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The Development of a Catalytic Synthesis of Münchnones: A Simple Four-Component Coupling Approach to α-Amino Acid Derivatives

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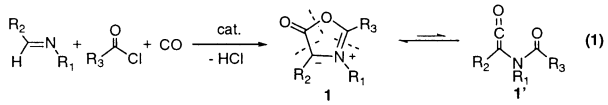
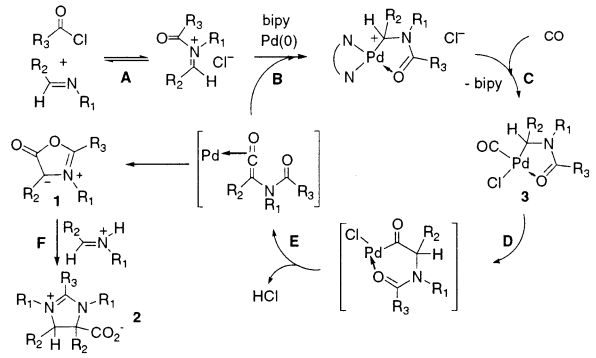
Mesoionic 1,3-oxazolium-5-oxides (e.g., Münchnones, **1**), and their α-amide substituted ketene tautomer (**1′**), are an important family of substrates for the synthesis of biologically relevant molecules.[1] Münchnones are versatile 1,3-dipolar addition substrates and have proven key in the construction of a range of natural products and pharmacologically relevant heterocycles, including pyrroles,[1,2a,b] imidazoles,[2c,d] pyrrolines,[2e] and indole derivatives.[2f] Alternatively, the less stable ketene **1′** can serve as a precursor to α-amino acid and peptide derivatives, via reaction with alcohols or N-terminated peptides,[3a] and their cycloaddition with imines provides access to peptide-based *β*-lactams.[3b] While the diversity of products accessible from **1** makes them attractive synthetic targets, their preparation to date has typically involved multistep processes. For example, the most common approach involves the dehydration of the appropriately substituted *N*-acyl amino acid derivative.[1] This route limits the utility of these compounds in the actual synthesis of amino acids and also imposes a necessary initial preparation of the amino acid precursor. As such, alternative transition metal-based syntheses of these compounds have become of growing relevance.[4] Perhaps the most well-established of these is the carbonylation of presynthesized chromium-carbenes,[4a,5,6] which has been employed to develop stoichiometric syntheses of a variety of α-amino acid derivatives, peptides, *β*-lactams, and pyrroles.



Despite the obvious potential advantages of a metal-catalyzed method to form Münchnones directly from readily available materials, to date this has not been reported. We[7] and others[8] have recently suggested the possibility of preparing peptide-based products from simple imine and carbon monoxide units, rather than the traditional routes employing α-amino acids. As described below, these investigations have led to the discovery of a metal-catalyzed method to prepare stable Münchnones, via a catalytic coupling of imines, carbon monoxide, and acid chlorides. The utility of this transformation is demonstrated in the design of a new one-pot catalytic synthesis of diprotected α-amino acid derivatives.

Our approach to the catalytic synthesis of Münchnones is shown in eq 1 and is based upon our recently observed palladium-catalyzed synthesis of imidazolines, the postulated mechanism for which is in Scheme 1.[7a,9] In particular, we surmised that oxidative addition of imine and acid chloride to Pd(0) (steps A, B), CO coordination (C), insertion (D), and *β*-hydride elimination (E) might provide a pathway to construct **1**, provided subsequent cycloaddition (F) to form **2** could be inhibited. During the course of these studies, it was observed that the HCl generated during catalysis is critical for the Münchnone cycloaddition step (F), implying that its removal might allow the build-up of **1**. Indeed, the reaction of (*p*-tolyl)-

Scheme 1. Mechanistic Rationale for Münchnone Formation



HC═NBn, PhCOCl, and 1 atm of CO with 5 mol % $Pd_2(dba)_3 \cdot CHCl_3$, bipyridine, and $NEt(^iPr)_2$ base leads to the disappearance of starting materials over 4 days and to the generation of **1a** as a minor product (5% yield, Table 1, entry 1). The formation of **1a**, albeit in very low yield, suggested this approach might indeed allow for the development of a one-pot catalytic synthesis of Münchnones from three basic building blocks (eq 1), which could be employed in a range of further transformations. With a working hypothesis for the mechanism of this transformation, we set out to improve the efficiency of this process.

First, it was noted that the imine and acid chloride are consumed during the catalysis, implying that the low yields of **1a** may result from the decomposition of the reactive Münchnone product,[1,10] rather than incomplete reaction. Our attention therefore turned toward tuning the palladium catalyst to allow for a more selective and mild reaction. In principle, this might be accomplished by allowing more facile access to CO-coordinated intermediate **3** (C), because steps A and B are known to be rapid.[7a] Consistent with this, the removal of bipy from the catalytic reaction increased the rate of Münchnone formation (from 4 days to 24 h) and led to a doubling of the yield (ca. 10%, entry 3).[11] Increasing the pressure of CO further facilitates the generation of **3** and increases the yield of **1a** to 13% (entry 4). However, this also led to the incomplete conversion of imine and acid chloride, due to the precipitation of palladium from the reaction.

The formation of palladium sediments can be inhibited by the addition of Cl^- and Br^- sources, as previously noted in "ligandless" catalysis,[12] and leads to a dramatic increase in the yield of **1a** (entries 5−7). In the case of $Bu_4N^+Br^-$, this allows for the formation of **1a** in a synthetically useful 69% yield.[11] The efficiency of the catalysis can be further improved by removal of the potentially coordinating dba ligand from the Pd(0) source via the use of [Pd(Cl)[η^2-CH(p-tolyl)NBn(COPh)]$_2$ (**4a**), generated by pretreating $Pd_2(dba)_3 \cdot CHCl_3$ with imine and acid chloride.[13] The use of catalyst **4a** leads to the formation of **1a** as essentially the only significant reaction product (83% yield, entry 8). Overall, this optimized protocol (Table 1) provides a straightforward and high yield catalytic route to prepare stable Münchnones.

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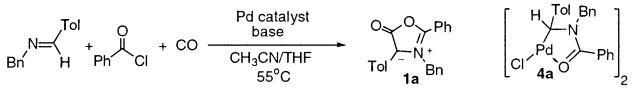
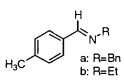
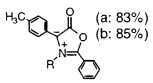
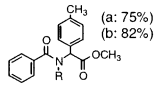
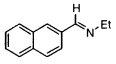
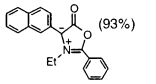
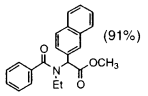
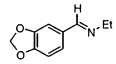
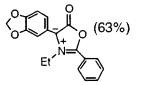
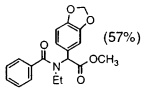
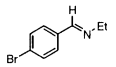
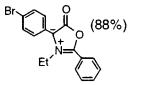
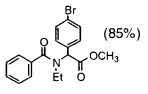
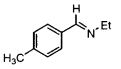
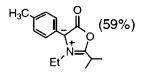
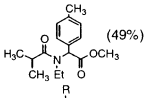
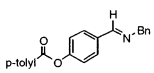
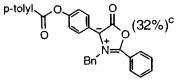
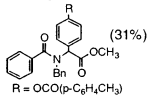
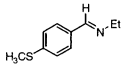
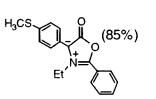
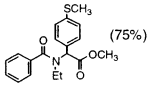
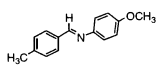
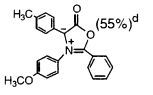
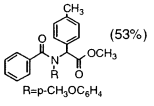
Table 1. Catalytic Synthesis of **1a**[a]



#	[CO]	Pd catalyst	base	additive	%**1a** (%**2**)[b]
1	1 atm	$Pd_2(dba)_3$·$CHCl_3$	$NEt(^iPr)_2$	bipy, 5%	5% (−)[c]
2	1 atm	$Pd_2(dba)_3$·$CHCl_3$		bipy, 5%	− (82%)[c]
3	1 atm	$Pd_2(dba)_3$·$CHCl_3$	$NEt(^iPr)_2$		10%
4	4 atm	$Pd_2(dba)_3$·$CHCl_3$	$NEt(^iPr)_2$		13%
5	4 atm	$Pd_2(dba)_3$·$CHCl_3$	$NEt(^iPr)_2$	LiCl	30%
6	4 atm	$Pd_2(dba)_3$·$CHCl_3$	$NEt(^iPr)_2$	LiBr	50%
7	4 atm	$Pd_2(dba)_3$·$CHCl_3$	$NEt(^iPr)_2$	Bu_4NBr	69%
8	4 atm	**4a**	$NEt(^iPr)_2$	Bu_4NBr	83%

[a] 0.48 mmol of imine and additive, 0.67 mmol of acid chloride, 0.74 mmol of base, and 5 mol % catalyst for 24−30 h at 55 °C. [b] NMR yield. [c] 4 days.

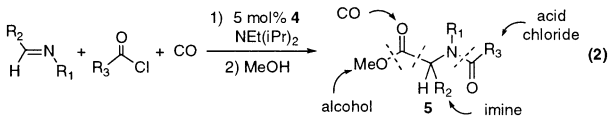
Table 2. Scope of Palladium-Catalyzed Münchnone Synthesis[a]

Cpd	Imine	Acid Chloride	Munchnone **1** (% yield)[b]	Amido Ester **5** (% yield)
a,b	 a: R=Bn b: R=Et	PhCOCl	 (a: 83%) (b: 85%)	 (a: 75%) (b: 82%)
c		PhCOCl	 (93%)	 (91%)
d		PhCOCl	 (63%)	 (57%)
e		PhCOCl	 (88%)	 (85%)
f			 (59%)	 (49%)
g		PhCOCl	 (32%)[c]	 (31%) R = OCO(p-$C_6H_4CH_3$)
h		PhCOCl	 (85%)	 (75%)
i		PhCOCl	 (55%)[d]	 (53%) R=p-$CH_3OC_6H_4$

[a] Analogous to Table 1, # 8.[13] [b] NMR. [c] $Pd_2(dba)_3$·$CHCl_3$ cat. [d] 96 h.

A useful feature of this catalytic reaction is the simplicity of the three separate building blocks, which are either commercially available (CO) or easily prepared (imines and acid chlorides). As such, this chemistry can be generalized to prepare a range of Münchnones, many of which have not been previously reported. Notably, functionalities such as aryl-halides, esters, ethers, and thioethers are tolerant to the catalysis conditions (Table 2), and both alkyl and aryl acid chloride and N-substituted imines can be employed. However, *C*-alkyl substituted imines do not yield Münchnones under these conditions. This is likely related to the established lower stability of these products[1,14] and may be addressable in the future with the use of in situ traps.

Considering the wide scope of products available from **1** and **1′**, this procedure should prove useful in the design of new catalytic syntheses for a range of Münchnone-based targets. As a preliminary illustration of this feature, we have used this catalytic Münchnone synthesis, followed by the addition of methanol, to design a new one-pot, four-component coupling route to diprotected α-amino acid derivatives (eq 2). α-Aryl amino acids have been demonstrated to be of utility in antimicrobial agents and enzyme inhibitors.[15] As shown in Table 2, diversely substituted amino acid derivatives can be prepared by modification of the starting imine and acid chloride. In addition to its simplicity, this transformation also provides what is to our knowledge the first example of the catalytic construction of α-amino acids from imines and carbon monoxide.



In summary, this report has described the development of the first catalytic synthesis of Münchnones, providing direct access to this general class of compounds from basic building blocks. Experiments directed toward the development of multicomponent catalytic syntheses of other peptidic and/or heterocyclic products based on **1** are currently underway.

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Supporting Information Available: Synthesis details on **1**, **4**, and **5** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Kacker, S.; Kim, J. S.; Sen, A. *Angew. Chem., Int. Ed*. **1998**, *37*, 1251.
(9) This mechanism is similar to those postulated for amidocarbonylation: (a) Beller, M.; Eckert, M.; Vollmuller, F.; Bogdanovic, S.; Geissler, H. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 1494. (b) Beller, M.; Eckert, M. *Angew. Chem., Int. Ed*. **2000**, *39*, 1010.
(10) Control reactions show **1a** decomposes in the presence of Pd_2dba_3·$CHCl_3$.
(11) Compound **2** is not observed in these reactions, nor are there any major (i.e., >5% yield) identifiable products other than **1**.
(12) (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev*. **2000**, *100*, 3009. (b) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.
(13) See the Supporting Information for the synthesis of **1**, **4**, and **5**.
(14) Side reactions of these *N*-acyl iminium salts may also inhibit **1** formation; enamides are observed in these reactions in ca. 30% yield.
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