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Asymmetric Conjugate Addition of Nitroalkanes to Enones Using a Sulfonamide−Thiourea Organocatalyst

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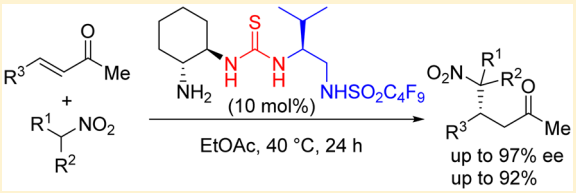
Supporting Information

ABSTRACT: The asymmetric conjugate addition of nitroalkanes to α,β-unsaturated ketones in the presence of a catalytic amount of a novel sulfonamide−thiourea organocatalyst resulted in the corresponding γ-nitro carbonyl products in high yields with excellent enantioselectivities (up to 97% ee).



Chiral γ-nitro carbonyl compounds are valuable synthetic intermediates in the fields of medicinal and organic chemistry because they can provide access to biologically active molecules.[1] To obtain chiral γ-nitro carbonyl compounds in an efficient and eco-friendly manner, asymmetric conjugate additions of nitroalkanes to enones using organocatalysts are among the most convenient methodologies.[2] Although several organocatalytic conjugate additions of nitroalkanes to α,β-unsaturated ketones have been reported, reports on the intermolecular conjugate addition of nitroalkanes to benzylideneacetones using organocatalysts are relatively rare.[3] In addition, most of these methods require long reaction times (>48 h) and high catalyst loadings (20 mol %), and do not provide both satisfactory yields and excellent enantioselectivities. To the best of our knowledge, there is no report that could meet all of these requirements, i.e., short reaction time (within 24 h), low catalyst loading (10 mol % or less), satisfactory yield (>80%), and excellent stereoselectivity (>95% *ee*), in the synthesis of γ-nitro ketones from benzylideneacetones. Therefore, the development of a novel organocatalyst that can efficiently promote the asymmetric conjugate addition of nitroalkanes to benzylideneacetone derivatives is highly desirable.

Organocatalysts with motifs involving multiple hydrogen-bond donors have attracted considerable interest since Wang et al. reported the asymmetric conjugate addition of 1,3-diketones to nitroalkenes using a sulfonamide−thiourea organocatalyst (Wang's catalyst).[4] Sulfonamide−thiourea organocatalysts can effectively catalyze several significant asymmetric reactions.[5]

Recently, we have reported that *N*-(β-aminoalkyl)-sulfonamides, which were derived from L-phenylalanine or L-valine, are good organocatalysts for several asymmetric reactions.[6] Among the tested *N*-(β-aminoalkyl)sulfonamides, organocatalysts **1** and **2** bearing the perfluorobutanesulfonamide group exhibited more preferable catalytic activity.[6] In addition, we demonstrated that an organocatalyst bearing the perfluorobutanesulfonamide and squaramide motif effectively promoted the asymmetric direct vinylogous aldol reaction of furan-2(5*H*)-one with aldehydes.[7] In our efforts to develop more effective organocatalysts by the modification of *N*-(β-aminoalkyl)sulfonamides **1** and **2**, we envisaged developing an organocatalyst bearing both the perfluorobutanesulfonamide and thiourea motif. Herein, we describe the highly efficient synthesis of chiral γ-nitro carbonyl compounds from benzylideneacetones using perfluorobutanesulfonamide−thiourea organocatalysts.

We examined organocatalysts **2**−**8** (Figure 1) for the enantioselective conjugate addition of nitromethane to (*E*)-4-phenylbut-3-en-2-one (**9a**) as shown in Table 1. *N*-(β-Aminoalkyl)sulfonamide **2** was a poor catalyst, affording a low yield and moderate stereoselectivity (entry 1). All examined sulfonamide−thiourea organocatalysts **3**−**8** con-

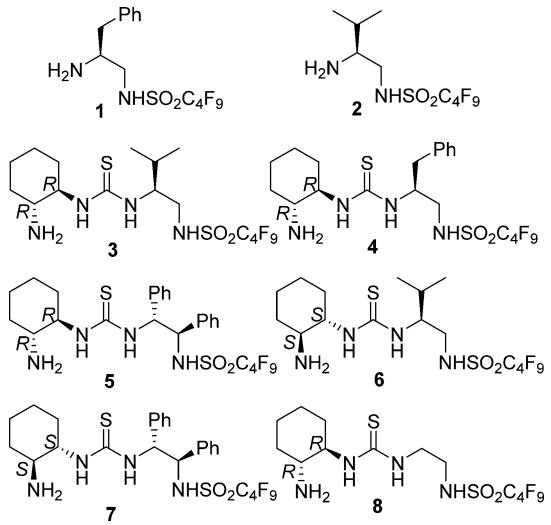


Figure 1. Structure of organocatalysts.

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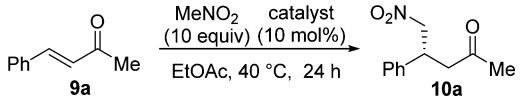
Table 1. Catalyst Screening



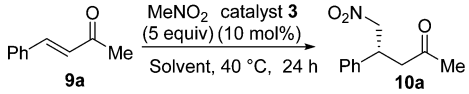
entry	catalyst	yield (%)[a]	% ee[b]
1	**2**	22	−76
2	**3**	88	97
3	**4**	85	95
4	**5**	3	95
5	**6**	57	−94
6	7	8	−97
7	**8**	60	95

[a]Isolated yield. [b]Enantiomeric excess was determined by chiral HPLC analysis.

trolled high enantiofacial selection in 94%−97% *ee* (entries 2−7). In particular, catalyst **3** derived from L-valine was the most suitable catalyst. Notably, excellent enantioselectivity was obtained when organocatalyst **8** was used; however, the yield was moderate (entry 7). This fact indicated that enantioselectivity was controlled by the chirality of the cyclohexanediamine, and the yield was increased by the L-valine unit.

The optimum reaction conditions for the conjugate addition of nitromethane to benzylideneacetones using catalyst **3** were investigated (Table 2). The reaction between (*E*)-4-phenylbut-3-en-2-one (**9a**) and nitromethane as test reactants was performed in the presence of a catalytic amount of **3** in various solvents at 40 °C. Among the examined representative reaction solvents, we found that ethyl acetate was the most suitable solvent in terms of both yield and enantioselectivity.

Table 2. Study of Solvents

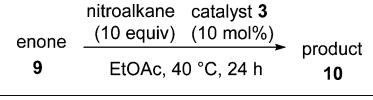


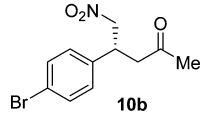
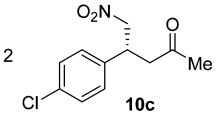
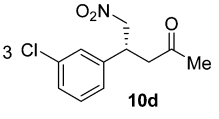
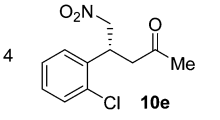
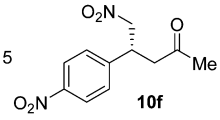
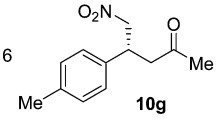
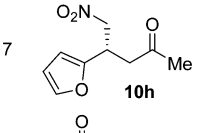
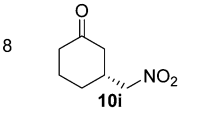
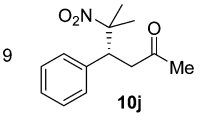
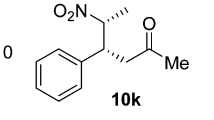
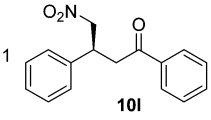
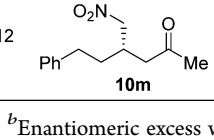
entry	solvent	yield (%)[a]	% ee[b]
1	MeOH	13	79
2	DMF	56	95
3	MeCN	60	97
4	*t*-BuOMe	80	97
5	$CHCl_3$	71	98
6	CH_2Cl_2	73	97
7	toluene	81	94
8	hexane	67	96
9	neat	81	94
10	EtOAc	85	97

[a]Isolated yield. [b]Enantiomeric excess was determined by chiral HPLC analysis.

With these optimal conditions in hand, the scope and limitations of the conjugate addition of nitroalkanes to *α,β*-unsaturated ketones **9** were examined (Table 3). Substrates **9b−f** bearing bromo, chloro, and nitro substituents as representative electron-withdrawing groups on the aromatic entity smoothly reacted with nitromethane in the presence of catalyst **3** to afford the corresponding adducts **10b−f** in high yields with excellent enantioselectivities (entries 1−5). The reaction of enone **9g** bearing a methyl substituent as electron-donating groups with nitromethane also proceeded well, affording the corresponding addition product **10g** with excellent enantioselectivity (entry 6). The conjugate additions to **9h** bearing a furan ring as a heterocycle provided the adduct

Table 3. Study of Substrate Scope



entry	product **10**	yield (%)[a]	% ee[b]
1	 **10b**	86	96
2	 **10c**	84	96
3	 **10d**	84	96
4	 **10e**	90	95
5	 **10f**	86	95
6	 **10g**	84	96
7	 **10h**	49	97
8	 **10i**	40	96
9	 **10j**	92	96
10	 **10k**	81[c]	95 (95)[d]
11	 **10l**	8	52
12	 **10m**	27	95

[a]Isolated yield. [b]Enantiomeric excess was determined by chiral HPLC analysis. [c]The ratio of *syn* and *anti* isomer was 53:47. [d]Enantiomeric excess of major isomer. Enantiomeric excess of minor isomer in parentheses.

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10h in moderate yield; however, excellent enantioselectivity was observed (entry 7). Cyclohex-2-en-1-one (**9i**) as a cyclic (*Z*)-enone reacted with nitromethane to give the corresponding γ-nitroketone **10i** with excellent stereoselectivity, albeit in moderate yield (entry 8). Furthermore, the reaction of enone **9a** with other types of nitroalkanes such as 2-nitropropane also resulted in the corresponding product **10j** in high yield with excellent enantioselectivity (entry 9). Although low diastereoselectivity was observed when nitroethane was used as the nucleophile, the enantioselectivities of the stereoisomers were excellent (entry 10). Chalcone (**9l**) was poor substrate to provide a low yield (entry 11). The reaction of **9m** as an aliphatic aldehyde resulted in a low yield; however, excellent enantioselectivity was obtained (entry 12). The stereochemistry of all products was determined by comparison with reported optical rotation and chiral-phase HPLC retention times.

Based on the stereochemistry of the obtained γ-nitro ketones, we propose that the conjugate addition of nitromethane to the enone using organocatalyst **3** proceeds via the transition state as shown in Figure 2. The primary amine group in **3** condenses

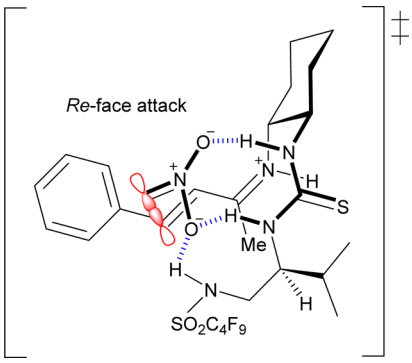

Figure 2. Plausible transition state.

with enone **9** to form the stable (*Z*)-eniminium intermediate. The three acidic protons of **3** can function as hydrogen-bond donors, providing a rigid interaction with the two oxygen atoms of nitromethane. These successful interactions can control the direction (*Re*-face attack) from which the nitromethide anion approaches the (*Z*)-eniminium intermediate. Finally, the transition state subsequently results in the addition product with excellent enantioselectivity.

In summary, the novel sulfonamide−thiourea organocatalyst **3** efficiently promoted the conjugate addition of nitroalkanes to α,β-unsaturated ketones to afford the corresponding chiral addition products in high yields with excellent enantioselectivities. Organocatalyst **3** provided a shorter reaction time, low catalyst loading, satisfactory yield, and excellent stereoselectivity for the synthesis of γ-nitro ketones from benzylideneacetones.

EXPERIMENTAL SECTION

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III Nanobay 400 MHz spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). The chemical shifts are expressed in ppm downfield from tetramethylsilane (δ = 0.00) as an internal standard. Mass spectra were recorded by an electrospray ionization-time-of-flight (ESI-TOF) mass spectrometer (Micromass LCT). Specific rotations were measured on a Jasco P-1030. Melting points were obtained with Yanaco MP-J3 and are uncorrected. For thin layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 F_{254}) were used. Flash column chromatography was performed on neutral silica gel (Kanto Silica gel 60N, 40−50 μm). Organocatalysts **1** and **2** were prepared by the previous reported methods.[6a,b]

Preparation of Organocatalyst 3. To a 50 mL round-bottomed flask were added sulfonamide **2** (2.03 g, 5.27 mmol) and dry Et_2O (17 mL). The solution was cooled to 0 °C followed by addition of CS_2 (2.1 mL, 34.8 mmol) and DCC (1.09 g, 5.27 mmol). The reaction mixture was stirred at room temperature for 23 h. After starting material was consumed, the solution was filtered and concentrated *in vacuo* to afford a crude product. Purification by flash column chromatography on silica gel (hexane/EtOAc = 20:1 to 10:1) afforded the mixture of isothiocyanate and a small amount of 1,3-dicyclohexylthiourea. This mixture was used without further purification in the next step. To a 50 mL round-bottomed flask was added a mixture of isothiocyanate (1.63 g), (1*R*,2*R*)-(−)-cyclohexanediamine (877 mg, 7.68 mmol), and THF (13 mL). The solution was stirred for 16 h. After starting material was consumed, the solution was concentrated *in vacuo* to afford a crude product. Purification by flash column chromatography on silica gel ($CHCl_3$/MeOH/H_2O = 9:1:0.08) afforded the pure **3** as a white crystal (1.90 g, 67% from **2**). Mp 128−129 °C; $[\alpha]^{27}_D$ = −13.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 1.11−1.21 (m, 2H), 1.37−1.47 (m, 1H), 1.64−1.90 (m, 4H), 2.00 (d, *J* = 10.9 Hz, 1H), 2.20 (d, *J* = 11.2 Hz, 1H), 2.94 (dt, *J* = 3.2, 11.3 Hz, 1H), 3.20 (t, *J* = 12.2 Hz, 1H), 3.31 (d, *J* = 11.5 Hz, 1H), 4.43−4.50 (m, 1H), 4.71−4.78 (m, 1H), 6.41 (d, *J* = 9.6 Hz, 1H), 6.64 (brs, 3H), 7.49 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 18.6, 24.0, 24.7, 29.8, 31.8, 32.2, 46.6, 54.9, 56.4, 60.3, 106.1−119.2 (complex signals of $-CF_2-$ and $-CF_3$), 182.8; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{16}H_{26}F_9N_4O_2S_2$ 541.1348; Found 541.1346. Anal. Calcd for $C_{16}H_{25}F_9N_4O_2S_2$: C, 35.55; H, 4.66; N, 10.37. Found: C, 35.31; H, 4.73; N, 10.22.

Preparation of Organocatalyst 4. To a 35 mL round-bottomed flask were added sulfonamide **1** (476 mg, 1.10 mmol) and dry THF (3.5 mL). The solution was cooled to 0 °C followed by addition of CS_2 (439 μL, 7.26 mmol) and DCC (227 mg, 1.10 mmol). The reaction mixture was stirred at room temperature for 22 h. After starting material was consumed, the solution was concentrated *in vacuo* to afford a crude product. Purification by flash column chromatography on silica gel (eluent was $CHCl_3$) afforded the mixture of isothiocyanate and 1,3-dicyclohexylthiourea. This mixture was used without further purification in the next step. To a 35 mL round-bottomed flask was added the mixture of isothiocyanate (704 mg), (1*R*,2*R*)-(−)-cyclohexanediamine (251 mg, 2.20 mmol), and THF (3.7 mL). The solution was stirred for 2 h. After starting material was consumed, the solution was concentrated *in vacuo* to afford a crude product. Purification by flash column chromatography on silica gel ($CHCl_3$/MeOH = 1:0 to 10:1) afforded the pure **4** as a white powder (510 mg, 79% from **1**). Mp 120−121 °C; $[\alpha]^{29}_D$ = −3.8 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ = 1.26−1.52 (m, 4H), 1.77−1.81 (m, 2H), 1.95−2.07 (m, 2H), 2.82−2.88 (m, 2H), 2.94 (dd, *J* = 7.1, 13.6 Hz, 1H), 3.08 (dd, *J* = 5.1, 12.8 Hz, 1H), 3.45−3.48 (m, 1H), 4.44 (m,1H), 4.58 (m, 1H), 7.15−7.19 (m, 1H), 7.24−7.30 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD): δ = 25.2, 25.8, 31.7, 32.7, 39.2, 56.7, 57.3, 58.3, 110.2−120.7 (complex signals of $-CF_2-$ and $-CF_3$), 127.3, 129.3, 130.4, 140.1, 184.2; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{20}H_{26}F_9N_4O_2S_2$ 589.1348; Found 589.1353. Anal. Calcd for $C_{20}H_{25}F_9N_4O_2S_2$: C, 40.82; H, 4.28; N, 9.52. Found: C, 40.78; H, 4.45; N, 9.25.

Preparation of Organocatalyst 5. To a 25 mL round-bottomed flask were added (1*R*,2*R*)-diphenylethylenediamine (1.06 g, 5.0 mmol), DMAP (112 mg, 1.0 mmol), THF (5.0 mL), triethylamine (1.4 mL, 10 mmol), and perfluoro-1-butanesulfonyl fluoride (1.08 mL, 6.0 mmol). The solution was stirred at 60 °C for 38 h. After starting material was consumed, the reaction mixture was added to water and extracted three times with EtOAc. The EtOAc layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH = 1:0 to 50:1) to afford the pure *N*-((1*R*,2*R*)-2-amino-1,2-diphenylethyl)-1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonamide as a white crystal (1.48 g, 60%). Mp 171−172 °C; $[\alpha]^{23}_D$ =

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−13.0 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 3.48 (brs, 3H), 4.39 (d, *J* = 3.1 Hz, 1H), 4.76 (d, *J* = 3.1 Hz, 1H), 7.32−7.38 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 60.3, 64.6, 110.0−118.5 (complex signals of $-CF_2-$ and $-CF_3$), 126.0, 126.5, 128.1, 128.3, 128.8, 128.9, 139.3, 140.1; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{18}H_{16}F_9N_2O_2S$ 495.0783; Found 495.0790.

To a 35 mL round-bottomed flask were added *N*-((1*R*,2*R*)-2-amino-1,2-diphenylethyl)-1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonamide (1.59 g, 3.22 mmol) and dry THF (10 mL). The solution was cooled to 0 °C followed by addition of CS_2 (1.25 mL, 21.3 mmol) and DCC (666 mg, 3.23 mmol). The reaction mixture was stirred at room temperature for 20 h. After starting material was consumed, the solution was concentrated *in vacuo* to afford a crude product. Purification by flash column chromatography on silica gel (hexane/EtOAc = 20:1 to 5:1) afforded the mixture of isothiocyanate and 1,3-dicyclohexylthiourea. This mixture was used without further purification in the next step. To a 100 mL round-bottomed flask was added the mixture (1.93 g), (1*R*,2*R*)-(−)-cyclohexanediamine (738 mg, 6.46 mmol), and THF (20 mL). The solution was stirred at room temperature for 48 h. After starting material was consumed, the solution was concentrated *in vacuo* to afford a crude product. Purification by flash column chromatography on silica gel ($CHCl_3$/MeOH = 1:0 to 20:1) afforded the pure **5** as a white powder (496 mg, 24%). Mp 233−234 °C; $[\alpha]^{29}_D$ = +34.2 (*c* 1.00, DMSO); ^1H NMR (400 MHz, DMSO-d_6): δ = 1.05−1.33 (m, 4H), 1.63 (m, 2H), 1.85−1.94 (m, 2H), 2.91−2.96 (m, 1H), 3.98 (m, 1H), 4.63 (brs, 1H), 5.34 (brs, 1H), 7.08−7.22 (m, 6H), 7.37−7.45 (m, 4H), 7.80 (brs, 1H), 7.88 (brs, 1H), 8.11 (brs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.2, 23.7, 29.4, 31.0, 52.7, 54.9, 64.9, 65.0, 107.0−118.4 (complex signals of $-CF_2-$ and $-CF_3$), 125.5, 125.7, 127.0, 127.5, 142.9, 146.4, 182.4; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{25}H_{28}F_9N_4O_2S_2$ 651.1504; Found 651.1504. Anal. Calcd for $C_{25}H_{27}F_9N_4O_2S_2$: C, 46.15; H, 4.18; N, 8.61. Found: C, 46.11; H, 4.19; N, 8.58.

Preparation of Organocatalyst 6. To a 35 mL round-bottomed flask was added sulfonamide **2** (1.30 g, 3.38 mmol) and dry Et_2O (11 mL). The solution was cooled to 0 °C and added CS_2 (1.31 mL, 22.3 mmol) and DCC (702 mg, 3.38 mmol). The reaction mixture was stirred at room temperature for 11 h. After starting material was consumed, the solution was concentrated *in vacuo* to afford a crude product. Purification by flash column chromatography on silica gel (hexane/EtOAc = 10:1) afforded the mixture of isothiocyanate and 1,3-dicyclohexylthiourea. This mixture was used without further purification in the next step. To a 35 mL round-bottomed flask was added a mixture of isothiocyanate (1.38 g), (1*S*,2*S*)-(−)-cyclohexanediamine (776 mg, 6.80 mmol), and THF (14 mL). The solution was stirred at room temperature for 72 h. After starting material was consumed, the solution was concentrated *in vacuo* to afford a crude product. Purification by flash column chromatography on silica gel ($CHCl_3$/MeOH = 1:0 to 30:1) afforded the pure **6** as a white powder (1.03 g, 56%). Mp 168−170 °C; $[\alpha]^{29}_D$ = −25.7 (*c* 1.00, MeOH); ^1H NMR (400 MHz, CD_3OD): δ = 0.96 (d, *J* = 6.5 Hz, 3H), 0.98 (d, *J* = 6.5 Hz, 3H), 1.29−1.47 (m, 4H), 1.80 (m, 3H), 2.00−2.07 (m, 2H), 2.98−3.03 (m, 1H), 3.12−3.18 (m, 1H), 3.41 (d, *J* = 11.1 Hz, 2H), 4.54 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ = 19.1, 20.0, 25.2, 25.7, 31.3, 32.2, 32.8, 51.2, 56.3, 58.4, 64.2, 109.8−123.2 (complex signals of $-CF_2-$ and $-CF_3$), 183.0; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{16}H_{26}F_9N_4O_2S_2$ 541.1348; Found 541.1352. Anal. Calcd for $C_{16}H_{25}F_9N_4O_2S_2$: C, 35.55; H, 4.66; N, 10.37. Found: C, 35.37; H, 4.76; N, 10.15.

Preparation of Organocatalyst 7. To a 35 mL round-bottomed flask were added *N*-((1*R*,2*R*)-2-amino-1,2-diphenylethyl)-1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonamide (1.04 g, 2.10 mmol) and dry THF (7 mL). The solution was cooled to 0 °C followed by addition of CS_2 (812 μL, 13.9 mmol) and DCC (434 mg, 2.10 mmol). The reaction mixture was stirred at room temperature for 18 h. After starting material was consumed, the solution was concentrated *in vacuo* to afford a crude product. Purification by flash column chromatography on silica gel (hexane/EtOAc = 10:1) afforded the mixture of isothiocyanate and 1,3-dicyclohexylthiourea. This mixture was used without further purification in the next step. To a 35 mL round-bottomed flask was added a mixture of isothiocyanate (1.20 g), (1*S*,2*S*)-(−)-cyclohexanediamine (480 mg, 4.20 mmol), and THF (14 mL). The solution was stirred at room temperature for 60 h. After starting material was consumed, the solution was concentrated *in vacuo* to afford a crude product. Purification by flash column chromatography on silica gel ($CHCl_3$/MeOH = 1:0 to 30:1) afforded the pure **7** as a white powder (833 mg, 61%). Mp 147−148 °C; $[\alpha]^{29}_D$ = +1.5 (*c* 1.00, MeOH); ^1H NMR (400 MHz, CD_3OD): δ = 1.35−1.36 (m, 3H), 1.4−1.55 (m, 1H), 1.78−1.80 (m, 2H), 1.96−1.98 (m, 1H), 2.06−2.09 (m, 1H), 2.98 (dt, *J* = 4.0, 11.1 Hz, 1H), 4.47 (brs, 1H), 4.56 (d, *J* = 9.2 Hz, 1H), 5.55 (d, *J* = 9.2 Hz, 1H), 7.03−7.14 (m, 10H); ^{13}C NMR (100 MHz, CD_3OD): δ = 25.1, 25.7, 31.3, 32.5, 56.8, 57.4, 66.9, 68.0, 109.4−123.1 (complex signals of $-CF_2-$ and $-CF_3$), 127.6, 127.8, 128.6, 128.9, 129.0, 129.2, 141.8, 143.6, 184.8; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{25}H_{28}F_9N_4O_2S_2$ 651.1504; Found 651.1502. Anal. Calcd for $C_{25}H_{27}F_9N_4O_2S_2$: C, 46.15; H, 4.18; N, 8.61. Found: C, 45.95; H, 4.20; N, 8.38.

Preparation of Organocatalyst 8. To a 200 mL round-bottomed flask were added ethylenediamine (24 mL, 0.36 mol) and CH_2Cl_2 (80 mL). Perfluoro-1-butanesulfonyl fluoride (1.08 mL, 6.0 mmol) was added dropwise at room temperature. After 96 h of stirring, the reaction mixture was filtered and wash with CH_2Cl_2 to afford the white crystalline residue (1.11 g, 3.24 mmol, 54%). The monosulfonamide residue was used without further purification in the next step.

To a 35 mL round-bottomed flask was added sulfonamide (582.1 mg, 1.70 mmol) and dry DMF (6 mL). The solution was cooled to 0 °C followed by addition of CS_2 (675 μL, 11.2 mmol) and DCC (351 mg, 1.70 mmol). The reaction mixture was stirred at room temperature for 20 h. After starting material was consumed, a reduction in pressure removed the CS_2, and then (1*R*,2*R*)-(−)-cyclohexanediamine (388 mg, 3.4 mmol) was added. After 24 h, the reaction mixture was added to water and extracted three times with EtOAc. The EtOAc layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH = 1:0 to 30:1) to afford the pure **8** as a white powder (187 mg, 22%). Mp 151−152 °C; $[\alpha]^{28}_D$ = +4.4 (c 0.50, MeOH); ^1H NMR (400 MHz, CD_3OD): δ = 1.32−1.48 (m, 4H), 1.79−1.80 (m, 2H), 2.05−2.09 (m, 2H), 2.92 (m, 1H), 3.28 (m, 2H), 3.40−3.41 (m, 2H), 4.39 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ = 25.3, 25.7, 32.0, 32.8, 46.0, 47.6, 56.5, 57.9, 110.2−120.7 (complex signals of $-CF_2-$ and $-CF_3$), 184.4; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{13}H_{20}F_9N_4O_2S_2$ 499.0878; Found 499.0889. Anal. Calcd for $C_{13}H_{19}F_9N_4O_2S_2$: C, 31.33; H, 3.84; N, 11.24. Found: C, 31.19; H, 3.87; N, 11.16.

Typical Procedure for Asymmetric Conjugate Addition and Characterization Date of the Products (10a−m). To a solution of (*E*)-4-phenylbut-3-en-2-one (**9a**, 29.2 mg, 0.200 mmol) in ethyl acetate (0.1 mL) were added to organocatalyst **3** (10.8 mg, 0.020 mmol) and nitromethane (108 μL, 2.00 mmol) at room temperature. After stirring in a closed tube at 40 °C for 24 h, the reaction mixture was directly purified by flash column chromatography on silica gel with a 3:1 mixture of hexane and ethyl acetate to afford the pure **10a** (36.6 mg, 88%) as a white powder.

*(R)-5-Nitro-4-phenylpentan-2-one (**10a**).*[3a] White solid, 36.6 mg, 88% yield (97% ee). $[\alpha]^{23}_D$ = −5.0 (*c* 0.50, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 2.12 (s, 3H), 2.92 (d, *J* = 7.0 Hz, 2H), 3.97−4.05 (m, 1H), 4.60 (dd, *J* = 7.6, 12.3 Hz, 1H), 4.70 (dd, *J* = 6.9, 12.3 Hz, 1H), 7.21−7.35 (m, 5H); ^{13}C NMR (100 MHz, CDCl3): δ = 30.4, 39.0, 46.1, 79.5, 127.4, 127.9, 129.1, 138.8, 205.4. The enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using a ChiralPak AS-H column (hexane/*i*-PrOH = 60:40), flow rate = 1.0 mL/min, λ = 220 nm, t_{minor} = 8.2 min, t_{major} = 10.6 min.

*(R)-4-(4-Bromophenyl)-5-nitropentan-2-one (**10b**).*[3a] White solid, 49.4 mg, 86% yield (96% ee). $[\alpha]^{25}_D$ = −2.7 (*c* 1.13, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 2.13 (s, 3H), 2.87 (dd, *J* = 7.0, 18.1 Hz, 1H), 2.92 (dd *J* = 7.0, 18.1 Hz, 1H), 3.95−4.02 (m, 1H), 4.57 (dd, *J* = 7.9, 12.5 Hz, 1H), 4.68 (dd, *J* = 6.6, 12.5 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.4, 38.4, 45.9, 79.0, 121.9, 129.1, 132.2, 137.8, 205.0. The enantiomeric excess of the product was determined by chiral stationary

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phase HPLC analysis using a ChiralPak AD-H column (hexane/*i*-PrOH = 90:10), flow rate = 0.9 mL/min, λ = 220 nm, t_{minor} = 15.1 min, t_{major} = 17.5 min.

(R)-4-(4-Chlorophenyl)-5-nitropentan-2-one (**10c**).[3d] White solid, 40.5 mg, 84% yield, 96% ee. $[\alpha]^{24}_{D}$ = −3.3 (*c* 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.13 (s, 3H), 2.87 (dd, *J* = 7.0, 18.0, 1H), 2.92 (dd, *J* = 7.0, 18.0 Hz, 1H), 3.96−4.03 (m, 1H), 4.57 (dd, *J* = 7.9, 12.4 Hz, 1H), 4.68 (dd, *J* = 6.6, 12.4 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.4, 38.4, 46.0, 79.2, 128.8, 129.3, 133.8, 137.3, 205.0. The enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using a ChiralPak AD-H column (hexane/*i*-PrOH = 85:15), flow rate = 0.9 mL/min, λ = 220 nm, t_{minor} = 10.6 min, t_{major} = 11.9 min.

(R)-4-(3-Chlorophenyl)-5-nitropentan-2-one (**10d**).[3d] Colorless oil, 40.6 mg, 84% yield, 96% ee. $[\alpha]^{26}_{D}$ = −4.9 (*c* 0.53, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14 (s, 3H), 2.91 (d, *J* = 7.0 Hz, 2H), 3.96−4.03 (m, 1H), 4.58 (dd, *J* = 7.8, 12.5 Hz, 1H), 4.69 (dd, *J* = 6.7, 12.5 Hz, 1H), 7.10−7.14 (m, 1H), 7.21−7.29 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.4, 38.6, 45.9, 79.0, 125.8, 127.6, 128.2, 130.4, 134.9, 140.9, 204.9. The enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using a ChiralPak AS-H column (hexane/*i*-PrOH = 90:10), flow rate = 0.9 mL/min, λ = 210 nm, t_{minor} = 32.8 min, t_{major} = 52.7 min.

(R)-4-(2-Chlorophenyl)-5-nitropentan-2-one (**10e**).[3d] Colorless oil, 43.4 mg, 90% yield, 95% ee. $[\alpha]^{25}_{D}$ = −24.8 (*c* 0.53, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17 (s, 3H), 2.97 (dd, *J* = 6.0, 18.0 Hz, 1H), 3.06 (dd, *J* = 7.8, 18.0 Hz, 1H), 4.43−4.50 (m, 1H), 4.74 (dd, *J* = 6.4, 12.6 Hz, 1H), 4.78 (dd, *J* = 6.9, 12.6 Hz, 1H), 7.19−7.25 (m, 3H), 7.39−7.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.2, 35.8, 44.5, 77.4, 127.4, 128.4, 129.0, 130.4, 133.7, 136.0, 205.3. The enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using a ChiralPak AS-H column (hexane/*i*-PrOH = 90:10), flow rate = 0.9 mL/min, λ = 210 nm, t_{minor} = 22.7 min, t_{major} = 26.8 min.

(R)-5-Nitro-4-(4-nitrophenyl)pentan-2-one (**10f**).[3a] Brown solid, 43.3 mg, 86% yield, 95% ee. $[\alpha]^{26}_{D}$ = −4.6 (*c* 0.53, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.16 (s, 3H), 2.93 (dd, *J* = 6.9, 18.2 Hz, 1H), 2.99 (dd, *J* = 6.9, 18.2 Hz, 1H), 4.11−4.18 (m, 1H), 4.65 (dd, *J* = 8.2, 12.8 Hz, 1H), 4.75 (dd, *J* = 6.3, 12.8 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 2H), 8.20 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.3, 38.6, 45.6, 78.6, 124.2, 128.6, 146.4, 147.5, 204.4. The enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using a ChiralPak AD-H column (hexane/*i*-PrOH = 90:10), flow rate = 0.9 mL/min, λ = 254 nm, t_{minor} = 41.9 min, t_{major} = 57.7 min.

(R)-5-Nitro-4-(p-tolyl)pentan-2-one (**10g**).[3d] White solid, 37.0 mg, 84% yield, 96% ee. $[\alpha]^{25}_{D}$ = −2.2 (*c* 1.27, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.11 (s, 3H), 2.31 (s, 3H), 2.90 (d, *J* = 7.0 Hz, 2H), 3.93−4.00 (m, 1H), 4.57 (dd, *J* = 7.7, 12.2 Hz, 1H), 4.67 (dd, *J* = 6.9, 12.2 Hz, 1H), 7.10 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 30.4, 38.7, 46.2, 79.6, 127.2, 129.7, 135.7, 137.6, 205.6. The enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using a ChiralPak AD-H column (hexane/*i*-PrOH = 90:10), flow rate = 0.9 mL/min, λ = 220 nm, t_{minor} = 10.3 min, t_{major} = 11.5 min.

(S)-4-(Furan-2-yl)-5-nitropentan-2-one (**10h**).[3a] Brown oil, 19.5 mg, 49% yield, 97% ee. $[\alpha]^{24}_{D}$ = −7.5 (*c* 0.74, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.18 (s, 3H), 2.90 (dd, *J* = 7.4, 18.0 Hz, 1H), 2.98 (dd, *J* = 6.4, 18.0 Hz, 1H), 4.07−4.14 (m, 1H), 4.66 (dd, *J* = 6.9, 12.5 Hz, 1H), 4.70 (dd, *J* = 6.3, 12.5 Hz, 1H), 6.14 (d, *J* = 3.2, 1H), 6.30 (dd, *J* = 2.0, 3.2 Hz, 1H), 7.34 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.2, 32.9, 43.5, 77.1, 107.1, 110.5, 142.3, 151.7, 205.1. The enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using a ChiralPak AD-H column (hexane/*i*-PrOH = 90:10), flow rate = 0.9 mL/min, λ = 220 nm, t_{minor} = 11.2 min, t_{major} = 12.8 min.

(R)-3-(Nitromethyl)cyclohexan-1-one (**10i**).[8] Colorless oil, 13.0 mg, 40% yield, 96% ee. $[\alpha]^{25}_{D}$ = +10.6 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47−1.57 (m, 1H), 1.69−1.80 (m, 1H), 1.97−2.02 (m, 1H), 2.09−2.16 (m, 1H), 2.14−2.21 (m, 1H), 2.26−2.34 (m, 1H), 2.42−2.53 (m, 2H), 2.60−2.71 (m, 1H), 4.34 (dd, *J* = 6.6, 11.9 Hz, 1H), 4.39 (dd, *J* = 7.2, 11.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2, 28.2, 37.2, 40.9, 44.5, 80.1, 208.2. The enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using a ChiralPak IC column (hexane/*i*-PrOH = 60:40), flow rate = 0.8 mL/min, λ = 220 nm, t_{minor} = 16.4 min, t_{major} = 20.4 min.

(R)-5-Methyl-5-nitro-4-phenylhexan-2-one (**10j**).[3d] Pale-yellow solid, 43.3 mg, 92% yield, 96% ee. $[\alpha]^{25}_{D}$ = +40.7 (*c* 0.62, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 3H), 1.55 (s, 3H), 2.03 (s, 3H), 2.72 (dd, *J* = 3.5, 17.0 Hz, 1H), 3.09 (dd, *J* = 10.6, 17.0 Hz, 1H), 3.93 (dd, *J* = 3.5, 10.6 Hz, 1H), 7.18−7.20 (m, 2H), 7.26−7.33 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4, 25.8, 30.4, 44.0, 48.8, 91.1, 127.9, 128.6, 129.2, 137.6, 205.2. The enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using a ChiralPak AS-H column (hexane/*i*-PrOH = 90:10), flow rate = 0.9 mL/min, λ = 210 nm, t_{major} = 12.3 min, t_{minor} = 19.0 min.

(4R,5R)-5-Nitro-4-phenylhexan-2-one (**10k** *major*).[3d,9] Colorless oil, 19.2 mg, 43% yield, 95% ee. $[\alpha]^{26}_{D}$ = −13.1 (*c* 0.52, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (d, *J* = 6.6 Hz, 3H), 2.01 (s, 3H), 2.74 (dd, *J* = 4.2, 17.1 Hz, 1H), 2.97, (dd, *J* = 9.5, 17.1 Hz, 1H), 3.71 (ddd, *J* = 4.2, 9.5, 9.9 Hz, 1H), 4.77 (dq, *J* = 6.6, 9.9 Hz, 1H), 7.19−7.21 (m, 2H), 7.25−7.29 (m, 1H), 7.31−7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 30.4, 45.3, 46.3, 87.1, 127.9, 128.2, 129.1, 138.2, 205.0. The enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using a ChiralPak AS-H column (hexane/*i*-PrOH = 99:1), flow rate = 0.9 mL/min, λ = 220 nm, t_{major} = 41.2 min, t_{minor} = 47.0 min.

(4R,5S)-5-Nitro-4-phenylhexan-2-one (**10k** *minor*).[3d,9] Colorless oil, 16.8 mg, 38% yield, 95% ee. $[\alpha]^{26}_{D}$ = −1.1 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (d, *J* = 6.7 Hz, 3H), 2.11 (s, 3H), 2.90 (dd, *J* = 7.6, 17.6 Hz, 1H), 3.05 (dd, *J* = 6.7, 17.6 Hz, 1H), 3.70−3.76 (m, 1H), 4.84−4.91 (m, 1H), 7.13−7.15 (m, 2H), 7.24−7.33 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.7, 30.6, 44.5, 44.7, 85.8, 127.9, 128.1, 128.8, 137.8, 205.8. The enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using a ChiralPak AS-H column (hexane/*i*-PrOH = 99:1), flow rate = 0.9 mL/min, λ = 220 nm, t_{minor} = 45.6 min, t_{major} = 51.2 min.

(S)-4-Nitro-1,3-diphenylbutan-1-one (**10l**).[3d,8] White solid, 4.1 mg, 8% yield, 52% ee. $[\alpha]^{28}_{D}$ = −9.3 (*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.43 (dd, *J* = 7.5, 17.7 Hz, 1H), 3.49 (dd, *J* = 6.5, 17.7 Hz, 1H), 4.23 (dddd, *J* = 6.5, 6.6, 7.5, 7.9 Hz, 1H), 4.69 (dd, *J* = 7.9, 12.5 Hz, 1H), 4.84 (dd, *J* = 6.6, 12.5 Hz, 1H), 7.25−7.29 (m, 3H), 7.32−7.36 (m, 2H), 7.44−7.48 (m, 2H), 7.55−7.60 (m, 1H), 7.91−7.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.4, 41.7, 79.7, 127.6, 128.0, 128.2, 128.9, 129.2, 133.7, 136.5, 139.3, 197.0. The enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using a ChiralPak AS-H column (hexane/*i*-PrOH = 90:10), flow rate = 0.9 mL/min, λ = 254 nm, t_{major} = 25.9 min, t_{minor} = 35.9 min.

(S)-4-(Nitromethyl)-6-phenylhexan-2-one (**10m**).[3d] Colorless oil, 12.6 mg, 27% yield, 95% ee. $[\alpha]^{27}_{D}$ = −4.7 (*c* 0.57, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.70−1.76 (m, 2H), 2.16 (s, 3H), 2.53−2.74 (m, 5H), 4.48 (dd, *J* = 5.1, 11.9 Hz, 1H), 4.51 (dd, *J* = 5.4, 11.9 Hz, 1H), 7.15−7.22 (m, 3H), 7.27−7.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.6, 32.8, 33.1, 33.2, 44.7, 78.2, 126.4, 128.4, 128.7, 140.7, 206.6. The enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using a ChiralPak AS-H column (hexane/*i*-PrOH = 90:10), flow rate = 0.9 mL/min, λ = 210 nm, t_{minor} = 20.3 min, t_{major} = 25.5 min.

■ ASSOCIATED CONTENT

Supporting Information

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Spectra data and copies of all new compounds (PDF)

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