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Activation of Carbon–Oxygen Bonds by Palladium: Toward a Mild, Catalytic Approach to α-Amino Acid Derivatives

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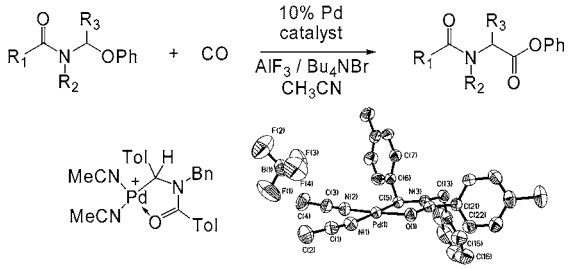
ABSTRACT



A Lewis acid mediated method to induce the carbon–oxygen bond of amide-substituted ethers to undergo addition to palladium is described. The product of this reaction has been crystallographically characterized. This reaction suggests the potential use of such ethers as an alternative to organic halides in palladium catalyzed carbon–carbon bond formation. As an illustration of this potential, this reaction has been used to design a mild, catalytic route to α-amino acid derivatives from α-phenoxyamides and carbon monoxide.

The transition-metal-based cleavage of covalent bonds (e.g., by oxidative addition) is a central transformation in organometallic chemistry and metal catalysis. In palladium catalysis alone, this reaction is involved in Heck couplings, allylations, cross-coupling chemistry (e.g., Stille, Suzuki, Hiyama, Sonogashira couplings), reductions, and many other important reactions.[1,2] In general, the substrates employed in catalytic reactions involving oxidative addition to palladium contain either highly polarized R−X bonds (e.g., organic halides, triflates, iodonium salts, esters) or relatively weak or accessible bonds.[3] Conversely, the use of the less polarized and stable carbon−oxygen bonds of ethers in such bond activation processes is more limited.[4,5] While allylic and propargylic ethers have been employed in palladium catalysis,[4b,6] examples of ethers in such reactions usually involve compounds with strain (e.g., epoxides)[7] or require the in situ conversion of the ether to a more reactive unit (e.g., protonation with strong acids to an organic halide).[8] Indeed, ethers are often useful as alcohol protecting groups in many palladium-catalyzed reactions.

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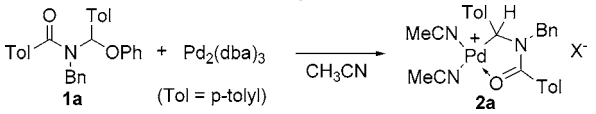
Considering the availability of ethers, as well as their stability toward most chemical transformations, a method to employ new versions of these substrates in palladium catalysis could prove useful. We describe below our efforts toward the development of a mild, Lewis acid-based method to induce amide-substituted ethers of the form **1** to undergo addition to palladium. This has been exploited to design a catalytic route to construct α-amino acid derivatives from α-phenoxyamides and carbon monoxide.

Our initial efforts toward this chemistry probed the stoichiometric reaction of the α-phenoxy substituted amide **1a** with Pd_2dba_3. The use of amide-substituted ethers stems from the our recent observation that in situ generated α-chloroamides can undergo an unusually rapid oxidative addition to palladium(0), as well as catalytic carbonylation to synthesize a range of 1,3-oxazolium 5-oxide (i.e., Münchnone) derived products (e.g., amino acids, pyrroles, imidazoles, *β*-lactams).[9] The activation of α-haloamides, formed by protonation of in situ generated hydroxyamides, is also postulated by Beller and others in the well-established palladium-catalyzed amidocarbonylation reaction.[2c,10] Ethers such as **1a** are much less hydrolytically and thermally sensitive than α-chloroamides, and can be generated with a diverse range of substituents, suggesting they could prove attractive building blocks. However, as shown in Table 1

Table 1. Reaction of α-Phenoxyamide **1a** with Palladium[a]



entry	ligand	additive	*T* (°C)	yield[b] (%)
1			80	
2	P(*o*-Tol)$_3$		80	
3	P^{t}Bu$_3$		80	
4	DPPF		80	
5		AlF_3	80	
6		$Sc(OTf)_3$	80	
7		BF_3	25	42[d]
8		BF_3[c]	25	89[d]

[a] 0.20 mmol of **1a**, 0.10 mmol of Pd_2dba_3, 0.30 mmol of ligand, or 0.20 mmol of additive in 2 mL of CH_3CN. [b] Isolated yield. [c] 2 equiv of BF_3. [d] X = BF_4.

(entry 1), the C−O bond of **1a** is completely unreactive toward cleavage by $Pd_2dba_3CHCl_3$, even upon warming to 100 °C. The addition of various electron-rich phosphine ligands also has no influence on the reaction.

It is well-established that Lewis acid additives can weaken the C−O bond of substrates such as **1** and make these more susceptible to nucleophilic attack, presumably via interaction with the ether oxygen.[11] The addition of many common Lewis acid additives to this reaction simply leads to recovered starting materials. However, the use of BF_3 results in a rapid reaction over the course of 5 min at ambient temperature, and formation of the C−O activation product: palladacycle **2a** in 42% yield.

Complex **2a** is generated as a BF_4^- salt, presumably via the disproportionation of an in situ generated F_3BOPh^- with BF_3 to form the more stable BF_2OPh and BF_4^-.[12] As shown in entry 8, the addition of 2 equiv of BF_3, one to occupy the phenoxy anion as BF_2OPh, results in the almost quantitative formation of **2a**. The structure of complex **2a** has been confirmed X-ray crystallography. As shown in Figure 1, the

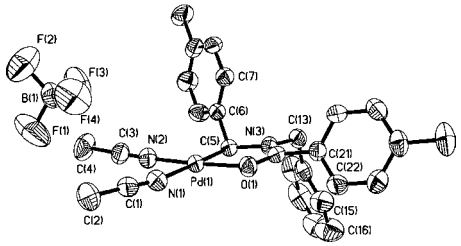


Figure 1. X-ray structure of **2a.** Selected bond lengths (Å): Pd(1)−C(5) 2.000(3), Pd(1)−O(1) 2.003(2), O(1)−C(20) 1.272(4), N(3)−C(20) 1.311(4) Selected bond angles (deg) N(2)−Pd(1)-C(5) 93.64-(13), C(5)−Pd(1)-O(1) 83.22(12) O(1)−Pd(1)-N(1) 96.06(11), N(1)−Pd(1)-N(2) 87.03(13).

lack of anion coordination in **2a** leaves two empty coordination sites on palladium, which are occupied by acetonitrile solvent. The C═O bond length in **2a** (1.272 Å) is longer than a normal amide carbonyl (1.23 Å), while the C−N bond (1.311 Å) is shortened, suggesting resonance stabilization of the amide coordination to palladium. This chelation, along with the formation of BF_2OPh, likely provides the driving force for the rapid cleavage of the C−O bond in **1a**.

With the stoichiometric reaction of **1** with palladium in hand, we became interested in the potential use of this transformation in catalysis. In particular, the carbonylation of **1** could provide a one step method to access α-amino acid derivatives, via a mechanism similar to that in Scheme 1. As

Scheme 1. Mechanism of Catalytic Amino Acid Synthesis

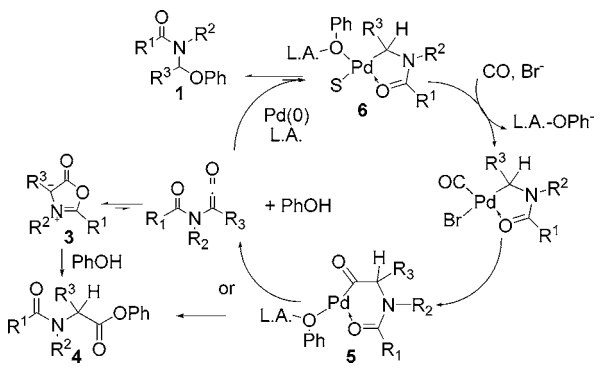


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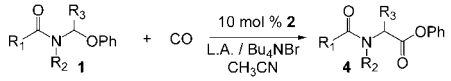
Table 2. Palladium Catalyzed α-Amido Ester Synthesis[a]



entry	L.A.	R^1	R^2	R^3	yield (yield)[e]
1	-	Ph	Et	p-tolyl	10% (**3a**)
2	BF_3[b]	Ph	Et	p-tolyl	25% (**3a**)
3	AlF_3	Ph	Et	p-tolyl	83% (75%)[d]
4	AlF_3[c]	Ph	Et	p-tolyl	43%
5	AlF_3	Ph		p-tolyl	72%
6	AlF_3	p-tolyl	Bn		55%
7	AlF_3			p-tolyl	72%
8	AlF_3	Ph			94%
9	AlF_3		Bn	p-tolyl	77%
10	AlF_3	Ph	Et		74%
11	AlF_3		Bn	p-tolyl	62%
12	AlF_3	R^1,R^2 = 		H	56%

[a] 0.20 mmol of **1**, 0.020 mmol of **2**, 0.10 mmol of Bu_4NBr, 0.40 mmol of Lewis acid, 4 atm of CO in 2 mL of CH_3CN, 65 °C for 14 h. [b] 30 mol %. [c] 25 °C, 24 h. [d] Yield in parentheses for 30 mol % of AlF_3.

shown in Table 2, initial attempts at this reaction lead to carbonylation of the catalyst **2a** to form Münchnone (**3a**, entry 1, 10%) but leave **1a** unreacted. The addition of 25 mol % of BF_3 can enhance this yield of **3a** (25%), while further BF_3 leads instead to the decomposition of the α-phenoxyamide **1a**. The latter results from a slow background reaction between **1a** and BF_3, as established by control experiments. Notably, under no conditions is the expected α-amino ester **4** formed. These data imply BF_3 may be too Lewis acidic for catalysis and irreversibly complexes the phenoxide as BF_2OPh, allowing the buildup of **3a** in solution.

In contrast to the results with BF_3, the use of the slightly less potent Lewis acid AlF_3 in this reaction (entry 3) allows a high yield catalytic carbonylation and also releases the phenoxy anion to generate α-amino acid derivative **4a**. Mechanistically, it is interesting that AlF_3 does not induce a stoichiometric reaction of **1a** to form a stable palladacycle (Table 1). In addition, control experiments show no appreciable interaction between AlF_3 and **1a**.[13] While the role of AlF_3 in allowing carbonylation to occur has not been fully elucidated, one postulate is that its interaction with phenoxide stabilizes a reversible oxidative addition of the C−O bond in **1a** (e.g., complex **6**).

This palladium-catalyzed carbonylation of α-phenoxyamides occurs with a range of substituents on each of the three positions of **1**. This includes aryl, heteroaryl, or alkyl units on R^1 or R^2, as well as aromatic or functional aromatic substitutents at R^3. Alkyl units at R^3 were found to be incompatible with carbonylation. The use of bulky or electron-withdrawing nitrogen substituents (entries 8, 12) and hydrogen at R^3 (entry 12) are notable, since none of these units can be used in the previously reported carbonylation of imines and acid chlorides.[9] In addition, the conditions needed for the carbonylation of the ether bond in **1** (room temperature, 4 atm CO, entry 4) are milder than those we have previously reported, as well as that of the related amidocarbonylation reaction (ca. 100 °C, 60 atm CO), and do not require the concomitant use of strong protic acids (e.g., sulfuric acid).[2c,14] Together, these provide both a mild and relatively general approach to highly substituted α-amino acid derivatives.

In conclusion the carbon oxygen bond of α-phenoxyamides has been found to undergo rapid activation by palladium(0) and Lewis acids to form a crystallographically characterized palladacycle. This provides a new class of stable, ether base substrates that can be incorporated into palladium-catalyzed chemistry. By coupling this step with catalysis, this can provide a mild approach to construct nonnatural α-amino acid derivatives or, with potent Lewis acids, Münchnones. Experiments directed toward the use of this rapid C−O activation in other catalytic processes to access α-substituted amide products are in progress.

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Supporting Information Available: Synthesis and characterization of **2a** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) This ionization suggests **2a** is better considered as an intermediate in an ionic oxidative addition, rather than a formal oxidative addition product.
(13) ^1H NMR spectra of **1a** in CD_3CN show no changes in the presence of AlF_3.
(14) The use of phenoxyamides **1** also obviates the need for a second step of addition of alcohols to the in situ generated münchnone (ref 9a), making this an operationally more straightforward amino acid synthesis.