Cobalt-catalyzed reductive Mannich reactions of 4-acryloylmorpholine with *N*-tosyl aldimines†‡

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Using cobalt catalysis, diethylzinc promotes the conjugate reduction of 4-acryloylmorpholine to produce the corresponding ethylzinc enolate, which reacts with *N*-tosyl aldimines to afford β-aminoamides.

Chiral β-amino acids and their derivatives are important compounds due to their presence in natural products and biologically active compounds, as building blocks for the assembly of β-peptides, and as precursors to β-lactams.[1] One of the most powerful methods for accessing β-aminocarbonyl compounds is the Mannich reaction,[2] and recent years have witnessed many advances in the development of new procedural variants,[2b] and catalytic asymmetric variants[3] using chiral metal-based catalysts[4] or organocatalysts.[5] These reactions typically require either the use of preformed enolates such as silyl enol ethers, or acid/base-mediated enolization of aldehydes, ketones, or relatively acidic ester equivalents such as malonate esters and glycine imine esters. An alternative strategy for enolization that has received more limited attention in Mannich reactions is the use of α,β-unsaturated carbonyl compounds as "latent enolates".[6] Here, conjugate reduction of an α,β-unsaturated carbonyl compound with a hydride source generates an enolate that is then trapped with a suitable imine. Reductive Mannich reactions have been described in racemic form by Isayama,[7a] and the groups of Morken,[7b] Matsuda,[7c] Krische,[7d] and Nishiyama.[7e] In addition, Córdova and Zhao reported a sequential organocatalytic asymmetric conjugate reduction–Mannich reaction of β,β-disubstituted α,β-unsaturated aldehydes.[8]

In recent studies, we disclosed that ethylzinc enolates may be generated *via* conjugate reduction by treatment of α,β-unsaturated amides with diethylzinc and a substoichiometric quantity of a cobalt salt,[9] and that these enolates could be trapped *in situ* with ketones in both intramolecular[9] and intermolecular[10] aldol reactions. In this communication, we show that zinc enolates generated in this fashion also undergo intermolecular Mannich reactions with *N*-sulfonyl aldimines.

Our preliminary experiments commenced with reaction of commercially available 4-acryloylmorpholine (**1**) with a range of benzaldehyde-derived imines to identify the optimum nitrogen protecting group (Table 1). Using *N*-tosyl imine **2** and THF as solvent, the desired Mannich product was obtained as a 68 : 32 ratio of *anti* : *syn* diastereoisomers, which were isolated in 47% and 14% yields respectively (entry 1).[11] Switching the solvent to CH_2Cl_2 afforded improved results (entry 2). Although *N*-(2-thienyl)sulfonyl imine **3**[4c] provided a slight improvement in the diastereoselectivity, the isolated yield of the major *anti* isomer **6b** was modest (entry 3). *N*-Diphenylphosphinoyl imine **4** and *N*-*tert*-butoxycarbonyl imine **5** provided only complex mixtures, with minimal quantities of Mannich products being detected (entries 4–5).

Based upon these results, we examined the scope of the reductive Mannich reaction of **1** (Table 2). A range of *N*-tosyl imines were found to undergo reductive coupling with **1** in moderate to good

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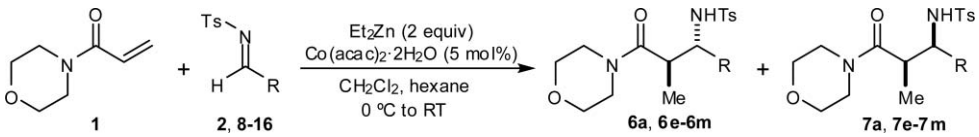
Table 1 Cobalt-catalyzed reductive Mannich reaction of 4-acryloylmorpholine (**1**) with various *N*-protected aldimines[a]

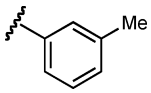
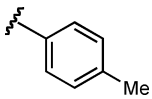
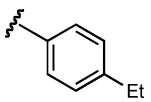
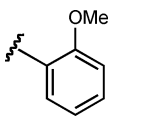
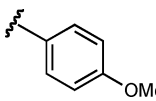
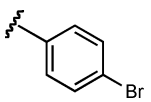
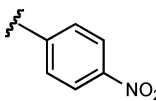
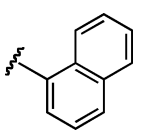
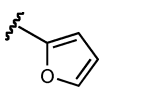
1 2-5 6a-6d 7a-7d

Entry	R	Imine	Solvent	Products	*Anti* : *syn*[b]	Yield (%)[c] *Anti* (**6**)	Yield (%)[c] *Syn* (**7**)
1	Ts	**2**	THF	**6a/7a**	68 : 32	47	14
2	Ts	**2**	CH_2Cl_2	**6a/7a**	80 : 20	72	11
3	SO_2(2-thienyl)	**3**	CH_2Cl_2	**6b/7b**	83 : 17	52	10
4	P(O)Ph_2	**4**	CH_2Cl_2	**6c/7c**	n/a	0[d]	0[d]
5	Boc	**5**	CH_2Cl_2	**6d/7d**	n/a	0[d]	0[d]

[a] Reactions were conducted using 1.1 mmol of **1** and 1.0 mmol of imine for 5 h. [b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c] Isolated yields. [d] A complex mixture was obtained.

Table 2 Cobalt-catalyzed reductive Mannich reaction of 4-acryloylmorpholine (**1**) with assorted *N*-tosyl aldimines[a]



Entry	R	Imine	Products	*Anti* : *syn*[b]	Yield (%)[c] *Anti* (**6**)	Yield (%)[c] *Syn* (**7**)
1	Ph	**2**	**6a/7a**	80 : 20	72	11
2		**8**	**6e/7e**	78 : 22	65	9
3		**9**	**6f/7f**	88 : 12	67	11
4		**10**	**6g/7g**	86 : 14	78	—[d]
5		**11**	**6h/7h**	87 : 13	49	7
6		**12**	**6i/7i**	87 : 13	54	8
7		**13**	**6j/7j**	83 : 17	44	—[d]
8		**14**	**6k/7k**	n/a	0[e]	0[e]
9		**15**	**6l/7l**	82 : 18	49	11
10		**16**	**6m/7m**	64 : 36	36	17

[a] Reactions were conducted using 1.1 mmol of **1** and 1.0 mmol of imine for 5 h. [b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [c] Isolated yields. [d] The *syn*-Mannich product could not be isolated in pure form. [e] A complex mixture was obtained.

yields and with up to 88 : 12 dr. Imines prepared from benzaldehyde derivatives containing electron-donating substituents such as methyl (entries 2–3), ethyl (entry 4), and methoxy (entries 5–6) groups provided better results than those containing electron-withdrawing groups (entries 7–8). The process is not restricted to imines derived from substituted benzaldehydes. Imines **15** and **16**, containing 1-naphthyl and 2-furyl groups respectively, were also tolerated in the reaction (entries 9–10). At the current level of development, we have not yet been able to induce β-substituted α,β-unsaturated morpholine amides or *N*-tosylimines derived from aliphatic aldehydes to undergo the reductive Mannich reaction with satisfactory yields.[12]

In conclusion, we have developed a new variant of the reductive Mannich reaction, involving the coupling of commercially available 4-acryloylmorpholine (**1**) with a range of aromatic *N*-tosyl aldimines using diethylzinc as the stoichiometric reductant, and an inexpensive cobalt salt as the precatalyst. Furnishing acyclic *anti*-β-aminoamides as the major isomers, these reactions complement existing *syn*-selective reductive Mannich reactions[7a,d] and Morken's methodology that provides β-lactams as the products.[7b] Compared with existing *anti*-selective reductive Mannich reactions that give acyclic products using β-unsubstituted α,β-unsaturated carbonyls as pronucleophiles,[7c,e] the present method delivers products with comparable or higher levels of diastereoselectivity. Expansion of the substrate scope of these reactions, and the development of asymmetric variants will be the subjects of future work in this area.

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12 Reactions conducted using $CoCl_2$–Cy_2PPh (see ref. 9 and 10) in place of $Co(acac)_2 \cdot 2H_2O$ offered no improvement.