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Highly Enantioselective and Regioselective Organocatalytic Direct Mannich Reaction of Methyl Alkyl Ketones with Cyclic Imines Benzo[*e*][1,2,3]oxathiazine 2,2-dioxides

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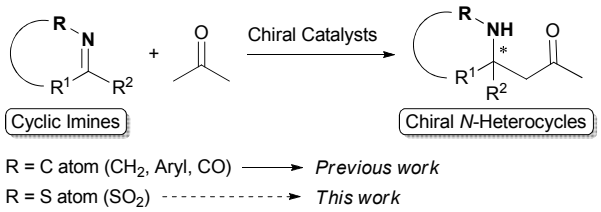
A highly enantioselective direct Mannich reaction of methyl alkyl ketones with cyclic imines benzo[*e*][1,2,3]oxathiazine 2,2-dioxides, catalyzed by the combination of cinchona alkaloid derived primary amine and TFA, is disclosed. For unsymmetrical methyl alkyl ketones, it is favoured that specific regioselective addition to the imine substrates occurs at the less-substituted methyl group by steric control.

The catalytic asymmetric Mannich reaction, is an example of addition to C=N intermediates[1] using a variety of nucleophiles, including enolized carbonyl compounds in presence of a chiral catalyst. The Mannich products, optically active β-amino-carbonyl compounds, can be used as important intermediates for biologically active compounds.[2] Enantioselective direct variants with unmodified carbonyl donors are especially attractive, with highly enantioselective processes based on organocatalysis is reported over the past decade.[1-2] An important aspect of Mannich reactions is the construction of polyfunctionized chiral nitrogen-containing compounds through extending a variety of imine acceptors. Resulting Mannich products are very useful nitrogen-containing heterocycles with a stereogenic centre at the α-position, while the cyclic imines were employed as electrophilic acceptors in the catalytic asymmetric Mannich reactions. However, Mannich addition to cyclic imines has received much less attention compared with the well-researched acyclic imines. In addition, only carbon-substituted cyclic imines adjacent to the nitrogen of N=C have been studied in enantioselective Mannich-type reactions, such as, *N*-alkyl,[3] aryl,[4] acyl[5] substituent groups (Scheme 1). The extension to other cyclic imines continues to be an interesting line of research for catalytic asymmetric Mannich reactions, especially for ones bearing non-carbon N-substituted groups.



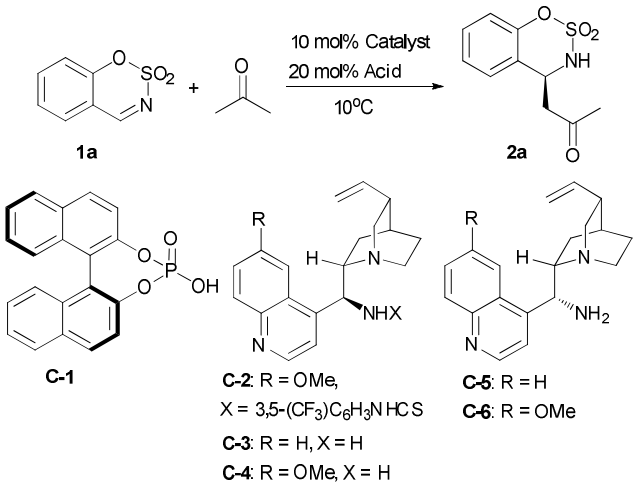
Scheme 1. Catalytic asymmetric Mannich reaction of cyclic imines.

Catalytic asymmetric addition to cyclic N-sulfonyl imines is one of the most useful reactions for the synthesis of optically active *N*-heterocycles bearing sulfonamide functionality in the ring. Sultams and sulfamidates are typical examples, which are key structural motifs in biologically active natural products and pharmaceuticals[6] and also play an important role in organic synthesis.[7] In combination with asymmetric catalysis, cyclic imines benzo[*e*][1,2,3]oxathiazine 2,2-dioxides **1**[8] have proven to be versatile building blocks for the synthesis of chiral benzo-fused cyclic sulfamidate heterocycles.[9] Recent publications indicate that the corresponding cyclic aldimines or ketimines **1** can be used as electrophilic substrates in various enantioselective reactions, such as Pd-catalyzed hydrogenation,[10] Rh-catalyzed additions with organic boron reagents,[11] phosphine-catalyzed [3+2] cycloadditions with allenoates,[12] [4+2] cycloaddition with acyclic enones or ynones catalyzed by the combination of chiral primary amine and *o*-fluorobenzoic acid,[13] and the Cu-catalyzed decarboxylative Mannich reaction of β-ketoacids.[14] In our previous research we were the first to demonstrate an organocatalytic process of imines **1**.[12a] Continuing with our interest in Mannich reaction of cyclic imines,[4d-e] here we report the highly enantioselective Mannich reaction of benzo[*e*][1,2,3]oxathiazine 2,2-dioxides **1** with ketones using alkaloid derived primary-tertiary diamine catalysts (Scheme 1). Furthermore, for various unsymmetrical methyl alkyl ketones, the specific regioselective addition to the imines **1** preferably occurs at the less-substituted methyl group by steric control, despite the fact that the highly regioselective addition remains a challenge for catalytic asymmetric Mannich reaction of ketones.[15]

Condition optimization studies began with the model reaction of imine **1a** and acetone (Table 1). (*S*)-Proline was an excellent organocatalyst for the activation of carbonyl compounds via nucleophilic enamine intermediates,[2a-d,f] and also functions as a highly efficient catalyst for asymmetric Mannich reaction of some cyclic imines.[3a-c,4,5b] However, with (*S*)-proline as a catalyst the reaction was unsuccessful (entry 1). Other amine catalysts such as chiral Børnsted acid **C-1** and cinchona alkaloid produced thiourea **C-2**, which have previously enabled Mannich reactions,[16] also failed to promote the reaction (entries 2-3). Interestingly, the desired product **2a** was formed, albeit in low yield for 72 hours, catalyzed by cinchonidine derived primary amine **C-3**, with a moderate *ee* value (entry 4, 57%). Fortunately, in the presence of trifluoroacetic acid (TFA) as a cocatalyst, the

reaction worked well with 90% *ee* (entry 5). The achieved yield and enantioselectivities were further enhanced by screening primary amine catalysts afforded from cinchona alkaloids and solvents (entries 9-13). The best result was obtained when the reaction was catalyzed by the combination of **C-4** (10 mol%) and TFA (20 mol%) in toluene at 10°C for 12 hours (entry 9, 99% yield and 96% *ee*).[17]

Table 1. Optimization of reaction conditions [a]

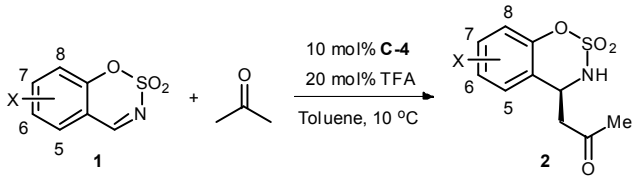


Entry	Catalyst	Acid	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1[d]	(*S*)-Proline	-	DMSO	12	NR	-
2	**C-1**	-	THF	96	NR	-
3	**C-2**	-	THF	96	NR	-
4	**C-3**	-	THF	72	21	57
5	**C-3**	TFA	THF	22	57	90
6	**C-4**	TFA	THF	22	51	90
7	**C-5**	TFA	THF	22	53	-85[e]
8	**C-6**	TFA	THF	22	48	-83[e]
9	**C-4**	TFA	Toluene	12	99	96
10	**C-4**	TFA	CH_2Cl_2	15	85	93
11	**C-4**	TFA	CH_3CN	60	69	50
12	**C-4**	TFA	MeOH	60	54	54
13	**C-4**	TFA	DMF	60	54	50

[a] Unless otherwise noted, reactions were conducted with imine **1a** (0.05 mmol), acetone (0.5 mmol), **C-3** (0.005 mmol, 10 mol%) and TFA (0.01 mmol, 20 mol%) in 0.5 mL of solvent at 10°C. [b] Isolated yield. [c] Determined by HPLC using a chiral column. [d] 30 mol% (*S*)-proline was used at room temperature. [e] The minus *ee* value indicates that the opposite enantiomer was obtained as the major form.

With the optimal reaction conditions established, the Mannich reaction of a variety of imines **1** and acetone was carried out (Table 2), with the reaction displaying a broad substrate scope. Various substituents in the phenyl ring of cyclic imines **1**, such as fluoride, chloride, bromide, methyl and methoxy, were well tolerated under the reaction conditions, and the corresponding Mannich products were obtained with high yields and enantioselectivities (entries 2-8). Cyclic imines, **1i-k**, that contain two substituents that lead to steric hindrance, were also suitable substrates for the Mannich reaction, affording excellent enantioselectivities (93-97% *ee*, entries 9-11). For cyclic imine **1k**, bearing two *tert*-butyls, more time was required to complete the reaction, probably due to the greater steric effects (entry 11). The absolute configuration of representative product **2c** was determined as *S* by single-crystal X-ray analysis.[18] The absolute configurations of all other Mannich products were assigned by analogy. It was proved that the carbon nucleophile of an enamine transition state formed from acetone and primary amine catalyst **C-4** attacks the cyclic imine **1** from the *si*-face (Figure 1).

Table 2. Asymmetric Mannich reaction of various imines **1a** with acetone[a]



Entry	X (**1**)	Time (h)	**2**	Yield (%)[b]	*ee* (%)[c]
1	H (**1a**)	12	**2a**	99	96
2	6-F (**1b**)	19	**2b**	96	96
3	6-Cl (**1c**)	19	**2c**	87	97
4	6-Br (**1d**)	19	**2d**	92	91
5	6-Me (**1e**)	19	**2e**	99	95
6	6-OMe (**1f**)	19	**2f**	99	95
7	7-OMe (**1g**)	20	**2g**	97	96
8	8-OMe (**1h**)	19	**2h**	93	95
9	6,8-Br_2 (**1i**)	21	**2i**	76	97
10	6-Cl, 8-Br (**1j**)	21	**2j**	80	96
11	6,8-*t*Bu_2 (**1K**)	45	**2k**	85	93

[a] Reaction conditions: imine **1** (0.15 mmol), acetone (1.5 mmol), **C-3** (0.015 mmol, 10 mol%) and TFA (0.03 mmol, 20 mol%) in toluene (1.5 mL) at 10°C. [b] Isolated yield. [c] Determined by HPLC using a chiral column.

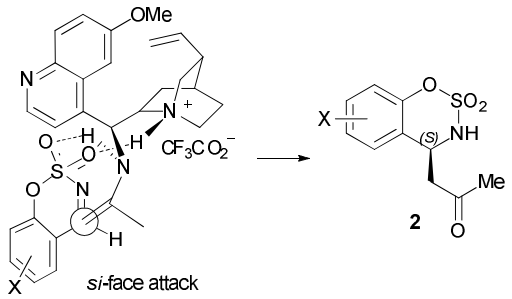
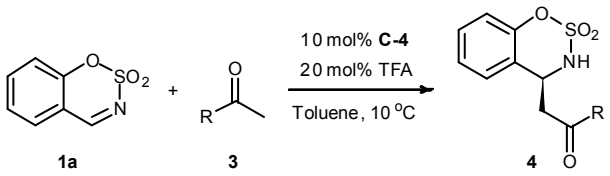


Figure 1. Proposed transition state.

Next, a variety of unsymmetrical methyl alkyl ketones were evaluated as Mannich donors, which could give rise to the formation of regioisomers. As shown in Table 3, Mannich products **4** with specific regioselective additions were produced more readily with a less-substituted methyl moiety on the ketone donors, bearing excellent enantioselectivities (entries 1-12). Only cyclohexylacetone **3e** led to a slight decrease in enantioinduction

(87% ee), but displayed a faster reaction rate (entry 5). The regioselectivities can be attributed to a feature in organocatalysis with chiral primary amines. The reactive intermediate, preferentially formed from methyl alkyl ketones **3** and primary amine catalyst, is the di-substituted enamine with less steric repulsion but not the more stable tri- or tetra-substituted enamine.[15] However, pinacolone **3j** did not furnish the expected product due to more steric impediment of the *tert*-butyl group (entry 13).

Table 3. Asymmetric Mannich reaction of **1a** with different unsymmetrical methyl alkyl ketones[a]



Entry	R (**3**)	**4**	Yield (%)[b]	*ee* (%)[c]
1[d]	Et (**3a**)	**4a**	99	96
2	*n*-Pr (**3b**)	**4b**	99	95
3	*n*-Bu (**3c**)	**4c**	94	97
4	$(CH_3)_2CHCH_2$ (**3d**)	**4d**	99	96
5[d]	$CyclohexylCH_2$ (**3e**)	**4e**	92	87
6	4-$FC_6H_4CH_2$ (**3f**)	**4f**	65	92
7	4-$ClC_6H_4CH_2$ (**3g**)	**4g**	82	94
8	4-$MeOC_6H_4CH_2$ (**3h**)	**4h**	90	94
9	$PhCH_2CH_2$ (**3i**)	**4i**	72	96
10	*i*-Pr (**3j**)	**4j**	50	96
11	Cyclohexyl (**3k**)	**4k**	75	97
12	Cyclopropyl (**3l**)	**4l**	57	95
13	*t*-Bu (**3m**)	**4m**	NR	-

[a] Reaction conditions: imine **1a** (0.15 mmol), acetone (0.75 mmol), **C-3** (0.015 mmol, 10 mol%) and TFA (0.03 mmol, 20 mol%) in toluene (1.5 mL) at 10°C for 4 days. [b] Isolated yield. [c] Determined by HPLC using a chiral column. [d] 3days.

Conclusions

In summary, we have demonstrated the highly enantioselective and regioselective direct Mannich reaction of various methyl alkyl ketones with cyclic imines benzo[*e*][1,2,3]oxathiazine 2,2-dioxides using alkaloid derived primary-tertiary diamine as an organocatalyst. The specific regioselective addition preferably occurs at the less-substituted methyl group on unsymmetrical methyl alkyl ketones by steric control. This is the first example of asymmetric Mannich reaction using *N*-sulfonyl cyclic imines as acceptors. Further applications of other ketones in asymmetric direct Mannich reactions of these *N*-sulfonyl cyclic imines is worthy of future investigation.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details and characterization for the new compounds. X-ray data for **2c** (CCDC 1016210). See DOI: 10.1039/b000000x/

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17 For more results on the optimization of reaction conditions, please see supporting information.

18 CCDC 1016210 (**2c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.