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Asymmetric conjugate addition of aldehydes to vinyl sulfone using a diaminomethylenemalononitrile organocatalyst

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ABSTRACT

Diaminomethylenemalononitrile organocatalyst **5** promotes the asymmetric conjugate addition of branched aldehydes to vinyl sulfone to afford the corresponding adducts with all-carbon quaternary stereocenters in excellent yields with up to 91% ee.

Chiral thiourea derivatives as hydrogen-bond donors play important roles in the field of asymmetric organocatalysis. In particular, Takemoto catalyst **1** and its derivatives are versatile organocatalysts and promote various important asymmetric reactions (Fig. 1).[1] Two sets of weakly acidic hydrogens in the thiourea group promote molecular recognition by forming hydrogen bonds with substrates. Recently, organocatalysts with the squaramide skeleton, such as **2**, have attracted a great deal of attention because it can be utilized as an alternative to the thiourea group to afford excellent catalytic activities in various asymmetric reactions.[2,3] Therefore, the development of novel catalysts with a skeleton, not previously utilized in organocatalysis, is one of the most challenging research themes in organic chemistry.

All-carbon quaternary stereocenters are ubiquitous and important motifs in many natural products and bioactive compounds; however, relatively harsh conditions are needed for their construction. Furthermore, possible electrophile–nucleophile combinations are limited due to their steric hindrance.[4] Therefore, stereoselective formation of carbon–carbon bonds for the construction of all-carbon quaternary stereocenters is not generally straightforward, and the development of efficient synthetic methods for their construction using environmentally benign oraganocatalysts is highly desirable.[5] The conjugate addition of branched aldehydes to 1,1-bis(benzenesulfonyl)ethylene (**6**) is one of the most efficient approaches for stereoselective construction of all-carbon quaternary centers; however, the successful conjugate addition of branched aldehydes to vinyl sulfone **6** for the construction of such quaternary stereocenters has been rarely reported.[6,7] In addition, high enantioselectivities are obtained only when using organocatalysts with the β-aminosulfonamide skeleton.[7]

We developed an efficient and novel organocatalyst for the conjugate addition of branched aldehydes to vinyl sulfone. Herein, we reported the efficient conjugate addition of branched aldehydes **7** to **6** using a novel organocatalyst **5** having a diaminomethylenemalononitrile skeleton.

We examined novel diaminomethylenemalononitrile organocatalysts **3**–**5**, as shown in Table 1. Among them, **5** was the most suitable for the conjugate addition to **6**. Organocatalyst **5** was prepared as shown in Scheme 1. The treatment of **9**, which is prepared by a reported method,[8] with 3,5-bis(trifluoromethyl)benzylamine (**10**) and cyclohexane diamine (**11**) in one pot afforded **5** with 69% yield.[9]

A study of the optimal solvent conditions for the enantioselective conjugate addition using **5** is shown in Table 2. The conjugate addition reactions were conducted with **6** and 2-phenylpropanal (**7a**) as test reactants in the presence of a catalytic amount of **5** and trifluoroacetic acid (TFA) at room temperature. Among the reaction solvents examined, CH_2Cl_2 was the most suitable (entries 2–12). Notably, when no TFA was added, a significant reduction in the yield was observed (entry 1). Furthermore, we examined the effects associated with the presence of other protic acids; however,

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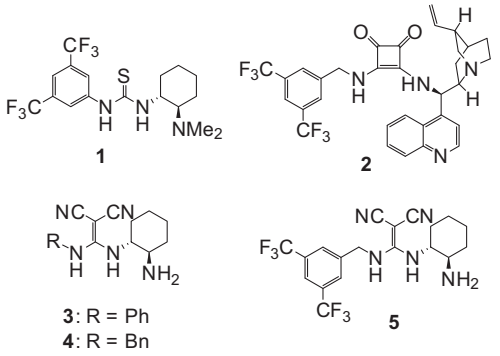
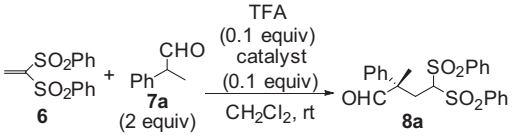


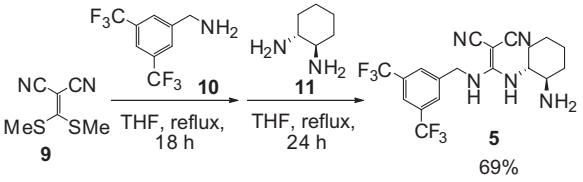
Figure 1. Structure of organocatalysts.

Table 1
Selection of organocatalysts



Entry	Catalyst	Time (h)	Yield[a] (%)	% ee[b]
1	**3**	21	93	64
2	**4**	48	88	78
3	**5**	24	88	89

[a] Isolated yield.
[b] Determined by HPLC analysis.

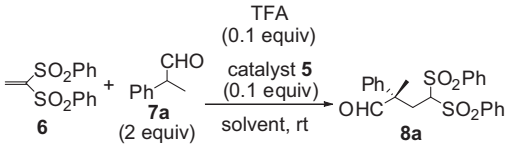


Scheme 1. Preparation of organocatalyst **5**.

TFA was found to be the most suitable additive (Table 3). The addition of 0.2 or 0.05 equiv of TFA resulted in a slight reduction in the enantioselectivity (entries 6 and 7). When the reaction was conducted at 0 °C, a reduction in both yield and stereoselectivity was observed (entry 8). Therefore, the optimal conditions were determined to be 0.1 equiv of **5** and 0.1 equiv of TFA in CH_2Cl_2 at room temperature (entry 1).

With these optimal conditions, the scope and limitations of the conjugate addition of branched aldehydes **7** to **6** were examined (Table 4).[10] We selected methyl and methoxy substituents as representative electron-donating group and halogen substituents as electron-withdrawing groups on the benzene ring. The reactions of branched aldehydes **7b**–**g** with **6** smoothly proceeded and resulted in the corresponding adducts in excellent yields (84–99%) with 82–91% ee (entries 2–7). Moreover, we examined the reactions between **6** and branched aldehydes **7h** and **7i** possessing a naphthalene skeleton. Although **6** smoothly reacted with **7h** to afford the corresponding adduct **8h** in excellent yield (95%) with 87% ee, the reaction with **7i** afforded the adduct **8i** only in low yield (37%) (entries 8 and 9). The conjugate addition of *N*-Boc α-aminophenylacetaldehyde (**7j**) to **6** gave the corresponding adduct **8j** in excellent yield (97%) but with low enantioselectivity (26% ee)

Table 2
Study of solvents



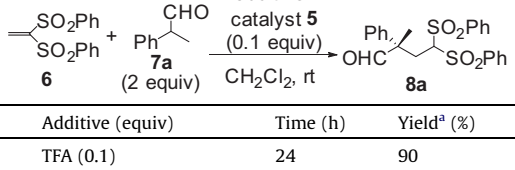
Entry	Solvent	Time (h)	Yield[a] (%)	% ee[b]
1[c]	CH_2Cl_2	24	19	—
2	CH_2Cl_2	24	90	89
3	$ClCH_2CH_2Cl$	24	97	79
4	$CHCl_3$	24	94	82
5	Toluene	21	83	64
6	Et_2O	48	95	66
7	EtOAc	24	90	−8[d]
8	THF	24	2	20
9	MeCN	26	89	−30[d]
10	EtOH	48	61	−37[d]
11	H_2O	24	78	2
12	Neat	24	91	17

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] Without TFA.
[d] Product with the opposite absolute configuration (R-isomer) was predominantly obtained.

(entry 10), whereas **5** promoted the reaction of 2-methoxy-2-phenylacetaldehyde (**7k**) with **6** to yield the corresponding adduct **8k** with high enantioselectivity (80% ee) (entry 11). The stereochemistry of the addition products **8a**–**k** obtained using **5** was determined by comparison with reported chiral-phase HPLC retention times and optical rotation data.[7]

We propose that the conjugate addition of aldehydes with **6** using **5** proceeds via a plausible transition state, as shown in Figure 2, on the basis of the stereochemistry of addition products **8a**–**i**. In this mechanism, the primary amino group of **5** condenses with **7a** to generate the *E*-enamine intermediates. Then, the two acidic protons of the diaminomethylenemalononitrile group successfully interact with the oxygen of vinyl sulfone to direct the approach of vinyl sulfone to the *Si* face of the enamine intermediates. This ultimately affords the corresponding addition products with high stereoselectivity. We speculate that the acidity of the two N–H groups is enhanced by the electron-withdrawing effect of the two cyano groups enabling them to strongly coordinate to vinyl sulfone and stabilize the rigid transition states during the

Table 3
Optimization of reaction conditions



Entry	Additive (equiv)	Time (h)	Yield[a] (%)	% ee[b]
1	TFA (0.1)	24	90	89
2	$PhCO_2H$ (0.1)	48	91	52
3	4-$NO_2C_6H_4CO_2H$ (0.1)	48	90	61
4	AcOH (0.1)	48	47	50
5	4-$MeOC_6H_4CO_2H$ (0.1)	48	48	45
6	TFA (0.2)	24	98	83
7	TFA (0.05)	48	88	83
8[c]	TFA (0.1)	46	57	67

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] The reaction was carried out at 0 °C.