Enantioselective Michael addition of ketones to maleimides catalyzed by bifunctional monosulfonyl DPEN salt†

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An unprecedented enantioselective Michael addition of various ketones to maleimides catalyzed by a simple bifunctional primary amine, monosulfonyl DPEN salt, is reported and provides the desired adducts in good to excellent yields (up to 99%) with excellent enantioselectivities (up to 99%).

It is well known that substituted maleimides are an important class of compounds that are found in many biologically interesting substances, such as substituted succinimides and functionalized pyrrolidines.[1] The catalytic asymmetric Michael addition to electron-deficient alkenes is a useful strategy for the construction of carbon–carbon bonds.[2] In sharp contrast, the asymmetric addition to maleimides remains elusive. To date, only several elegant protocols have been reported. Chiral metal complexes were kind of powerful catalysts in asymmetric addition of aryl boronic acids,[3] hydrazoic acid,[4] and hydroxyketones[5] to maleimides. Natural cinchona alkaloids[6] and chiral bicyclic guanidines[7] were also successfully used as catalysts for the Michael addition of 1,3-dicarbonyl compounds to maleimides. Wang demonstrated an ingenious domino Michael-Aldol reaction between 2-mercaptobenzaldehydes and malemindes catalyzed by chiral amine thiourea.[8] An efficient method for the addition of unmodified aldehydes to maleimides was reported by Córdova, employing chiral diphenylprolinol silyl ether as the enamine activation organocatalyst.[9]

In the past few years, chiral primary amines have been increasingly considered as powerful organocatalysts in many asymmetric reactions.[10] Many reports revealed that primary amines were suitable for the generation of nucleophilic enamines, which could lead to an efficient addition to electron-deficient alkenes.[11–13] To the best of our knowledge, only Barbas and co-workers reported the Michael addition of acetone to maleimide without asymmetric induction.[14] Therefore, catalytic asymmetric Michael addition of ketones to maleimides remains a challenge, and both stereoselectivity and substrate scope are highly desirable to explore. In this communication, we disclosed an enantioselective Michael addition of ketones to maleimides catalyzed by a chiral monosulfonyl DPEN salt in good yields (up to 99%) with excellent enantioselectivities (up to 99%).

Our investigation initially performed a model reaction between acetone (**5a**) and *N*-phenylmaleimide (**6a**) in the presence of benzoic acid at room temperature in dichloromethane. Several kinds of simple chiral primary amine catalysts were screened because they can activate acetone by formation of an enamine intermediate (Fig. 1). The results are summarized in Table 1. Bifunctional catalysts **1** and **2** readily

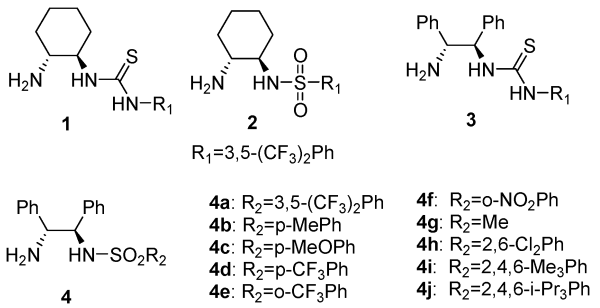
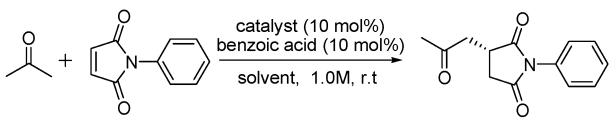


Fig. 1 Organocatalysts for the conjugate addition of ketones to maleimides.

Table 1 Screening of reaction conditions for the organic catalytic Michael Reaction of **5a** to **6a**[a]



Entry	Catalyst	Solvent	Conv.%[b]	ee%[c]
1	**1**	CH_2Cl_2	79	33
2	**2**	CH_2Cl_2	29	13
3	**3**	CH_2Cl_2	87	49
4	**4a**	CH_2Cl_2	72	93
5	**4b**	CH_2Cl_2	70	94
6	**4c**	CH_2Cl_2	78	93
7	**4d**	CH_2Cl_2	52	94
8	**4e**	CH_2Cl_2	56	90
9	**4f**	CH_2Cl_2	39	95
10	**4g**	CH_2Cl_2	36	94
11	**4h**	CH_2Cl_2	80	96
12	**4i**	CH_2Cl_2	79	96
13	**4j**	CH_2Cl_2	<5	nd
14[d]	**4h**	CH_2Cl_2	19	96
15	**4h**	Methanol	34	93
16	**4h**	Acetonitrile	36	94
17	**4h**	THF	47	98
18	**4h**	1,4-dioxane	34	97
19	**4h**	Et_2O	full	95
20	**4h**	*n*-Hexane	full	95
21	**4h**	Toluene	83	98

[a] Experimental conditions: The reaction was carried out in a 0.2 mmol scale in undistilled solvent with a 5 : 1 ratio of **5a** to **6a** for 48 h. [b] Conversion was determined by GC analysis of the crude product mixture. [c] Enantiomeric excess was determined by chiral HPLC analysis. [d] Without acidic additive.

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prepared from (*R*, *R*)-1,2-cyclohexanediamine showed moderate conversions with low enantioselectivities (entries 1–2). When the primary amine framework was switched to (*R*, *R*)-1,2-diphenylethylenediamine, to our delight, the sulfonamide catalyst **4a**[15] showed a promising result with an excellent ee value (93%) and good conversion (72%) (entry 4).

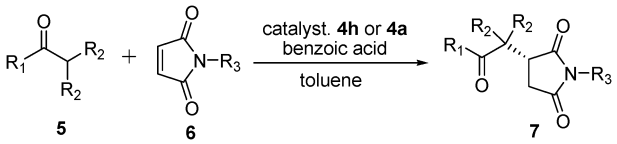
Encouraged by this result, we surveyed **4a**'s analogues **4b–j** bearing various sulfonyl groups for the model reaction. Excellent enantioselectivities and good conversions were obtained when catalysts **4b–c** were employed (entries 5–6). When **4e–f** with a CF_3 and NO_2 group in the *ortho* position of the phenylsulfonyl substituents were used, the catalytic activity decreased to moderate levels (entries 8–9). In the case of **4g**, replacing the aryl group with a less bulky methyl group, a moderate conversion was also observed (entry 10). **4h** and **4i** gave the best results both in catalytic activities and ee values (96% ee) (entries 11–12). Almost no reaction occurred when the more hindered catalyst **4j** was employed (entry 13). This indicates that suitable sterically hindered sulfonyl groups in **4** may play a role in enhancing both enantioselectivity and reactivity. Notably, in the absence of benzoic acid additive, the conversion significantly depreciated to 19% (entry 14). This result clearly evinces that acidic additives can promote the formation of enamine effectively and favor the catalytic reaction.

The reaction conditions were further optimized for **4h**. The solvent was found to have remarkable effects on the catalytic activity. In solvents of MeOH, CH_3CN, THF and 1,4-dioxane, the reaction became sluggish likely due to the great effect of the hydrogen-bonding between catalyst and solvent (entries 15–18). In contrast, high catalytic activities toward the reaction were generally obtained in non-polar solvents. Toluene was the best solvent giving the highest ee of 98% with good conversion (83%) (entry 21).

Under the optimized conditions, the scope of the catalytic asymmetric Michael addition was explored. Experiments of different ketones to *N*-substituted maleimides forming one stereogenic center are summarized in Table 2. It appears that for the aromatic maleimides, the patterns of the substituents have little effect on the reaction in terms of enantioselectivity (94–98%) and yield (87–98%) (entries 1–9). In addition, similar enantioselectivities were obtained in the reaction of acetone and *N*-alkyl substituted maleimides (entries 10–13). Interestingly, methyl isopropyl ketone **5b** as an α-branched ketone gave exclusive products at the sterically more hindered side with high yields and excellent enantioselectivities, but their reaction time was prolonged probably due to the steric reasons (entries 15–17). Moreover, the protocol also proved to be effective with respect to aromatic enones affording the expected Michael adducts (entries 18–22). A dramatically decreased reactivity was observed for aromatic ketones (entry 23).

The reaction appears quite general with respect to other acyclic ketones and cyclic ketones without compromising the yields as shown in Table 3. The addition of 3-pentanone to maleimide afforded the 1,4-adduct and approximately a 1 : 1 diastereomeric mixture was observed (entry 1), but both diastereomers were formed in excellent ee (96–99%). The reaction of long chain ketones gave considerably higher diastereoselectivities (> 4 : 1) (entries 2–3). Addition of the cyclic ketones also proceeded in high yields (> 93%) with good enantioselectivities (> 92%) in approximately 2 : 1 diastereomeric ratios (entries 6–8).

Table 2 Scope of organocatalytic conjugate addition of ketones to maleimides forming one stereogenic center[a]

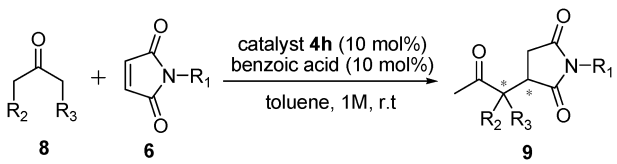


5 6 7

Entry	R_1	R_2	R_3	Yield[b] (%,7)	ee%[c]
1	Me	H	Ph(6a)	87(**7a**)	98
2	Me	H	*p*-CH_3Ph(6b)	91(**7b**)	98
3	Me	H	*p*-CF_3Ph(6c)	99(**7c**)	96
4	Me	H	*p*-BrPh(6d)	93(**7d**)	97
5	Me	H	*p*-ClPh(6e)	94(**7e**)	94
6	Me	H	*p*-OCH_3(6f)	96(**7f**)	98
7	Me	H	*m*-ClPh(6g)	94(**7g**)	98
8	Me	H	*m*-CF_3Ph(6h)	98(**7h**)	96
9	Me	H	*m*-CH_3Ph(6i)	97(**7i**)	96
10	Me	H	Bn(6j)	86(**7j**)	99
11[d]	Me	H	Pr(6k)	94(**7k**)	99
12[e]	Me	H	*i*-Pr(6l)	92(**7l**)	92
13[e]	Me	H	*t*-Bu(6m)	69(**7m**)	99
14[f]	Me	Me	Ph(6a)	93(**7n**)	93
15[f]	Me	Me	*p*-CF_3Ph(6c)	73(**7o**)	96
16[f]	Me	Me	*p*-BrPh(6d)	99(**7p**)	99
17[f]	Me	Me	*p*-ClPh(6e)	98(**7q**)	98
18[g]	*Trans*-PhC_2H_2	H	Ph(6a)	72(**7r**)	94
19[g]	*Trans*-PhC_2H_2	H	*p*-ClPh(6e)	62(**7s**)	98
20[g]	*Trans*-PhC_2H_2	H	*p*-CH_3Ph(6b)	95(**7t**)	95
21[g]	*Trans-o*-$FPhC_2H_2$	H	Ph(6a)	63(**7u**)	97
22[g]	*Trans-p*-$BrPhC_2H_2$	H	*p*-ClPh(6e)	72(**7v**)	91
23	Ph	H	Ph(6a)	< 10	nd

[a] Experimental conditions: The reaction was carried out using 0.05 mmol of catalyst **4h** (10 mol%) and benzoic acid (10 mol%), 0.5 mmol of **6**, and 2.5 mmol of ketones **5** (5.0 equiv.) in 0.50 mL toluene. [b] Isolated yield. [c] Determined by chiral HPLC analysis (see ESI for details). [d] Reaction time: 72 h. [e] 120 h. [f] 140 h. [g] Experimental conditions: The reaction was carried out using 0.1 mmol of catalyst **4a** (20 mol%) and benzoic acid (20 mol%), 0.5 mmol of **6**, and 1.0 mmol of enones **5** (2.0 equiv.) in 0.50 mL toluene at 50 °C.

Table 3 Scope of organocatalytic conjugate addition of ketones to maleimides forming two stereogenic centers[a]



8 6 9

Entry	6	R_2	R_3	Time/h	Yield[b](%, 9)	dr[c]	ee%[d]
1	6i	Et	Et	48	96(**9a**)	1 : 1	97 : 99
2	6a	*n*-Pr	*n*-Pr	48	96(**9b**)	> 4 : 1	99 : 95
3	6a	*n*-Bu	*n*-Bu	72	80(**9c**)	> 4 : 1	99 : 94
4	6j	$-(CH_2)_5-$		48	96(**9d**)	3 : 1	93 : 94
5	6a	$-(CH_2)_6-$		72	93(**9e**)	2 : 1	96 : 99
6	6c	$-(CH_2)_6-$		120	93(**9f**)	2 : 1	92 : 96

[a] Experimental condition: The reaction was carried out using 0.05 mmol of catalyst **4 h** (10 mol%) and benzoic acid (10 mol%), 0.5 mmol of **6**, and 2.5 mmol of **8** (5.0 equiv.) in 0.50 mL toluene. [b] Isolated yield. [c] The diastereoisomer ratios were determined by ^{1}H NMR of crude products. [d] Determined by chiral HPLC analysis (see Supporting Information for details).

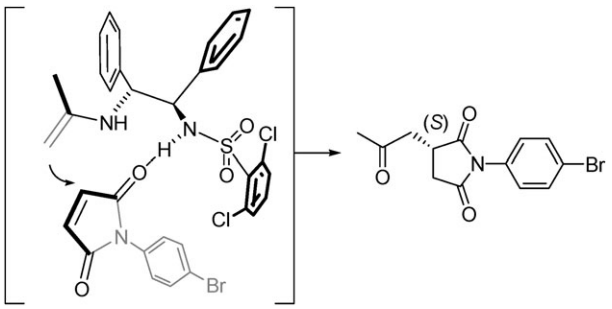


Fig. 2 Proposed transition state of the asymmetric Michael reaction catalyzed by monosulfonyl DPEN and absolute configuration of the adduct **7d**.

The *S* absolute configuration of the asymmetric Michael adduct **7d** was determined by X-ray crystallographic analysis (see ESI).† A transition state model was invoked to account for the observed stereochemical outcome of the reaction (Fig. 2). Acetone is activated through an enamine intermediate. The hydrogen bonding activation of the acceptor maleimide by the acidic proton of sulfonamide triggers the reaction to proceed *via* the enamine mechanism. This transition state model avoids the steric repulsion between the maleimide and the phenyl of the 1,2-diphenylethylenediamine and substituted sulfonyl group, as well as the maleimide and enamine. Therefore, the bulky substituent in the sulfonamide (2,4,6-*i*-$Pr_3C_6H_2$ in **3j**) induced strong steric repulsion between the maleimide and the substituted sulfonyl group, which diminished the hydrogen bonding interaction, and led to a very slow reaction rate (Table 1, entry 13).

In summary, we have demonstrated an unprecedented example in the asymmetric Michael addition of ketones to maleimides catalyzed by a simple bifunctional monosulfonyl DPEN salt, providing Michael adducts in good to excellent yields with excellent enantioselectivities. Further efforts to evaluate the scope of the catalytic chemistry are currently under the way.

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