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Asymmetric Conjugate Addition of Malonates to Enones Using Perfluorobutanesulfonamide Organocatalyst

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Perfluorobutanesulfonamide organocatalyst **4** efficiently promotes asymmetric conjugate additions of malonates to α,β-unsaturated ketones to afford the corresponding adducts with excellent enantioselectivities (up to 99% ee).

The catalytic enantioselective Michael addition of carbon nucleophiles to α,β-unsaturated carbonyl compounds is one of the most fundamental and important carbon–carbon bond-forming methods to synthesize useful chiral building blocks.[1,2] In particular, metal-free asymmetric Michael additions using organocatalysts have been intensively investigated over the past decade from the perspective of green chemistry.[2] Malonates are good Michael donors in organocatalysis because they can be easily converted to enolates under mild conditions by the two electron-withdrawing esters. Moreover, versatile products obtained by the reactions of malonates with α,β-unsaturated ketones can be readily converted to the corresponding δ-ketoesters as useful synthetic building blocks after decarboxylation.[3,4] Successful conjugate additions of malonates to α,β-unsaturated ketones using organocatalysts have been reported;[4,5] however, the development of organocatalysts that can catalyze the Michael addition of malonates to α,β-unsaturated enones more effectively is desirable. Recently, Du and co-workers reported the Michael addition of malonates to α,β-unsaturated enones using *p*-toluenesulfonamide organocatalyst;[6] however, their method requires 0.2 equiv of catalyst loading and long reaction times (72 h) to obtain adduct **7aa** from dibenzyl malonate (**6a**) and (*E*)-4-phenylbut-3-en-2-one (**5a**).

On the other hand, we have reported that perfluoroalkanesulfonamide organocatalysts such as **1** and **2** (Figure 1), which are easily prepared from L-phenylalanine, are excellent organocatalysts for a direct asymmetric aldol reaction.[7] In addition, we have recently reported the stereoselective construction of all-carbon quaternary centers by asymmetric conjugate additions of branched aldehydes to vinyl sulfone using organocatalysts **3** and **4** derived from L-valine.[8] To further demonstrate the effectiveness of perfluoroalkanesulfonamide organocatalysts derived from L-phenylalanine or L-valine, we attempted additional applications for other types of asymmetric conjugate additions using organocatalysts **1**–**4**. Herein, we would like to report the efficient conjugate additions of malonates to α,β-unsaturated ketones using a perfluorobutanesulfonamide organocatalyst **4**.

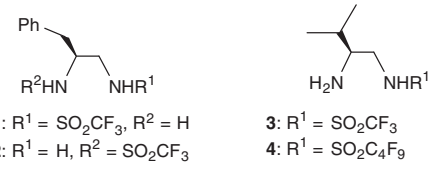
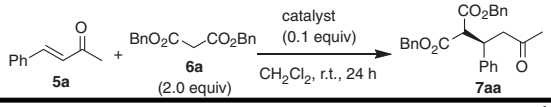


Figure 1. Structure of organocatalysts.

We examined β-aminosulfonamide organocatalysts **1**–**4**, which we previously reported for direct aldol reactions[7] and conjugate additions to vinyl sulfone,[8] as shown in Table 1. With the exception of **1** among these, excellent enantioselectivities were obtained (Entries 1–4). When using perfluorobutanesulfonamide **4**, the highest enantioselectivity was obtained. Therefore, we considered that **4** is the most suitable catalyst for the conjugate addition of **6a** to **5a**.

A study of the optimal solvent conditions for the asymmetric conjugate addition using **4** is shown in Table 2. The conjugate addition reactions were conducted with **6a** and **5a** as test reactants in the presence of a catalytic amount of **4** at room temperature. Among the reaction solvents examined, cyclohexane was the most suitable (Entries 1–7). Furthermore, we examined the amount of catalyst loading necessary for optimal

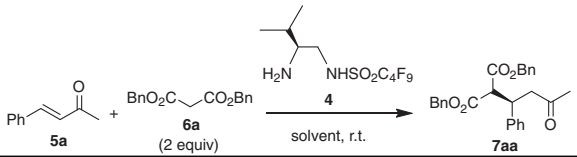
Table 1. Selection of organocatalysts



Entry	Catalyst	Yield[a]/%	%ee[b]
1	**1**	8	49
2	**2**	43	96
3	**3**	53	97
4	**4**	38	98

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

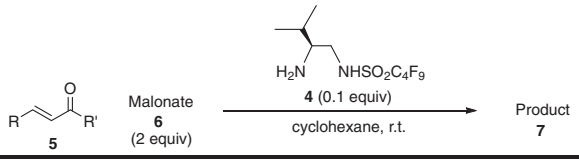
Table 2. Optimization of reaction conditions

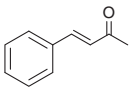
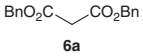
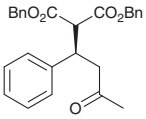
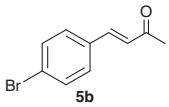
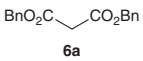
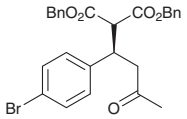
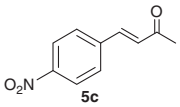
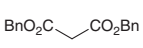
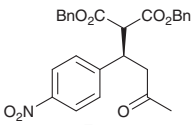
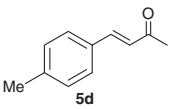
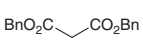
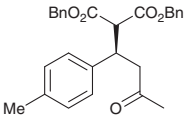
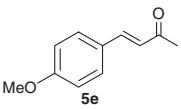
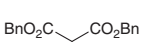
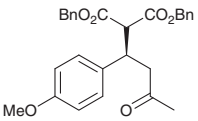
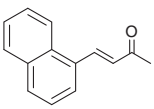
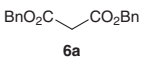
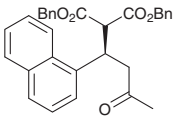
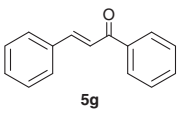
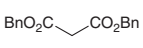
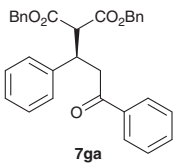
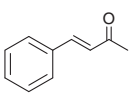
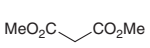
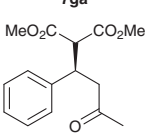
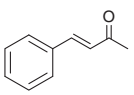
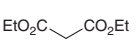
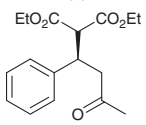
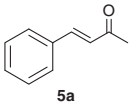
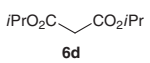
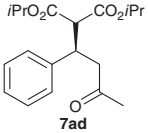


Entry	Solvent	**4**/equiv	Time/h	Yield[a]/%	%ee[b]
1	MeOH	0.1	24	64	76
2	MeCN	0.1	24	43	91
3	EtOAc	0.1	24	34	88
4	Et_2O	0.1	24	74	98
5	CH_2Cl_2	0.1	24	38	98
6	hexane	0.1	24	89	97
7	cyclohexane	0.1	24	96	98
8	cyclohexane	0.05	72	88	97
9	cyclohexane	0.01	136	35	98

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

Table 3. Conjugate additions using organocatalyst **4**



Entry	Enone	Malonate	Time/h	Product	Yield[a]/%	%ee[b]
1	 **5a**	 **6a**	24	 **7aa**	96	98
2	 **5b**	 **6a**	48	 **7ba**	85	98
3	 **5c**	 **6a**	96	 **7ca**	88	94
4	 **5d**	 **6a**	48	 **7da**	91	97
5	 **5e**	 **6a**	120	 **7ea**	94	99
6	 **5f**	 **6a**	88	 **7fa**	77	94
7	 **5g**	 **6a**	144	 **7ga**	14	99
8	 **5a**	 **6b**	72	 **7ab**	55	90
9	 **5a**	 **6c**	94	 **7ac**	60	96
10	 **5a**	 **6d**	144	 **7ad**	34	99

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

conditions. High enantioselectivities were retained, although a prolonged reaction time and lower yield were observed when the catalyst loading was lowered to 0.05 and 0.01 equiv (Entries 8 and 9). Therefore, the optimal conditions were determined to be 0.1 equiv of **4** in cyclohexane at room temperature (Entry 7).

With these optimal conditions in hand, the scope and limitations of the conjugate addition of malonate **6** to α,β-unsaturated ketones **5** were examined (Table 3).[9] We selected bromo and nitro substituents as representative electron-withdrawing groups on the benzene ring and methyl and methoxy substituents as the electron-donating groups. The reactions of substituted enones **5b**–**5e** with **6a** smoothly proceeded to give the corresponding adducts in high yields with excellent enantioselectivities (Entries 2–5). Moreover, we examined the reaction of **6a** with enone **5f** possessing a naphthalene skeleton; the corresponding adduct **7fa** was obtained with 94% ee (Entry 6). The reaction of chalcone **5g** as an inactive substrate[6] provided the addition product **7ga** in only 14% yield, although excellent stereoselectivity was obtained (Entry 7). Other malonates such as dimethyl malonate **6b**, diethyl malonate **6c**, and diisopropyl malonate **6d** also reacted with **5a** to afford the corresponding adducts (**7ab**, **7ac**, and **7ad**, respectively) with high enantioselectivities (90–99% ee), although the yields were only low to good (Entries 8–10). The stereochemistry of the addition products **7** obtained using **4** was determined by comparing them with the reported chiral-phase HPLC retention times and optical rotation data.[6]

We propose that the conjugate addition of malonates to enones using **4** proceeds via the following mechanism. The primary amino group of **4** condenses with **5** to generate iminium intermediates. Then, the acidic protons of the sulfonamide group successfully interact with the oxygen of **6** to direct the approach of malonates to the iminium intermediates. This ultimately affords the corresponding addition products with high stereoselectivity. We speculate that the acidity of the N–H groups is enhanced by the strong electron-withdrawing effect of the perfluorobutyl group, enabling them to strongly coordinate to the malonates and stabilize the rigid transition states during the conjugate addition.

In conclusion, sulfonamide organocatalyst **4**, which is a simple structure, efficiently catalyzes the conjugate addition of dibenzyl malonate (**6a**) to α,β-unsaturated ketones **5** at room temperature to afford the corresponding addition products **7** in high yields with excellent enantioselectivities. Furthermore, application of this catalyst in the synthesis of bioactive compounds is currently being investigated in our laboratory.

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9 A typical procedure for the conjugate additions using **4** is as follows: Dibenzyl malonate (**6a**, 102 µL, 0.410 mmol) was added to a solution of **5a** (30.0 mg, 0.205 mmol) and organocatalyst **4** (8.1 mg, 0.021 mmol) in 1.0 mL of cyclohexane 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 4:1 mixture of hexane and AcOEt to afford the pure **7aa** (86.7 mg, 96%) as a colorless powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95 (s, 3H), 2.88 (d, $J = 6.9$ Hz, 2H), 3.82 (d, $J = 9.7$ Hz, 1H), 4.00 (dt, $J = 9.7$, 6.9 Hz, 1H), 4.89 (s, 2H), 5.11 (d, $J = 12.3$ Hz, 1H), 5.15 (d, $J = 12.3$ Hz, 1H), 7.04–7.07 (m, 2H), 7.16–7.33 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.15, 40.44, 47.05, 57.30, 67.06, 67.24, 127.21, 128.05, 128.11, 128.18, 128.22, 128.36, 128.39, 128.52, 135.01, 135.13, 140.24, 167.33, 167.81, 205.79.

