Cycloaddition

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Palladium Catalyzed Synthesis of Münchnones from α-Amidoethers: A Mild Route to Pyrroles**

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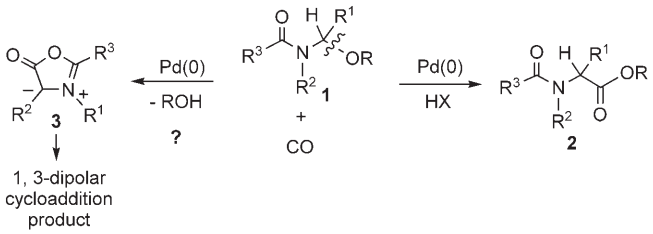
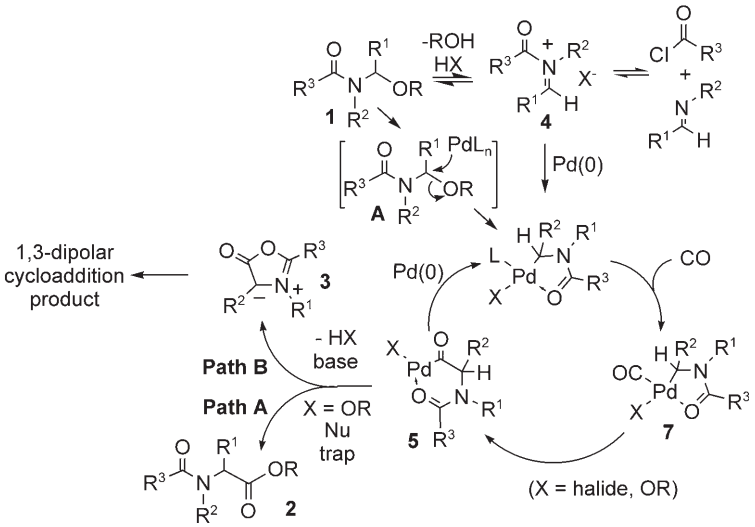
The metal-catalyzed carbonylation of α-amidoalcohols (**1**; e.g. aldehyde amidocarbonylation) has become an important method to construct α amino acids and related products (Scheme 1).[1] One useful feature of this reaction is the accessibility of the substrates (**1**), or their ether analogues, for use in carbonylation reactions. The preparation of **1** includes the in situ condensation of aldehydes and amides, the electrochemical oxidation of amides, the reduction of imides or imidates, or the acylation of imines.[2] The coupling of this synthesis with catalytic carbonylation allows the formation of amino acid derivatives, which have various substitutions, in a minimal number of steps and on large scale.[1] While effective, this reaction typically requires high reaction temperatures, high CO pressures (ca. 100 °C, 60 bar), and the use of strong acid additives. These are presumably related to the poor ability of palladium to directly activate



Scheme 1. Formation of dipolar cycloaddition reagents from **1**.

the C–O bond of **1**, which instead is believed to be converted into a more reactive iminium salt intermediate (**4**) under the reaction conditions (Scheme 2).[1,3] Whereas we have noted mild routes to C–O carbonylation with α-phenoxyamides, the reaction still employs relatively strong Lewis acids (e.g. AlF_3) to activate the substrate toward oxidative addition.[4,5]



Scheme 2. Postulated mechanism for the palladium-catalyzed carbonylation of **1**.

Considering the availability of α-amidoethers as building blocks, we became interested in the potential use of this chemistry to access other classes of products. In particular, we recently reported that the multicomponent coupling of imines, acid chlorides, and carbon monoxide with unsaturated substrates can provide a route to assemble various useful heterocycles (pyrroles, imidazoles, imidazolines, or β-lactams) by the formation of the münchnones (**3**).[6] Notably, this chemistry proceeds through carbonylative intermediates that are similar to those observed with α-amidoalcohols (Scheme 2, path B), but it occurs under mild conditions (4 atm CO, 55 °C) and does not require an acid to activate the intermediate α-chloroamide towards oxidative addition. These data suggested the potential of using the carbonylation of structurally versatile α-amidoethers to access a 1,3-dipolar cycloaddition manifold (Scheme 1) to synthesize heterocycles, rather than amino acid derivatives. We report herein the discovery of a mild method to directly activate the carbon–oxygen bond of α-amidoethers towards oxidative addition and carbonylation. This method has allowed the use of α-amidoethers in 1,3-dipolar cycloaddition chemistry by the formation of münchnones. In addition to demonstrating a new reactivity mode for the carbonylation of **1**, this process has been used to design a palladium-catalyzed synthesis of pyrroles.

In considering approaches to utilize α-amidoethers to access dipolar cycloaddition intermediates (Scheme 2, path B), a number of mechanistic challenges arise. Firstly, the reaction of **1** to form CO insertion intermediate **5** would formally generate a nucleophilic RO^- anion (X = OR), which

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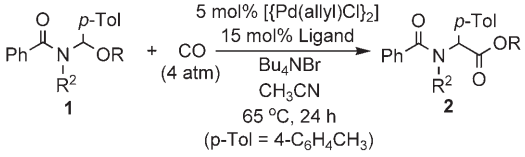
could react with the acyl-palladium ligand, or münchnone **3**, to form an α-amidoester rather than undergo cycloaddition (Scheme 2, path A, typical amidocarbonylation).[7,8] Additionally, even before this trapping, the diversion of complex **5** down path B requires a formal deprotonation of the β hydrogen to the palladium center. The latter is incompatible with the typically forcing and acidic conditions needed for the initial oxidative addition of **1**. Thus, a mild method to activate the C–O bond of **1** without acid co-catalysts is required.

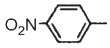
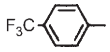
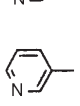
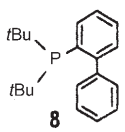
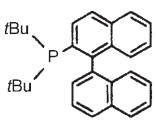
As shown in Table 1, in situ generated α-hydroxyamide **1a** is inert towards palladium-catalyzed carbonylation in the absence of an acid co-catalyst at temperatures up to 65 °C and CO pressures up to 4 atm.[9] Similar results were observed with phenoxy- and methoxy-substituted derivatives **1b** and **1c**, respectively. One postulated for the role of the acid in the catalysis is that it creates a C–O bond that is more susceptible to nucleophilic displacement by palladium, in an S_N2-type oxidative addition mechanism (Scheme 2, structure **A**). This suggests that increasing the electrophilicity of **1** could similarly facilitate this step. Whereas the incorporation of electron-withdrawing aromatic substituents onto **1** had no influence on the reaction (**1d, 1e**), the replacement of the phenyl group with a 3-pyridyl unit did indeed allow carbonylation to occur, forming an α-amidoester in moderate yield (**1h**, 54%).[10] Notably, the position of the pyridyl unit is critical for this reaction; neither the 2-pyridyl (**1f**) nor 4-pyridyl (**1g**) derivatives allow the reaction to occur. This lack of reactivity suggests that it is the increased leaving group capability of this substituent that is important for this activation, although coordination of the nitrogen atom to palladium could also be involved in the reaction pathway.[11]

The efficiency of this reaction can be additionally enhanced by modifying the palladium catalyst. The nucleophilic attack of palladium on **1h** should, in principle, be facilitated by more basic phosphine ligands on palladium. However, this ligand must also remain labile because it is ultimately displaced by CO to generate intermediate **7**. Bulky and basic *t*Bu_2P(2-biphenyl) ligand **8** has the correct balance of these features (Table 1, entry 12), leading to **2** in high yield. Overall, this provides the mildest set of conditions, of which we are aware, for the carbonylation of these substrates to give amino acid derivatives.

Since this reaction requires neither a strong acid to activate the C–O bond nor uses unstable iminium salt substrates, it is tolerant of a number of substituents at each of the positions of **1** (Table 2), including acid and base sensitive substrates. For example, when R^1 is a small enolizable alkyl unit, which is not compatible with our previous acid chloride approaches employing amine bases, the ether can be carbonylated in high yield (Table 2, entry 1). Similarly, acid sensitive electron-rich heterocycles (furan and indoles, Table 2, entries 2 and 3) can also be employed in the reaction. In addition, aryl or alkyl substituents can be used at R^2 or R^3, yielding several products that are not accessible by typical amidocarbonylation procedures.

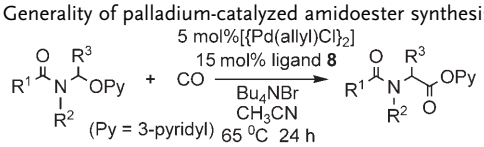
Table 1: C–O bond activation and carbonylation of amidoethers under mild conditions.[a]

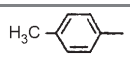
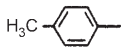
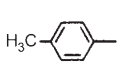
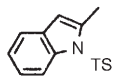
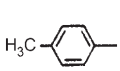
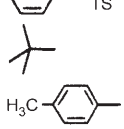
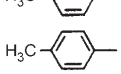
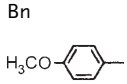
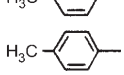
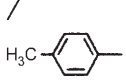
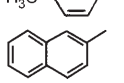
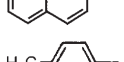


Entry	1	R^2	R	Ligand	Yield
1[b]	**1a**	H	H	P(*o*-Tol)$_3$	–
2	**1b**	Bn	Ph	P(*o*-Tol)$_3$	–
3	**1c**	Bn	Me	P(*o*-Tol)$_3$	–
4	**1d**	Bn		P(*o*-Tol)$_3$	–
5	**1e**	Bn		P(*o*-Tol)$_3$	–
6	**1f**	Bn		P(*o*-Tol)$_3$	–
7	**1g**	Bn		P(*o*-Tol)$_3$	–
8	**1h**	Bn		P(*o*-Tol)$_3$	54% (58%)[c]
9	**1h**	Bn		PMe_3	–
10	**1h**	Bn		P*t*Bu_3	8%
11	**1h**	Bn		P(nap)$_3$	50%
12	**1h**	Bn	  **8**		87%
13	**1h**	Bn	 		58%

[a] **1** (0.20 mmol), [{Pd(allyl)Cl}$_2$] (0.010 mmol), Bu_4NBr (0.10 mmol) ligand (0.030 mmol), 4 atm CO, CH_3CN (2 mL); Bn = $CH_2C_6H_5$. [b] Benzamide (0.20 mmol), *p*-tolualdehyde (0.20 mmol) used instead of **1**. [c] Catalyst used was [Pd(η^2-CH(tol)NBnCOPh)]$BF_4(CH_3CN)_2$ (**6**).[4]

Table 2: Generality of palladium-catalyzed amidoester synthesis.[a]



Entry	R^1	R^2	R^3	Yield
1	Me	Bn		74%
2		Bn		68%
3		Et	 TS	38%
4		Bn		86%
5				72%[b]
6		Bn		73%[b]
7				85%
8	Ph			58%[b]

[a] Conditions of Table 1 with 0.030 mmol ligand **8**. [b] Catalyst used was [Pd(η^2-CH(tol)NBnCOPh)]$BF_4(CH_3CN)_2$ (**6**).

Having developed a method for carbonylation of **1h** under mild conditions, we became interested in the potential to use this approach to access a 1,3-dipolar cycloaddition reaction manifold. In particular, the low nucleophilicity of the PyO^- group in **1h** and the lack of an acid co-catalyst, suggests that intermediate **5** could undergo in situ deprotonation and cyclization to form münchnone **3** (Scheme 2, path B), rather than trapping to amido acids. This was probed by performing the carbonylation in the presence of methyl phenylpropiolate as the münchnone trapping agent.[12] As anticipated, the addition of the alkyne under typical amidocarbonylation conditions (Table 3, entry 1) to phenoxy-substituted **1b** with AlF_3 resulted in the formation of an amido acid rather than a pyrrole.[13] Conversely, performing this reaction with the less basic 3-pyridyl substituent in **1h** resulted in the exclusive formation of pyrrole **9a** (Table 3, entry 3).[14] Notably, no amidoester is formed under these conditions.

This data demonstrates that münchnone intermediates are generated upon carbonylation of these α-amidoether derivatives, and that alkynes can effectively compete with 3-hydroxypyridine trapping of **3**. Considering the variety of alkynes that react with münchnones,[12] this approach can in principle provide access to a range of pyrroles. As a preliminary illustration of this feature, modification of the building blocks was used to construct a number of diversely substituted products (Table 3). This includes base sensitive R^1 groups (**9i**), bulky or aromatic R^2 groups (**9c**, **9l**), as well as base sensitive alkynes (**9d**), each of which are not readily incorporated into our previous imine/acid chloride chemistry. In addition to alkynes, electron-poor alkenes can also be employed to trap **3**, which undergo acid elimination to form pyrroles (**9f**, **9g**). Together, these provide an effective palladium-catalyzed approach to construct pyrroles, in which the substitution at any position on the product can be modified by changes to the alkyne or building block **1**.

In conclusion, a palladium-catalyzed route to directly activate the C–O bond of α-amidoethers has been developed, and applied to carbonylation chemistry. This method provides a mild way to construct amino acid derivatives, as well as access to a new mode of reactivity for these reagents: 1,3-dipolar cycloaddition. Considering that münchnones **3** can undergo cycloaddition reactions with a range of unsaturated substrates (e.g. alkynes, alkenes, imines, aldehydes, etc.),[11] this reactivity provides potential access to various classes of heterocycles. Studies towards the latter are currently in progress.

Experimental Section

Pyrrole synthesis: α-amidoether (0.20 mmol), catalyst **6** (0.020 mmol), Bu_4NBr (0.10 mmol), alkyne (0.30 mmol), and P*t*Bu_2-(biphenyl) (0.015 mmol) were dissolved in 2 mL CH_3CN in a 50 mL reaction bomb. The solution was degassed, carbon monoxide (60 psi) was added, and the mixture was stirred at 65 °C (24 h). The product was isolated after column chromatography by using silica gel 60 with hexanes/ethyl acetate as the eluent.

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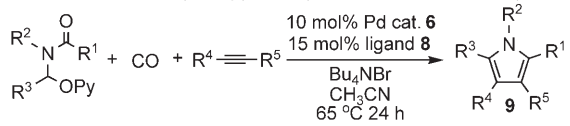
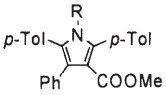
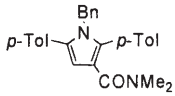
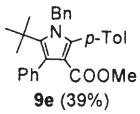
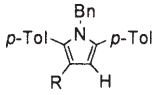
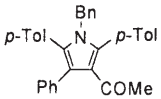
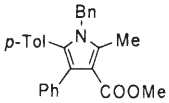
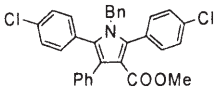
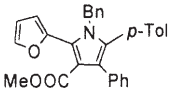
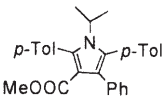
Table 3: Palladium-catalyzed pyrrole synthesis from **1** and alkynes.[a]



Entry	R^1	R^2	R^3	Alkyne	**9** (Yield)
1	Me	H	Ph	Ph—≡—COOMe	–[b]
2	*p*-Tol	Bn	Ph	Ph—≡—COOMe	–[c]
3	*p*-Tol	R	*p*-Tol	Ph—≡—COOMe	 **9a** (R=Bn, 68%) **9b** (R=Et, 72%) **9c** (R=An, 48%)
4	*p*-Tol	Bn	*p*-Tol	H—≡—$CONMe_2$	 **9d** (63%)
5	*p*-Tol	Bn		Ph—≡—COOMe	 **9e** (39%)
6	*p*-Tol	Bn	*p*-Tol		 **9f** (R=Ph, X=Br, 38%)[d] **9g** (R=CN, X=Cl, 48%)[d]
7	*p*-Tol	Bn	*p*-Tol	Ph—≡—COMe	 **9h** (54%)
8	Me	Bn	*p*-Tol	Ph—≡—COOMe	 **9i** (62%)
9		Bn		Ph—≡—COOMe	 **9j** (51%)
10		Bn	*p*-Tol	Ph—≡—COOMe	 **9k** (65%)
11	*p*-Tol		*p*-Tol	Ph—≡—COOMe	 **9l** (67%)

[a] See experimental section for conditions. [b] Acetamide/benzaldehyde (0.20 mmol), $PdCl_2$ (0.020 mmol), LiBr (0.07 mmol), PPh_3 (0.040 mmol), H_2SO_4 (0.010 mmol), 80 bar CO, 2 mL NMP, 120 °C. [c] **1b**, AlF_3 (0.40 mmol).[d] Collidine (0.30 mmol). An = 4-$C_6H_4OCH_3$; NMP = 1-methyl-2-pyrolidone.

Keywords: C–O activation · dipolar cycloaddition · palladium · pyrrole

[1] a) A. J. von Wangelin, H. Neumann, M. Beller, *Top. Organomet. Chem.* **2006**, *18*, 207–221; b) M. Beller, M. Eckert, *Angew.*

Chem. **2000**, *112*, 1026 – 1044; *Angew. Chem. Int. Ed.* **2000**, *39*, 1010 – 1027; c) M. Beller, M. Eckert, F. Vollmuller, S. Bogdanovic, H. Geissler, *Angew. Chem.* **1997**, *109*, 1534 – 1536; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1494 – 1496; d) D. A. Freed, M. C. Kozlowski, *Tetrahedron Lett.* **2001**, *42*, 3403 – 3406.

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