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Simple Diamine- and Triamine-Protonic Acid Catalysts for the Enantioselective Michael Addition of Cyclic Ketones to Nitroalkenes

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Organocatalytic, asymmetric carbon−carbon and carbon−heteroatom bond-forming reactions have been extensively investigated in recent years,[1] and the organocatalyzed Michael addition reaction is a continuing challenge.[2] Within this category, the conjugate addition of ketones to nitroalkenes is particularly interesting and challenging because it generates two contiguous stereocenters in a single step. Herein, we describe preliminary results on the highly enantioselective conjugate addition of cyclic ketones to nitroalkenes catalyzed at ambient temperature by structurally simple, pyrrolidine-based amine catalysts in conjunction with a protonic acid.

Recent investigations have examined the catalysis of the ketone−nitroalkene conjugate addition reaction with derivatives of chiral diamines,[2b,c] amino acids,[2d] and ionic liquids,[2e] but a significant amount of effort has been devoted to the modification of the proline motif. Chiral pyrrolidines in which a tertiary aminomethyl,[3] tetrazole,[4] tetrazolylmethyl,[5] pyrrolidinyl,[6] carboxymethyl,[7] trifluoromethylsulfonamido,[8] methylpyridyl,[9] or 1-((pyrrolidin-2-yl)-methyl)pyrrolidine[10] functionality replaces the carboxyl function in proline have been investigated. These pyrrolidine catalysts normally require low temperature and a large excess of ketone for good enantioselection.[11] A catalyst that overcomes these limitations would be advantageous.

We chose to investigate proline-derived triamines as organocatalysts for two reasons: (a) the potential for rate enhancement by the added amine functionality in a pyrrolidine-based diamine motif and (b) the possibility of employing a conformationally modified, protonated form of the catalyst. Triamines **2a** and **2b**[12] (Scheme 1) were chosen as candidates and were readily prepared from Boc-*S*-proline, as shown in Scheme 1. Diamine **2c** was prepared as an analogue of **2a**, lacking the tertiary amine.

Orienting experiments were conducted with cyclohexanone (**3**) and the nitrostyrene **4** as the Michael acceptor. Initially, the conjugate addition reaction was examined in a few solvents with triamine **2b** as the catalyst (Table 1). The reaction was slow and low yields of the conjugate addition product **5** were obtained after 3 days at ambient temperature (Table 1). Surprisingly, a substantial change in the nature of the solvent did not have a significant effect on the enantioselectivity (entries 1 and 2), and the highest selectivities were obtained in DMF. An improvement in selectivity was observed when the catalyst **2a** was employed in DMF. The use of an acid[6,9] (*p*TsOH) in conjunction with **2a** or **2b** had a dramatic effect on the yield and the diastereoselectivity as well as the enantioselectivity of this reaction (entries 4 and 8, Table 1).

The enantioselectivity with the **2b**/*p*TsOH combination was lower (83%) than with the **2a**/*p*TsOH combination (>99%). Use of 2,4-dinitrobenzenesulfonic acid decreased the enantioselectivity and trifluoroacetic acid deactivated the catalyst. Selectivity with catalyst **2c** was comparable to **2a**. Although **2a** provided **5** with 90% ee in toluene without any added acid, the enantioselectivity with **2a**/*p*TsOH in DMF was >99%. The poor solubility of the **2a**/*p*TsOH salt in toluene precluded further studies in this solvent. The

Scheme 1

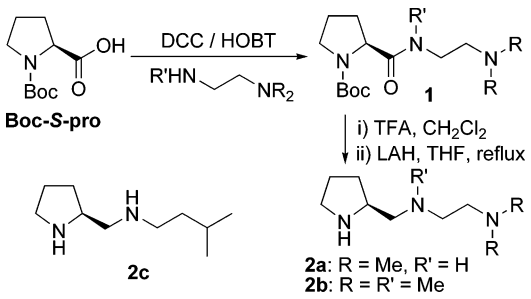
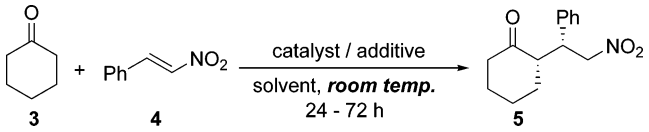


Table 1



entry[a]	cat.[b]	solvent	additive[b]	yield	syn/anti[c]	ee (%) syn[d]
1	**2b**	toluene		21	4/1	47
2	**2b**	ethanol		51	1/1	48
3	**2b**	DMF		29	4/1	56
4	**2b**	DMF	*p*TsOH	72	7/1	83[e]
5	**2a**	toluene		40	19/1	90
6	**2a**	*i*PrOH		8	2/1	25
7	**2a**	DMF		30	3/1	73
8	**2a**	DMF	*p*TsOH	90	19/1	>99[e]
9	**2a**	DMF	[f]	70	4/1	83[e]
10	**2a**	DMF	TFA	0		
11	**2c**	DMF	*p*TsOH	86	19/1	>99[e]

[a] 1.1 equiv of ketone. [b] 20 mol %. [c] ^{1}H NMR of crude products. [d] Chiral HPLC analysis. [e] 5 equiv of ketone. [f] 2,4-dinitrobenzenesulfonic acid.

observation that **2a** and **2c** are better catalysts than **2b** highlights the importance of the secondary−secondary diamine motif, which was examined by Yamamoto in asymmetric aldol reactions.[13] However, this class of diamines has been mostly overlooked in organocatalytic conjugate addition studies and, in one earlier investigation, generated aminals of the carbonyl substrates.[14]

The catalysts **2a** or **2c** in conjunction with *p*TsOH in DMF were employed in the conjugate addition of a few cyclic ketones to a variety of 2-nitrovinyl arenes at ambient temperature. In all cases, the syn diastereomer was obtained as the major product, and good diastereoselectivities and enantioselectivities were observed. These results are summarized in Table 2.

Enantioselectivities for nitroalkenes with substitution at the 4-position in the phenyl ring were very high. Moving the substituent to the 2-position lowered the enantioselectivity (Table 2, entries 4, 5, 7, 8, 11, and 13). In one case, the use of methanesulfonic acid instead of *p*TsOH significantly increased the diastereoselectivity as well as the enantioselectivity (Table 2, entries 5 and 6). Interestingly, increasing the size of the acid additive decreased the

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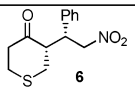
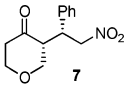
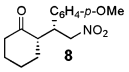
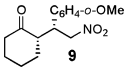
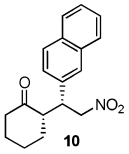
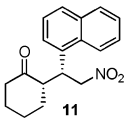
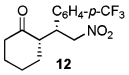
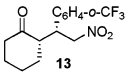
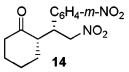
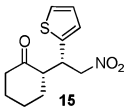
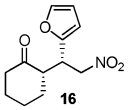
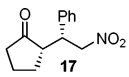
Table 2. Enantioselective Conjugate Addition of Cyclic Ketones to Nitroalkenes Catalyzed by **2a** or **2c**[a]

entry	product	cat./additive	yield (%)	syn/anti[b]	ee (%) syn[c]
1	 **6**	**2a**/*p*TsOH	78	19/1	99
2	 **7**	**2a**/*p*TsOH	99	19/1	85
3		**2c**/*p*TsOH	90	20/1	92
4	 **8**	**2a**/*p*TsOH	83	19/1	99
5	 **9**	**2a**/*p*TsOH	99	5/1	86
6		**2a**/$MeSO_3H$	95	50/1[d]	94[e], 99[d]
7	 **10**	**2a** *p*TsOH	90	19/1	>99
8	 **11**	**2a**/*p*TsOH	86	12/1	87
9		**2a**/2,4,6-tri-Me-$PhSO_3H$			
10			78	7/1	81
		2a/2,4,6-tri-*i*Pr-$PhSO_3H$	55	11/1	78
11	 **12**	**2a**/*p*TsOH	81	15/1	92
12		**2c**/*p*TsOH	95	20/1	96
13	 **13**	**2a**/*p*TsOH	89	19/1	90
14		**2c**/*p*TsOH	90	19/1	91
15	 **14**	**2a**/*p*TsOH	80	19/1	86
16		**2c**/pTsOH	90	19/1	90
17		**2c**/*p*TsOH	91	50/1	81
18		**2a**/$MeSO_3H$[d]	74	19/1	85
19		**2c**/$MeSO_3H$[d]	88	20/1	92
20	 **15**	**2a**/HCl	75	12/1	83
21		**2c**/HCl	99	19/1	84
22		**2a**/HCl[f]	70	8/1	79
23		**2c**/HCl[f]	75	10/1	72
24	 **16**	**2a**/$MeSO_3H$[d]	82	15/1	88
25	 **17**	**2a**/*p*TsOH	51	7/1	29
26		**2c**/*p*TsOH	33	2/1	49

[a] Reaction conditions: 5 equiv of ketone, DMF, 24 h, rt. [b] ^1H NMR or HPLC of crude products. [c] Chiral HPLC analysis. [d] Reaction at 0 °C for 45 h. [e] 11 h reaction. [f] Dichloromethane solvent.

enantioselectivity for the 1-naphthyl substrate (Table 2, entries 8−10). These results suggest that the conjugate base of the protonic acid influences enantioselection, and a large acid counterion is detrimental for *ortho*-substituted substrates.

Enantioselection for the heteroaryl-substituted nitroalkenes (Table 2, entries 17−24) is better with methanesulfonic acid as the additive. For the thiophenyl substrate, the **2c**/$MeSO_3H$ combination in DMF provided the best result (92% ee). In dichloromethane, **2a**/HCl was superior to **2c**/HCl (Table 2, entries 22 and 23). It is plausible that, in dichloromethane, the diamine pendant in **2a** has increased steric requirements. This may be due to internal hydrogen bonding in the ethylenediamine unit. The selectivity of the chain-extended conformer of **2a** is reflected by **2c**, which is incapable of internal hydrogen bonding in the side chain.

The stereochemical outcome may be explained by a synclinal transition state assembly[15] **A** (Figure 1) in which a protonated

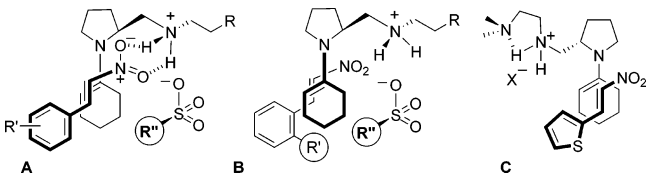


Figure 1. Transition state assemblies for conjugate additions with protonated **2a** or **2c**.

secondary amine delivers the nitroalkene by hydrogen bonding to provide the major product in all cases. For *ortho*-substituted nitroalkenes, a nonhydrogen-bonded assembly such as **B** may compete with **A** to avoid steric interactions (R′−R″) with a large acid counterion. This would reduce the enantioselection. In a noncoordinating solvent, an internally hydrogen-bonded ethylenediamine unit (**C**) may explain the higher enantioselection with **2a** as compared to **2c**.

In conclusion, we have developed simple, protonated triamine and diamine catalysts for the highly enantioselective conjugate addition of cyclic, six-membered ketones to nitroalkenes. The main advantages of these catalysts are the ease of synthesis and very good enantioselection at ambient temperature. For unhindered nitroalkenes, the enantioselection with these simple catalysts at ambient temperature is better than the enantioselection with structurally more complex pyrrolidine catalysts at subambient temperatures.[9,10] We are investigating the efficacy of these and related catalysts in other organocatalytic reactions.

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Supporting Information Available: Experimental methods and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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