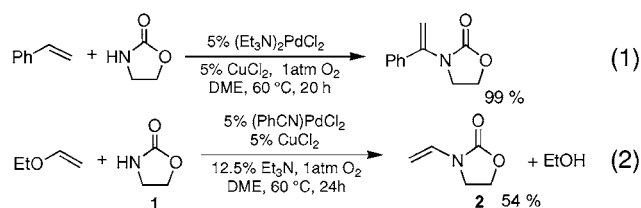
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palladium(II)-catalyzed vinyl transfer from vinyl ethers to nitrogen nucleophiles.¹¹

During our recent studies on the palladium(II)-catalyzed oxidative amination of olefins (for example, eq 1),^{10b} we observed that ethyl vinyl ether undergoes nonoxidative vinyl transfer to the nitrogen nucleophile (eq 2). This reaction represents a C–N cross-coupling reaction in which the vinyl ether is the electrophilic partner. However, palladium(0)-catalyzed cross-coupling reactions are generally incompatible with an aerobic atmosphere, and vinyl ethers are not expected to undergo efficient oxidative addition to palladium(0). The limited precedent for this class of reactions, together with growing synthetic interest in enamides,¹² prompted us to investigate this reactivity further.



A series of palladium(II) catalysts were explored to improve upon the reaction catalyzed by (PhCN)₂PdCl₂. The vinylation of 2-oxazolidinone was used to investigate the effects of both counterions and neutral donor ligands on palladium(II). The higher boiling point of butyl vinyl ether (BVE) relative to ethyl vinyl ether (eq 2) generally makes it a more convenient substrate in these reactions. BVE also served as the solvent in the reactions.

Recent results by Schlaf and co-workers on vinyl transfer to alcohols¹³ prompted us to include complexes bearing phenanthroline ligands (Table 1), and the (4,7-diphenyl-1,10-phenanthroline)palladium(II) trifluoroacetate complex, (DPP)-Pd(OCOCF₃)₂, displayed the highest catalytic activity. Use of this catalyst resulted in a quantitative yield within 3 min (Table 1, entry 3). Nearly identical activity is obtained if this catalyst is prepared in situ. The (phen)Pd(OCOCF₃)₂ complex (entry 6) also displays high activity, but its low solubility can lead to lower yields under certain conditions. Mercuric salts are known to promote vinyl transfer to oxygen nucleophiles (alcohols and carboxylic acids);¹⁴ however, these complexes proved to be less effective (Table 1, entries 11–14).

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Table 1. Catalyst Screening Results^a

entry	catalyst	yield ^b (%)
1	(PhCN) ₂ PdCl ₂	1
2	Pd(OCOCF ₃) ₂	2
3	(DPP)Pd(OCOCF ₃) ₂ ^c	100
4	(DPP)Pd(OAc) ₂	39
5	(DPP)PdCl ₂	<1
6	(phen)Pd(OCOCF ₃) ₂ ^d	91
7	(tmeda)Pd(OCOCF ₃) ₂ ^e	38
8	(PPh ₃) ₂ Pd(OCOCF ₃) ₂	6
9	(diphos)Pd(OCOCF ₃) ₂ ^f	6
10	Na ₂ PdCl ₄	0
11	Hg(OAc) ₂	<1
12	HgSO ₄	5
13	HgCl ₂	2
14	Hg(OCOCF ₃) ₂	26

^a Reaction conditions: 1.0 equiv of 2-oxazolidinone, 10 equiv of BVE, 0.05 equiv of catalyst, 75 °C, open to air, 3 min. ^b Yields determined by ¹H NMR with 1,3,5-*tert*-butylbenzene internal standard. ^c DPP = 4,7-diphenyl-1,10-phenanthroline. ^d phen = phenanthroline. ^e tmeda = tetramethylethylenediamine. ^f diphos = 1,2-bis(diphenylphosphino)ethane.

With the optimal catalyst in hand, we examined the scope of this reactivity with a series of nitrogen nucleophiles (Table 2). The reactions with saturated primary and secondary amines (e.g., morpholine and benzylamine) were unsuccessful under these conditions, possibly because of the ability of these reactants to coordinate strongly to palladium(II). A

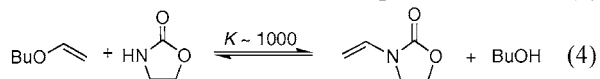
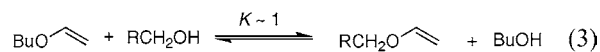
Table 2. Formation of Various Enamides^a

entry	nucleophile	time (h)	product	yield (%) ^b
1		1.3		91
2		3.5		95
3		4		92
4		3		89
5		24		76 ^c
6	Me-NHTs	2		64
7		4.5		87

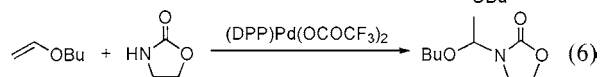
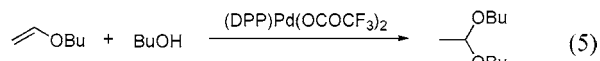
^a Reaction conditions: 1 equiv of nucleophile, 10 equiv of BVE, 5 mol % of (DPP)Pd(OCOCF₃)₂, 75 °C, open to air. ^b Isolated yield after flash column chromatography. ^c Ethyl vinyl ether used as the vinyl donor; room temperature.

series of less basic nucleophiles, however, were effective, including chiral derivatives of 2-oxazolidinone (entries 2–3) and 2-pyrrolidinone (entry 4). The primary nucleophile, trifluoroacetamide (entry 5), is also successful, although the product is rather sensitive to acidic conditions and elevated temperatures. Ethyl vinyl ether was used in place of BVE to facilitate product purification. The lower reaction temperatures required by this substrate led to a longer reaction time, but the product could be obtained in good yield. Use of other primary nucleophiles, acetamide and *p*-toluenesulfonamide, resulted in low conversion (10–30%). *N*-Alkylated *p*-toluenesulfonamides proved to be effective substrates, as both TsNHMe and the tosylated β -alanine methyl ester proceed in good yield to the enamide product (entries 6 and 7).

In palladium-catalyzed vinyl transfer to alcohols and carboxylic acids (eq 3),^{13,15} the reactions take place under equilibrium control. Therefore, the vinyl ether substrate is generally employed in large excess (≥ 20 equiv) to favor product formation. In principle, excess substrate is not required in the present reactions because formation of the vinyl amide is thermodynamically favored. Density functional calculations estimate the equilibrium constant for eq 4 to be in the range of 10^3 .¹⁶ Use of a 1:1 ratio of BVE and **1** results in $\geq 80\%$ yield of the vinyl transfer product, **2**, when the reaction is conducted in dimethoxyethane or toluene as the solvent. The formation of a dibutylacetal side product, which can arise from palladium-(or acid)-catalyzed addition of butanol to BVE (eq 5), reduces the yield under these conditions. This complication can be overcome by using



excess BVE. Attempts to prevent acetal formation by adding catalytic or stoichiometric amounts of base^{15b} (i.e., triethylamine and Na_2CO_3) were only moderately successful, in part, because the base also hinders the formation of the desired enamide. Only minor amounts of aminal product ($\leq 5\%$, eq 6) form in these reactions.¹⁷



These reactions differ from the recently developed palladium(0)-catalyzed cross-coupling methods for carbon–nitrogen bond formation in that the catalyst appears to remain in the +2 oxidation state throughout the reaction. Qualitative support for this mechanism is provided by the following experimental observations. The optimal catalysts, phenanthroline–palladium(II) complexes, are the same as those identified for vinyl transfer to oxygen nucleophiles, carboxylic acids, and alcohols.^{13,15b,d} A recent competition study by Jung and co-workers¹⁸ suggests that molecular oxygen reacts more rapidly with palladium(0) than aryl iodides. Vinyl ethers should be even less reactive than aryl iodides toward oxidative addition to palladium(0). This observation, together with the fact that these reactions proceed as effectively under pure oxygen or air than under an inert atmosphere, argue against the intermediacy of palladium(0). In fact, the presence of air can have a beneficial effect by rescuing any catalyst that is reduced to palladium(0) during the reaction.^{13,19,20} Palladium(II)-catalyzed reactions with alkenes also generally have more severe steric constraints than those with palladium(0).^{15c} Indeed, the reaction of ethyl 1-propenyl ether (**3**) proceeds much more slowly than that with vinyl ether substrates. Although the reaction between BVE and **1** is complete within three minutes (Table 1, entry 3), the reaction between **1** and **3** is only 48% complete after 24 h under comparable conditions.²¹

These observations are consistent with the following palladium(II)-catalyzed mechanism for vinyl transfer to

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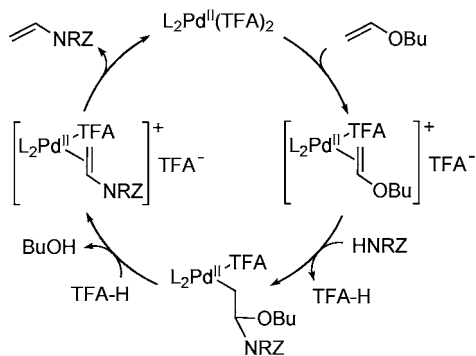
(21) The commercial source of **3** (Aldrich) consists of $\sim 2.5:1$ ratio of the *cis*- and *trans*-isomers. The relative reactivity of the two isomers is not readily apparent. Such analysis is complicated by the use of a large excess of **3** in the reaction (20-fold excess), side reactions that consume **3** (e.g., eqs 5 and 6), and the possibility of Pd-catalyzed equilibration of the isomers under the reaction conditions via transvinylation with the alcohol product (cf. eq 3).

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(16) The equilibrium constant for eq 4 was calculated to be 1001 (gas phase) and 1580 (diethyl ether: solvent dielectric = 4.355). Density functional theory (DFT) calculations using the B3^L-LYP^b functional with the 6-31++G** basis set were employed with the Gaussian 98^c suite of programs to perform gas-phase geometry optimizations on the substrates butyl vinyl ether and **1** and the corresponding products of the isodesmic reaction illustrated in Table 1. Additional geometry optimization calculations were performed using Tomasi's dipole polarizable continuum model^d (DPCM) with the specified dielectric of 4.355 corresponding to a diethyl ether reaction medium. Optimized structures were verified to be at a local minimum by calculation of the harmonic vibrational frequencies. (a) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098–3101. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789. (c) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Salvador, P.; Dannenberg, J. J.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.10; Gaussian, Inc.: Pittsburgh, PA, 2001. (d) Miertus, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117–129. (e) Miertus, S.; Tomasi, J. *Chem. Phys. Lett.* **1982**, *65*, 239–245. (f) Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys. Lett.* **1996**, *255*, 327–335.

Scheme 1. Proposed Mechanism for Palladium(II)-Catalyzed Vinyl Transfer to Nitrogen Nucleophiles



nitrogen nucleophiles (Scheme 1). Carbon–nitrogen bond formation arises from aminopalladation of the vinyl ether substrate. Whether this step takes place via internal or external attack of the nucleophile on the coordinated olefin

is not yet established. Subsequent β -alkoxide elimination yields the desired amination product.

In conclusion, our studies have led to the development of a new process for the synthesis of enamides via vinyl transfer from vinyl ethers. The $(DPP)Pd(OCOCF_3)_2$ catalyst is effective with a variety of amide and tosylamide nucleophiles, and this straightforward methodology represents a new palladium(II)-catalyzed example of C–N bond formation.

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Supporting Information Available: Experimental procedures, characterization data of products in Table 2, and NMR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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