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The Oxidative Mannich Reaction Catalyzed by Dirhodium Caprolactamate

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The Mannich reaction remains a fundamentally important carbon−carbon bond forming reaction in organic synthesis.[1] Access to valuable Mannich addition products is made possible via reactive iminium ions that undergo capture with a rich assortment of nucleophiles. However, despite its well-documented scope and utility, methods for the formation of iminium ions remain limited. Strategies such as condensation or α-fragmentation often require harsh reaction conditions and/or stoichiometric metal additives (Figure 1).[2] The *oxidative* Mannich reaction is an attractive alternative which involves the direct catalytic C−H oxidation of a 3° amine followed by nucleophilic capture (vide infra).[3,4] Herein we describe a mild, selective, and efficient oxidative Mannich reaction catalyzed by dirhodium caprolactamate [$Rh_2(cap)_4$] for the rapid construction of γ-aminoalkyl butenolides.

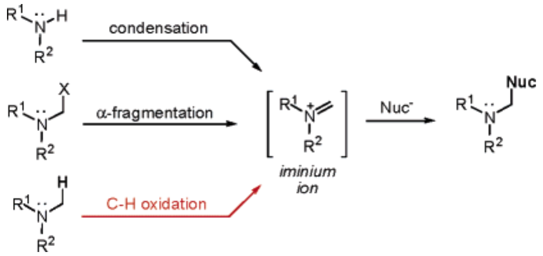


Figure 1. Iminium ion formation and nucleophilic capture.

$Rh_2(cap)_4$ (**1**) has been shown to be an effective catalyst for allylic and benzylic oxidation in conjunction with *tert*-butyl hydroperoxide.[5] We surmised that this technology could be extended to amines considering the oxidation potential of *N*,*N*-dimethylaniline **2** (relative to hydrocarbons).[6] Inspired by the research of Martin,[7] we chose 2-triisopropoxysilylfuran **3** to intercept the iminium ion formed in situ from catalytic C−H oxidation (Scheme 1). Siloxyfurans, which are easily prepared and bench-stable, allow the incorporation of functionally useful γ-butyrolactone moieties.[8] As an architectural element, γ-butyrolactones are found in approximately 10% of all natural products.[9]

Scheme 1

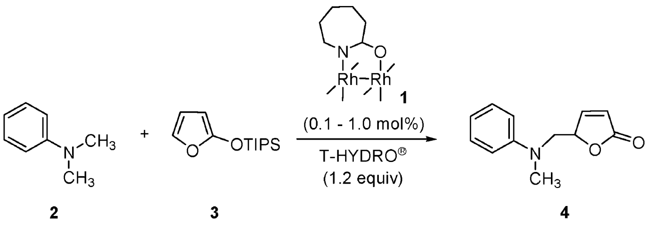
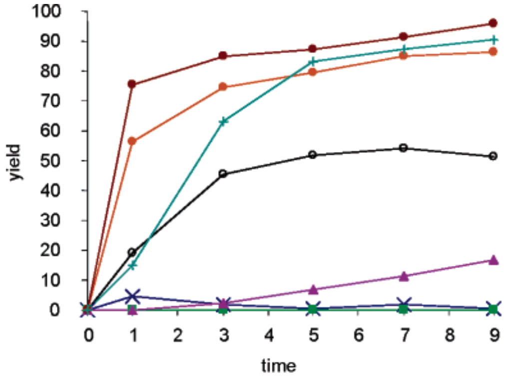


Table 1. Development of the Oxidative Mannich Reaction



entry	conditions[a]	key	yield (**4**)[b]
1	**1** (1.0 mol%), CH_2Cl_2, $NaHCO_3$ (50 mol%), rt	✕	--
2	**1** (1.0 mol%), MeOH, $NaHCO_3$ (50 mol%), rt	■	--
3	**1** (1.0 mol%), MeOH, rt	▲	17
4	**1** (1.0 mol%), MeOH, 60 °C	●	86
5	**1** (1.0 mol%), EtOH, 60 °C	○	51
6	**1** (1.0 mol%), **2** (2.0 equiv), **3** (1.0 equiv), MeOH, 60 °C	●	96 (95[c])
7	**1** (0.1 mol%), **2** (2.0 equiv), **3** (1.0 equiv), MeOH, 60 °C	+	90 (78[c])

[a] Reactions were performed using **2** (1.0 equiv), **3** (1.5 equiv), T-HYDRO (1.2 equiv), and solvent (0.27 M/[substrate]) unless otherwise noted. [b] Yield was determined by ^1H NMR using an internal standard. [c] Isolated yield of the analytically pure compound after chromatography (SiO_2).

We initiated our investigation using conditions previously developed for benzylic oxidation[5b] (Table 1, entry 1) and found only trace amounts of Mannich product **4**. Mindful of the stabilization afforded to iminium ions by polar solvents, we examined the reaction in methanol. No Mannich reaction was observed in the presence of base additive; however, removal of $NaHCO_3$ from the reaction yielded **4** in 17% over 9 h (entries 2 and 3). Heating the solution to 60 °C dramatically increased both rate and product yield (entry 4). Ethanol, a solvent of choice for green chemistry,[10] was also suitable for the oxidative Mannich reaction albeit in moderate yield (entry 5). Final modifications to the stoichiometry of the reaction provided optimal conditions for the formation of **4** at both 1.0 and 0.1 mol % catalyst loading (entries 6 and 7, respectively). It should be noted that *all* of the reactions were performed in the presence of air using inexpensive T-HYDRO (70% *t*-BuOOH in water) with undistilled reagent-grade solvents.

The oxidative Mannich reaction catalyzed by **1** was easily extended to a diverse collection of amine substrates (Table 2). Noteworthy examples include an amine containing a proximal olefin (entry 4) as well as an aromatic aldehyde (entry 5). Unsymmetrical amines (entries 6 and 7) were α-CH_3 selective (regioisomeric α-methylene addition products were not observed). Substituted 2-siloxyfurans (entries 10 and 11), including a useful 5-allyl-2-siloxyfuran[11] (entry 12), were also viable participants in the oxidative Mannich reaction.

Mechanistically, we have determined that the reaction proceeds through an iminium ion generated from α-CH_3 amine oxidation followed by nucleophilic capture. In the absence of exogenous siloxyfuran, the oxidation of **2** in MeOH yielded α-methoxy amine **5** (62% yield, 30 min, rt) without evidence of mixed peroxide **6** (Scheme 2, eq 1).[12] However, replacing methanol as the solvent with non-nucleophilic CH_2Cl_2 gave **6**[13] in 60% yield under the same conditions (eq 2).[14] We isolated **6** and observed an equilibrium in

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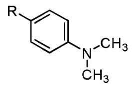
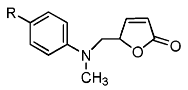
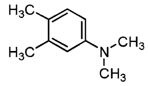
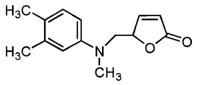
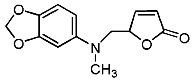
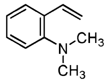
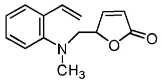
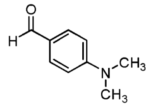
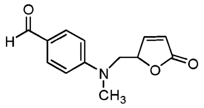
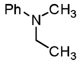
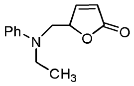
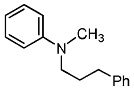
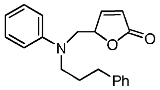
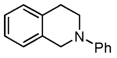
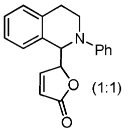
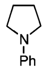
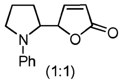
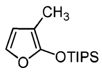
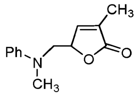
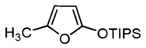
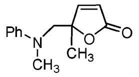
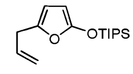
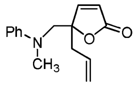
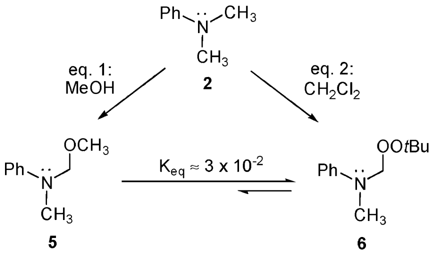
Table 2. The Oxidative Mannich Reaction Catalyzed by $Rh_2(cap)_4$[a]

entry	amine	2-siloxyfuran	product	yield[b]
1		**3**	 R = CH_3 = *t*-Bu = Br	76 (79)[c] 89 (84) 78 (66)
2		**3**		78
3		**3**		57[d]
4		**3**		60
5		**3**		50
6		**3**		64
7		**3**		53
8		**3**		79
9		**3**		89
10	**2**			86
11	**2**			72
12	**2**			75

[a] Reaction conditions: amine (2.0 equiv), 2-siloxyfuran (1.0 equiv), $Rh_2(cap)_4$ (1.0 mol %), T-HYDRO (1.2 equiv), MeOH (0.27 M/[2-siloxyfuran]), 60 °C, 3−5 h. [b] Isolated yield after chromatography. [c] Yields in parentheses were for reactions performed using 0.1 mol % of $Rh_2(cap)_4$ over 16 h. [d] Reaction time 1 h.

Scheme 2



MeOH between **5** and **6** that largely favored the mixed peroxide ($K_{eq} \approx 3 \times 10^{-2}$). From close examination of the oxidation of **2** in MeOH (eq 1), the production of **5** to the exclusion of **6** in the reaction (at low conversion) clearly indicated that **5** was produced as the *kinetic* product from a catalytically generated iminium ion rather than an equilibrium product from **6**. Therefore, we have ruled out the intermediacy of **6** in the dirhodium-catalyzed oxidative Mannich reaction. The intermediacy of **5** and its overall contribution toward carbon−carbon bond formation is under investigation.[15]

In conclusion, we have developed an oxidative Mannich reaction catalyzed by $Rh_2(cap)_4$ that allows for synthesis of valuable γ-aminoalkyl butenolides from readily available amines. Efforts are currently underway to extend this technology to other nucleophiles as well as assessing the role of $Rh_2(cap)_4$ in the catalytic generation of iminium ions.

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Supporting Information Available: Experimental procedures and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The use of CH_3NO_2 as a solvent gave nitromethane-captured product (not shown) and mixed peroxide **6**. For CH_3NO_2 capture, see ref 4a.
(15) Nucleophilic capture of iminium ions with methanol is competitive with 2-siloxyfuran in the reaction. α-Methoxyamines are observed as side products.

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