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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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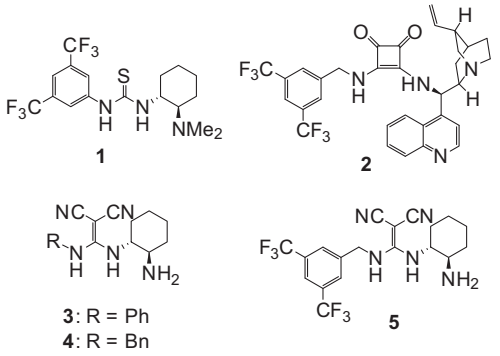
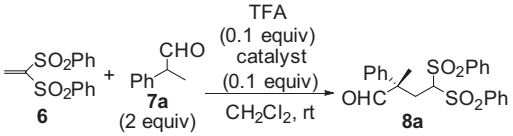


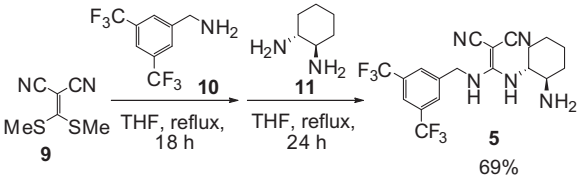
Figure 1. Structure of organocatalysts.

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.

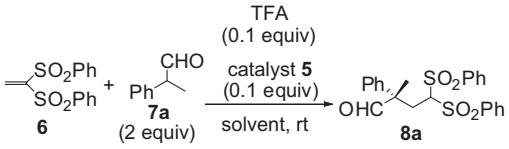


Scheme 1. Preparation of organocatalyst **5**.

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



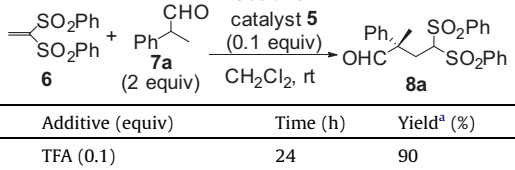
Entry	Solvent	Time (h)	Yield[a] (%)	% ee[b]
1[c]	CH_2Cl_2	24	19	—
2	CH_2Cl_2	24	90	89
3	$ClCH_2CH_2Cl$	24	97	79
4	$CHCl_3$	24	94	82
5	Toluene	21	83	64
6	Et_2O	48	95	66
7	EtOAc	24	90	−8[d]
8	THF	24	2	20
9	MeCN	26	89	−30[d]
10	EtOH	48	61	−37[d]
11	H_2O	24	78	2
12	Neat	24	91	17

[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

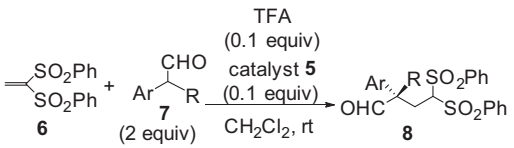
Table 3
Optimization of reaction conditions

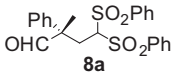
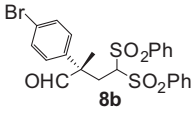
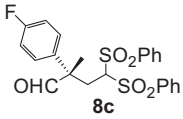
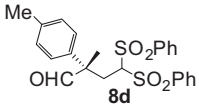
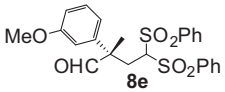
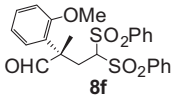
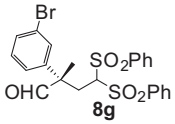
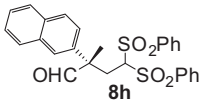
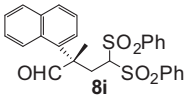
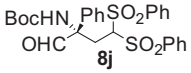
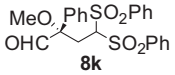


Entry	Additive (equiv)	Time (h)	Yield[a] (%)	% ee[b]
1	TFA (0.1)	24	90	89
2	$PhCO_2H$ (0.1)	48	91	52
3	4-$NO_2C_6H_4CO_2H$ (0.1)	48	90	61
4	AcOH (0.1)	48	47	50
5	4-$MeOC_6H_4CO_2H$ (0.1)	48	48	45
6	TFA (0.2)	24	98	83
7	TFA (0.05)	48	88	83
8[c]	TFA (0.1)	46	57	67

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

Table 4
Conjugate additions using organocatalyst **5**



Entry	Product	Time (h)	Yield[a] (%)	% ee[b]
1	 **8a**	24	90	89
2	 **8b**	24	99	89
3	 **8c**	48	97	83
4	 **8d**	48	96	82
5	 **8e**	24	84	91
6	 **8f**	48	97	89
7	 **8g**	24	88	85
8	 **8h**	48	95	87
9	 **8i**	48	37	82
10	 **8j**	48	97	26
11	 **8k**	48	69	80

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

conjugate addition. However, the stereochemistry of **8j** and **8k** obtained had the opposite absolute configuration to those of **8a–i**, and the reason is not clear.

In conclusion, the novel organocatalyst **5**, which is based on the diaminomethylenemalononitrile skeleton, can be easily prepared from 2-[bis(methylthio)methylene]malononitrile (**9**) in one pot. Organocatalyst **5**, which is a relatively simple structure, efficiently catalyzes the conjugate addition of various branched aldehydes to **6** at room temperature to afford the corresponding addition products featuring all-carbon quaternary stereocenters in excellent yields with high enantioselectivities. The superior performance is probably due to the diaminomethylenemalononitrile skeleton of **5**. This report is the first example applying this unit as a framework for organocatalysts. Further application of this catalyst in the synthesis of bioactive compounds is currently being investigated in our laboratory.

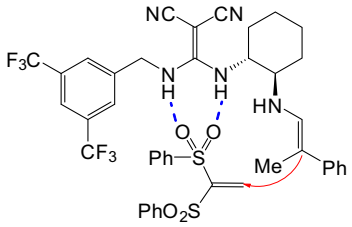


Figure 2. Plausuble transition state model for conjugate additions.

Acknowledgments

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9. Organocatalyst **5**: colorless powder; mp = 128 °C; $[\alpha]_D^{24}$ + 16.6 (c 0.99, MeOH); ^{1}H NMR (500 MHz, CD_3OD): δ = 1.15–1.36 (m, 4H), 1.73 (m, 2H), 1.87 (m, 1H), 1.93–1.95 (m, 1H), 2.53–2.58 (m, 1H), 3.28 (m, 1H), 4.75 (s, 2H), 7.93 (s, 1H), 7.96 (s, 2H); ^{13}C NMR (500 MHz, CD_3OD): δ = 25.8, 26.0, 33.4, 33.7, 35.3, 47.5, 55.6, 62.3, 120.1, 122.5, 124.8 (q, $^1J_{C-F}$ = 272 Hz), 129.0, 133.0 (q, $^2J_{C-F}$ = 33.6 Hz), 142.5; Anal. Calcd for $C_{19}H_{19}F_6N_5$: C, 52.90; H, 4.44; N, 16.23. Found: C, 52.83; H, 4.26; N, 16.13.
10. A typical procedure of the conjugate additions using **5** is as follows: To a solution of **6** (35.8 mg, 0.116 mmol) and organocatalyst **5** (5.0 mg, 0.0116 mmol) in 1.0 mL of CH_2Cl_2 was added 2-phenylpropanal (**7a**, 31.1 μL, 0.232 mmol) and trifluoroacetic acid (0.9 μL, 0.0116 mmol) at room temperature. After stirring at room temperature for 24 h, the reaction mixture was directly purified by flash column chromatography on silica gel with a 3:1 mixture of hexane and AcOEt to afford the pure **8a**[7] (46.2 mg, 90%) as a colorless powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 3H), 2.82 (dd, *J* = 5.8, 16.4 Hz, 1H), 2.95 (dd, *J* = 3.4, 16.4 Hz, 1H), 4.42 (dd, *J* = 3.4, 5.8 Hz, 1H), 7.26–7.29 (m, 2H), 7.36–7.73 (m, 11H), 7.87 (d, *J* = 8.2 Hz, 2H), 9.60 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.6, 30.9, 53.1, 80.2, 127.6, 128.1, 129.1, 129.3, 129.7, 129.8, 134.6, 137.3, 137.8, 138.3, 201.4.