Synthetic Methods

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Enesulfonamides as Nucleophiles in Catalytic Asymmetric Reactions**

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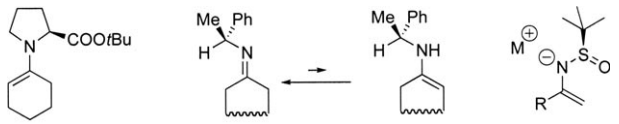
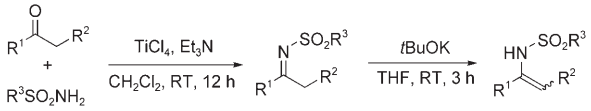
Enamines and metalated enamines are useful as nucleophiles in synthesis because of the resonance-donating property of the nitrogen atom, which is greater than that of oxygen atoms, thus they are more reactive than the enols and enolates.[1] Asymmetric reactions of enamines and metalated enamines have been reported. Yamada et al. first reported the chiral nonracemic enamines **1** which were derived from ketones and secondary amines[2] and subsequently several chiral enamines such as **2**, based on this concept, have been developed and successfully employed.[3] Recently the research group of Ellman reported the first use of metalated enamines **3** derived from chiral *N*-sulfinylimines in addition reactions to aldehydes.[4] Since in this case primary sulfinamide-derived *N*-sulfinylimines were employed, the products were β-hydroxy-*N*-sulfinylketimines which could be reduced stereoselectively to afford either the *syn*- or *anti*-1,3-amino alcohols.



1 **2** **3**

Although high diastereoselectivity was observed in many of the above cases, stoichiometric amounts of the chiral component (as well as stoichiometric amounts of a strong base to prepare the metalloenamines) were necessary. Recently we reported the development of highly diastereo- and enantioselective addition reactions of enecarbamates to ethyl glyoxylate.[5] These reactions proceeded smoothly with high selectivity in the presence of a catalytic amount of a chiral Lewis acid, and was marked by a stereospecific conversion of α-substituted ketone-derived enecarbamates into 1,3-imino alcohols. Despite the importance of enecarbamates, direct methods of synthesizing enecarbamates from the corresponding ketones have not been developed to the same extent as other types of enamines or imines.[6] Herein we report the first asymmetric nucleophilic addition reactions of a wide range of readily prepared enesulfonamides.[7] The enesulfonamides could be rapidly and efficiently synthesized from the corresponding ketones and underwent smooth reactions with a range of electrophiles such as ethyl glyoxylate, azodicarboxylate, and phenylglyoxal in stereoselective fashion. The product sulfonylimines could be readily reduced to the corresponding sulfonamides, which are important functional groups in medicinal chemistry.[8]

Enesulfonamides were synthesized from the corresponding ketones via the *N*-sulfonylimine intermediates (Scheme 1).[9] Separation of the geometric isomers was



Scheme 1. Synthesis of the enesulfonamides (see the Supporting Information for experimental procedure).

achieved by column chromatography on silica gel or recrystallization.[10] In contrast to the enecarbamates, which were synthesized from the corresponding nitriles or α,β-unsaturated carboxylic acids,[6] a wide range of enesulfonamides could be synthesized directly from the corresponding ketones and sulfonamides by modification of a previously reported method.[9]

The reaction of enesulfonamides with ethyl glyoxylate, which was freshly distilled from a commercially available solution of the polymer in toluene, was performed in the presence of the complex formed between Cu^{I} and diimine ligand **5**. Our investigation began with a survey of the electronic effect of the sulfonyl group of the enesulfonamide. The proposed reaction mechanism involves an aza-ene-type reaction, in which both the acidity of the sulfonamide hydrogen atom and the electron density of the double bond should affect the reaction rate. Accordingly, the reaction rates of (*Z*)-enesulfonamides **4** with different sulfonyl groups were measured and it was revealed that the enesulfonamide that contained a *p*-methoxybenzenesulfonyl group was the most reactive, while the reaction in the case of the enesulfonamide that contained a *p*-chlorobenzenesulfonyl group was the slowest. These results indicate that the reactivity of the system is more strongly influenced by the electron density of the double bond rather than by the acidity of the sulfonamide hydrogen. The synthesis of methyl sulfonyl protected enesulfonamides failed under the same reaction conditions as were used in the syntheses of the aryl sulfonyl protected enesulfonamides.

To determine the diastereo- and enantioselectivity of the reaction, **6a** was hydrolyzed to the corresponding ketone **7a**

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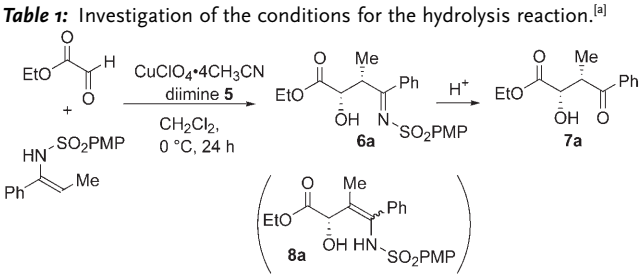
under the conditions reported in Table 1, entry 1.[5] However, the yield and diastereoselectivity were much lower than those expected from the kinetic study shown in Figure 1. We reasoned that isomerization of **6a** to **8a** might occur during hydrolysis, thus leading to lower yields and diastereoselectivity.[11] Further investigation revealed that more concentrated acidic conditions were necessary to accomplish hydrolysis of imines without erosion of yield or selectivity (Table 1, entry 2).

We next examined several enesulfonamides, and the results are summarized in Table 2. Although an enesulfonamide with the *p*-methoxybenzenesulfonyl group on the nitrogen atom was found to be more reactive (Figure 1), it was important to demonstrate the reactivity of enesulfonamides with other sulfonyl groups on the nitrogen atom because the products obtained after reduction (see below) retained the sulfonamide group that is often present in druglike molecules. It was found that enesulfonamides with sulfonyl groups other than *p*-methoxybenzenesulfonyl reacted with ethyl glyoxylate to afford the adducts in good

Table 1: Investigation of the conditions for the hydrolysis reaction.[a]



Entry	Solvent	Acid	*t* [min]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1	EtOH (3 mL)	conc. HBr (0.3 mL)	1.5	43	77:23	97
2	EtOH (0.5 mL)	conc. HBr (0.5 mL)	2.0	93	93:7	98
3	EtOH (0.5 mL)	conc. HBr (1 mL)	2.0	58	96:4	98

[a] Addition reactions were performed with ethyl glyoxylate (0.4 mmol) and enesulfonamide **4** (0.2 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C for 24 h in the presence of the catalyst (5 mol %). Hydrolysis was performed at RT. [b] Yield of isolated product **7a**. [c] Determined by ^{1}H NMR spectroscopy after hydrolysis of **6a** to **7a**. [d] *ee* value of the major diastereomer of **7a** determined by HPLC analysis.

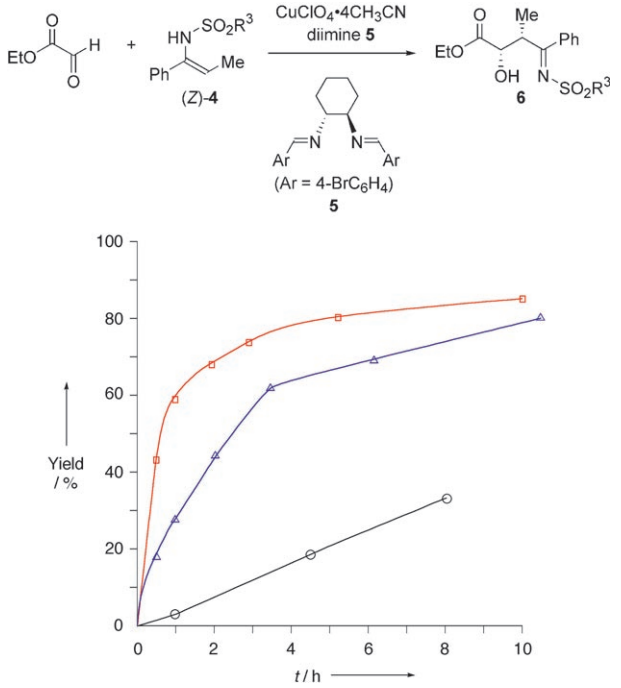
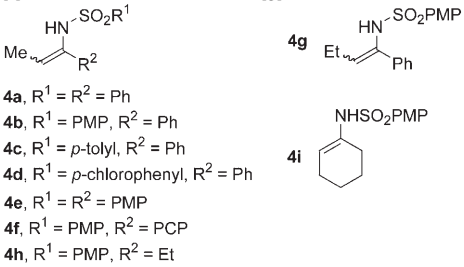


Figure 1. Kinetic study using enesulfonamides with different sulfonyl groups (red squares: R^3 = *p*-methoxyphenyl (PMP), blue triangles: R^3 = *p*-tolyl, black circles: R^3 = *p*-chlorophenyl). All reactions were performed in CH_2Cl_2 at 0 °C in the presence of $CuClO_4 \cdot CH_3CN$ (5 mol %) and **5** (5.5 mol %) and the yields were determined by ^{1}H NMR spectroscopy.

Table 2: Reactions of **4** with ethyl glyoxylate catalyzed by the complex Cu^I–**5**.[a]

Entry	**4**	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1	(*E*)-**4a**	49	6:64	97
2	(*Z*)-**4a**	50	93:7	93
3	(*E*)-**4b**	71	8:92	99
4	(*Z*)-**4b**	93	93:7	98
5	(*Z*)-**4c**	63	96:4	98
6	(*E*)-**4d**	65	26:74	87
7	(*Z*)-**4d**	68	79:21	90
8	(*E*)-**4e**	85	4:96	99
9	(*Z*)-**4e**	93	93:7	98
10[e]	(*Z*)-**4e**	89	98:2	97
11	(*E*)-**4f**	69	<1:>99[f]	98
12	(*Z*)-**4f**	70	87:13[f]	88
13	(*E*)-**4g**	50	6:94	75
14	(*Z*)-**4g**	95	86:14	92
15[g]	(*E*)-**4h**	95	8:92	98
16	(*Z*)-**4h**	96	94:6	71
17	**4i**	85	13:87	97

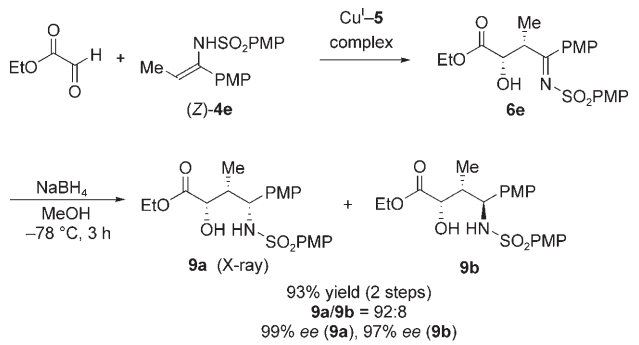
[a] All reactions were performed with ethyl glyoxylate (0.4 mmol) and enesulfonamide **4** (0.2 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C for 24 h in the presence of the catalyst (5 mol %) unless otherwise stated. In all the reactions, the pure geometric isomer of **4** was used. [b] Yield of isolated ketone product **7**. [c] Determined by ^{1}H NMR spectroscopy after hydrolysis of **6** to **7**. [d] *ee* value of the major diastereomer of **7** determined by HPLC analysis. [e] Catalyst (0.2 mol %), CH_2Cl_2 (1.0 mL). [f] Diastereomeric ratio of **6**. [g] Reaction carried out at −20 °C.



4a, $R^1 = R^2$ = Ph
4b, R^1 = PMP, R^2 = Ph
4c, R^1 = *p*-tolyl, R^2 = Ph
4d, R^1 = *p*-chlorophenyl, R^2 = Ph
4e, $R^1 = R^2$ = PMP
4f, R^1 = PMP, R^2 = PCP
4h, R^1 = PMP, R^2 = Et

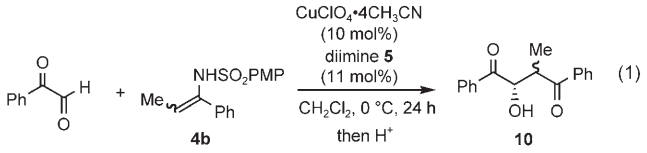
yields with high selectivities (Table 2, entries 1–7). The reactions proceeded stereoselectively: *E* enesulfonamides gave *anti* adducts, whereas *Z* enesulfonamides gave *syn* adducts with high diastereo- and enantioselectivities in most cases.[12] The reaction was not limited only to aromatic ketone-derived enesulfonamides (Table 2, entries 1–14) but also could be effected with enesulfonamides derived from aliphatic and cyclic ketones (Table 2, entries 15–17). Moreover, the catalyst loading could be reduced to as little as 0.2 mol% without loss of activity (Table 2, entry 11). It is noteworthy that aliphatic ketone-derived enesulfonamides could be directly synthesized from the corresponding ketones in two steps, whereas the synthesis of aliphatic ketone-derived enecarbamates needed several steps.[6]

The reactions of enesulfonamides are more atom economical than those of metal enolates as the initial imine-type products **6** contain all the atoms that make up both the substrates (ethyl glyoxylate and enesulfonamide).[13] The sulfonylimine initially formed could be converted into the corresponding sulfonamide by reduction. Accordingly, treatment of **6e** (synthesized from (*Z*)-**4e**) with $NaBH_4$ afforded the sulfonamide **9** stereoselectively (Scheme 2).



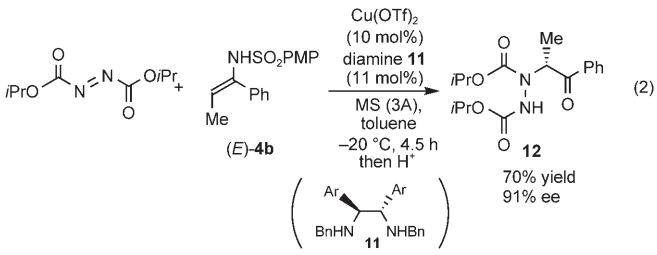
Scheme 2. Diastereoselective reduction of the sulfonylimine **6e**. $NaBH_4$ (0.4 mmol) was added to a solution of **6e** (0.2 mmol, the crude product from the Cu-catalyzed addition) in MeOH (2.5 mL) at −78 °C.

The enesulfonamides also reacted with electrophiles other than ethyl glyoxylate. Using the previously described procedure, phenylglyoxal reacted with enesulfonamide **4b** in the presence of the Cu^I–diimine complex, to afford the 2-hydroxy-1,4-diketone **10** in good yield with good selectivities [Eq. (1)]. The amination of enesulfonamide (*E*)-**4b** using



(1)

azodicarboxylate was catalyzed by a Cu^{II}–diamine complex[14] and provided the desired compound **12** in good yield with high enantioselectivity [Eq. (2); Ar = 3,5-xylyl, Bn = benzyl, MS = molecular sieves, Tf = trifluoromethanesulfonyl].



(2)

In summary, novel highly diastereo- and enantioselective Cu-catalyzed addition reactions of enesulfonamides have been developed. It has been shown that in the addition reactions to ethyl glyoxylate we obtained high yields as well as excellent diastereo- and enantioselectivities, even using only 0.2 mol% of the catalyst. In addition, the sulfonylimine thus obtained could be reduced to the corresponding sulfonamide diastereoselectively, thus providing access to chiral sulfonamides which are biologically important compounds. Phenylglyoxal and azodicarboxylate were also found to be good electrophiles in the nucleophilic addition of enesulfonamides. Further investigations on the precise mechanism of this reaction as well as the application of this methodology to the synthesis of biologically active compounds are in progress.

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[10] In most cases, geometric isomers are separated by preparative HPLC. Recrystallization is also effective when one isomer is much more crystalline than the other. See the Supporting Information for details.

[11] Enesulfonamide **8a** is partially hydrolyzed under the acidic conditions, which caused both the yield and selectivity to decrease once **8a** is formed.

[12] Diastereoselectivity observed in this reaction can be explained by the same transition-state model as in the reaction with enecarbamates. See the Supporting Information.

[13] In a strict sense, a stoichiometric amount of titanium chloride and potassium *tert*-butoxide were necessary to prepare the enesulfonamides. An investigation of the synthesis of enesulfonamides using no or a catalytic amount of a metal reagent is underway.

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