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Highly enantioselective Michael addition of ketones to nitroolefins catalyzed by (*S*)-pyrrolidine arenesulfonamide

Bukuo Ni, Qianying Zhang and Allan D. Headley*

Department of Chemistry, Texas A&M University-Commerce, Commerce, TX 75429-3011, USA

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Abstract—A new type of catalyst for the asymmetric Michael addition reaction has been designed and synthesized. This catalyst, (*S*)-pyrrolidine arenesulfonamide **1**, resulted in high yields (up to 93%), excellent diastereoselectivities (*syn*/*anti* ratio up to 99/1), and excellent enantioselectivities (ee up to 99%) for various cyclic ketones and nitroolefins.

1. Introduction

The organocatalytic asymmetric Michael addition reaction has emerged as one of the most powerful and efficient methods for C–C bond formation in synthetic organic chemistry.[1] Several highly efficient chiral organocatalysts have been designed and synthesized for this reaction.[2] Proline and its pyrrolidine-type chiral amine derivatives are among the organocatalysts that have been found to be highly successful for asymmetric organic transformations.[3] The pioneering works by Hanessian,[3a] List,[3b] and Enders[3c] serve to demonstrate that L-proline is a very effective catalyst for asymmetric Michael addition reactions, the key step for these reactions being the formation of an enamine intermediate. Owing to the poor solubility of proline in many organic solvents, numerous novel proline derivatives, such as pyrrolidine-pyridine,[4] aminomethylpyrrolidine,[5] 2,2′-bipyrrolidine,[6] pyrrolidinelterazole,[7] (*S*)-(+)-2-pyrrolidinemethanol,[8] pyrrolidine-thiourea,[9] and pyrrolidine-based chiral ionic liquids[10] which have improved solubility, have been developed and used as excellent organocatalysts in asymmetric Michael addition reactions.

Recently, Wang et al.[11] described the synthesis of (*S*)-pyrrolidine trifluoromethanesulfonamide and hydrophobic polyfluorous pyrrolidine sulfonamide that effectively catalyzes diastereo- and enantioselective Michael addition reactions of ketones and aldehydes with nitroolefins. However, a relatively low enantioselectivity was obtained when nitrostyrene, which contained an election-withdrawing CF_3 group, was used as a Michael acceptor. Although the catalysts developed to date exhibit a relatively high reactivity and selectivity, the development of new catalysts that are capable of improving diastereo- and enantioselectivity for the asymmetric Michael reaction at room temperature is still warranted.

2. Results and discussion

It has been proposed that the asymmetric Michael reaction catalyzed by proline proceeds via an enamine intermediate, and that both the secondary amine of the pyrrolidine ring and the carboxylic acid functionalities are required for the catalytic activity. Herein, we have designed a new type of proline-derived catalyst, (*S*)-pyrrolidine arenesulfonamide **1**, which has proven to be an effective organocatalyst for reactions where proline derivatives are normally used. The two electron-withdrawing trifluoromethyl groups on the phenyl ring, combined with sulfonyl group are expected to effectively increase the acidity of the sulfonamide hydrogen and as a result, facilitate required proton transfer. Catalyst **1** can be easily prepared from the commercially available *N*-Boc-(*S*)-2-aminomethylpyrrolidine and 3,5-bis(trifluoromethyl)benzenesulfonyl chloride, as shown in Scheme 1. Herein, we report the results of the studies using **1** as catalyst to promote highly diastereo- and enantioselective Michael addition reactions of ketones with nitroolefins.

Initially, the Michael reaction of cyclohexanone and nitrostyrene in various solvents was examined at room temperature using (*S*)-pyrrolidine arenesulfonamide **1** as the

* Corresponding author. E-mail: allan_headley@tamu-commerce.edu

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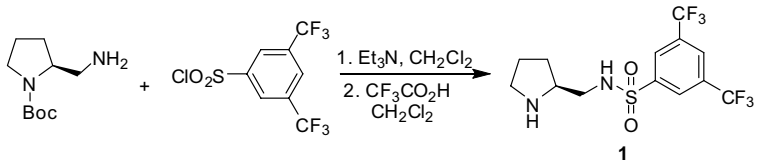
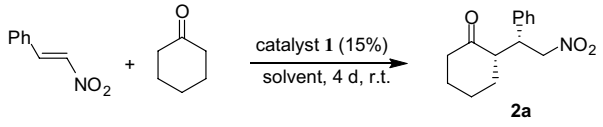


Scheme 1. Synthesis of (*S*)-pyrrolidine arenesulfonamide.

catalyst, the results are summarized in Table 1. Both CH_3CN and THF gave high diastereoselectivities, but yields were low (8–10%) (Table 1, entries 1 and 2). Dichloromethane and an ionic liquid [BMIM]BF_4 were also poor solvents in terms of product yields (Table 1, entries 4 and 5). DMSO, *i*-PrOH, and DMF were superior solvents and showed good yields, high enantioselectivities, and diastereoselectivities (Table 1, entries 6–8). Based on these results, *i*-PrOH was chosen as the solvent to study the effectiveness of catalyst **1**. The Michael addition reaction proceeded smoothly at room temperature to give the desired adduct **2a** in 83% yield with high enantioselectivity (94% ee) and diastereoselectivity (*syn*/*anti* = 98/2).

Table 1. Solvent effect for asymmetric Michael addition reaction of cyclohexanone and *trans*-β-nitrostyrene

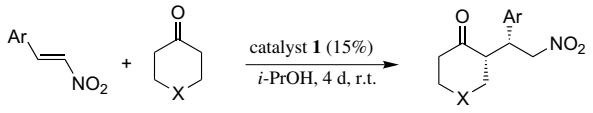


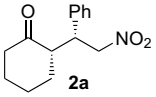
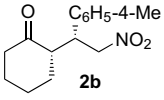
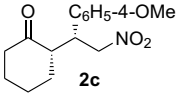
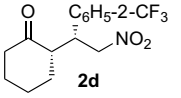
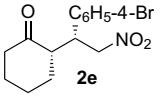
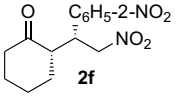
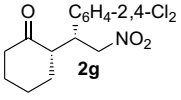
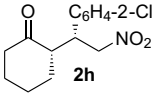
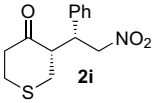
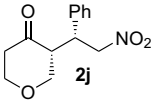
Entry	Solvent	Yield[a] (%)	ee[b] (%)	dr (*syn*/*anti*)[d]
1	CH_3CN	10	[c]	96/4
2	THF	8	[c]	93/7
3	DCM	<5	[c]	[c]
4	Neat	8	[c]	[c]
5	[BMIM]BF_4	5	[c]	[c]
6	DMSO	61	83	95/5
7	***i*-PrOH**	**83**	**94**	**98/2**
8	DMF	85	92	92/8

[a] Yield of isolated product.
[b] Determined by chiral HPLC analysis (Chiralpak AS-H).
[c] Not determined.
[d] Determined by ^{1}H NMR spectroscopy (400 MHz).

Having established the standard reaction conditions for the Michael addition of cyclohexanone with *trans*-β-nitrostyrene, we next investigated the scope of the Michael reaction for which catalyst **1** is effective with a series of ketones and nitroolefins in *i*-PrOH as the solvent; the results were shown in Table 2. From these results, it is obvious that all cyclic ketones efficiently undergo Michael reactions with different aryl-substituted nitroolefins in the presence of 15 mol % of catalyst **1** in *i*-PrOH at room temperature to give the Michael adducts **2a**–**i** in high yields with excellent enantio- (92–99% ee) and diastereoselectivities (*syn*/*anti* ratio up to 99/1). The results in Table 1 also show that the nature of the substituents on aryl groups slightly influences the yields and enatioselectivities. For nitroolefins with electron-rich groups (methyl and methoxy), the reaction proceeded smoothly to afford Michael adduct **2b**,**c** in nearly enantiomerically pure form (99% ee) and with excellent diastereoselectivities, although the isolated yields were

Table 2. Asymmetric Michael reaction of cycloketones to nitroolefins



Entry	Product	Yield[a] (%)	ee[b] (%)	dr (*syn*/*anti*)[c]
1	 **2a**	83	94	98/2
2	 **2b**	77	99	96/4
3	 **2c**	65	99	99/1
4	 **2d**	87	95	99/1
5	 **2e**	83	94	94/6
6	 **2f**	91	93	99/1
7	 **2g**	93	96	98/2
8	 **2h**	92	95	99/1
9	 **2i**	92	92	98/2
10	 **2j**	90	93	91/9

[a] Isolated yield.
[b] Determined by Chiral HPLC.
[c] Determined by ^{1}H NMR.

relatively low (65–77%) (Table 2, entries 2 and 3). For nitroolefins with electron-withdrawing groups, the Michael adducts **2d**–**h** were obtained in high yields (83–93%) with excellent enantio- (93–96% ee) and diastereoselectivities (*syn*/*anti* ratio up to 99/1) (Table 2, entries 4–7). Moreover, tetrahydrothiopyran-4-one and tetrahydro-4*H*-pyran-4-one were also suitable substrates as Michael donors (Table 2, entries 8 and 9). Compared to the results obtained by Wang et al.[11b] in which (*S*)-pyrrolidine trifluoromethanesulfonamide was used as the catalyst, the (*S*)-pyrrolidine arenesulfonamide **1** is superior in enantioselectivity for nitroolefins bearing electron-deficient aryl groups.[12]

3. Conclusion

In conclusion, a new catalyst, (*S*)-pyrrolidine arenesulfonamide **1**, was prepared and successfully applied to the asymmetric Michael addition reaction of cyclic ketones with nitroolefins. The reactions proceeded smoothly at room temperature to give high yields (up to 93%), excellent diastereoselectivities (*syn*/*anti* ratio up to 99/1), and excellent enantioselectivities (ee up to 99%). The design of improved catalysts and their application to other types of reactions are currently being investigated in our laboratory.

4. Experimental

4.1. (*S*)-2-[(2,6-Trifluoromethanebenzenesulfonyl)aminomethyl]pyrrolidine 1

To a solution of *N*-Boc-(*S*)-2-aminomethylpyrrolidine (500 mg, 2.5 mmol) in CH_2Cl_2 (15 mL) was added Et_3N (0.42 mL, 3.0 mmol). The solution was cooled to 0 °C and 3,5-bis(trifluoromethyl)benzenesulfonyl chloride (782 mg, 2.5 mmol) was added. After the addition, the reaction mixture was brought to room temperature and stirred for 17 h, diluted in CH_2Cl_2 (60 mL) and washed with 1 M HCl (5 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (15 mL). The organic phase was dried over Na_2SO_4 and concentrated to give the residue, which was used for the next step without further purification.

The above compound was dissolved in a 1/1 mixture of trifluoroacetic acid and dichloromethane (10 mL) and the solution was stirred for 2 h at rt, at which time the solvent was evaporated under reduced pressure. The pH was adjusted to 8 with aqueous $NaHCO_3$ and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The organic phase was dried over $NaSO_4$ and the solvent was evaporated to give the residue, which was recrystallized from ethyl acetate and hexane to give the pure title compound **1** (1.05 g, 88% for two steps). Mp: 189–191 °C; $[\alpha]_D^{20} = -10$ (*c* 0.30, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 8.44 (s, 2H), 8.33 (s, 1H), 3.75–3.65 (m, 1H), 3.40–3.13 (m, 4H), 2.21–2.00 (m, 3H), 1.65–1.78 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 144.3, 134.1 (q, $J = 137.2$ Hz, 2C), 128.7, 125.5, 122.7; IR (neat) $\nu = 1687$, 1352, 1278, 1129 cm^{-1}; HRMS (ESI) *m*/*z* (%) calcd for $C_{13}H_{15}F_6N_2O_2S$: 377.0753, found: 377.0752.

4.2. The data for the Michael addition reaction

4.2.1. (*S*)-2-((*R*)-2-Nitro-1-phenylethyl)cyclohexanone 2a.[4] Typical procedure: Catalyst **1** (11 mg, 15 mol %) was dissolved in *i*-PrOH (1 mL) and cyclohexanone (59 mg, 0.6 mmol) and β-nitrostyrene (30 mg, 0.2 mmol) was added. The reaction mixture stirred at room temperature for 4 days. The reaction mixture was concentrated in vacuum and the residue was purified by flash silica gel column (eluent: hexane/ethyl acetate = 4/1) to give the Michael adduct **2a** (41 mg, 83%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.23 (m, 3H), 7.20–7.14 (m, 2H), 4.94 (dd, $J = 12.4$ and 4.4 Hz, 1H), 6.43 (dd, $J = 12.4$ and 10.0 Hz, 1H), 3.76 (dt, $J = 9.6$ and 4.4 Hz, 1H), 2.74–2.64 (m, 1H), 2.52–2.34 (m, 2H), 2.13–2.03 (m, 1H), 1.83–1.50 (m, 4H), 1.30–1.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9, 137.7, 128.9, 128.2, 127.8, 78.9, 52.5, 43.9, 42.7, 33.2, 28.5, 25.0; $[\alpha]_D^{20} = -23.2$ (*c* 0.15, CH_2Cl_2); *syn*/*anti* = 98/2; ee = 94%; HPLC (Chiralpak AS-H, *i*-propanol/hexane = 10/90, flow rate 0.7 mL/min, $\lambda = 238$ nm): $t_{minor} = 22.7$ min, $t_{major} = 35.2$ min.

4.2.2. (*S*)-2-((*R*)-1-(4-Methylphenyl)-2-nitroethyl)cyclohexanone 2b.[11b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, $J = 8.0$ Hz, 2H), 7.04 (d, $J = 8.0$ Hz, 2H), 4.91 (dd, $J = 12.4$ and 4.8 Hz, 1H), 4.62 (dd, $J = 12.4$ and 10.0 Hz, 1H), 3.72 (dt, $J = 10.0$ and 4.8 Hz, 1H), 2.71–2.62 (m, 1H), 2.51–2.32 (m, 2H), 2.31 (s, 3H), 2.12–2.02 (m, 1H), 1.82–1.50 (m, 4H), 1.30–1.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0, 137.4, 134.6, 129.6, 128.0, 79.0, 52.6, 43.6, 42.7, 33.2, 28.5, 25.0, 21.0; $[\alpha]_D^{20} = -17.9$ (*c* 0.36, CH_2Cl_2); *syn*/*anti* = 96/4; ee = 99%; HPLC (Chiralpak AS-H, *i*-propanol/hexane = 10/90, flow rate 0.8 mL/min, $\lambda = 254$ nm): $t_{minor} = 15.4$ min, $t_{major} = 25.9$ min.

4.2.3. (*S*)-2-((*R*)-1-(4-Methoxyphenyl)-2-nitroethyl)cyclohexanone 2c.[4] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, $J = 8.8$ Hz, 2H), 6.83 (d, $J = 8.8$ Hz, 2H), 4.95 (dd, $J = 12.4$ and 4.4 Hz, 1H), 4.58 (dd, $J = 12.4$ and 10.0 Hz, 1H), 3.78 (s, 3H), 3.72 (dt, $J = 10.0$ and 4.4 Hz, 1H), 2.69–2.60 (m, 1H), 2.53–2.33 (m, 2H), 2.13–2.04 (m, 1H), 1.82–1.50 (m, 4H), 1.30–1.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0, 137.4, 134.6, 129.6, 128.0, 79.0, 52.6, 43.6, 42.7, 33.2, 28.5, 25.0, 21.0; $[\alpha]_D^{20} = -11.8$ (*c* 0.31, CH_2Cl_2); *syn*/*anti* = 99/1; ee = 99%. HPLC (Chiralpak AD, *i*-propanol/hexane = 10/90, flow rate 0.5 mL/min, $\lambda = 254$ nm): $t_{minor} = 25.5$ min, $t_{major} = 31.8$ min.

4.2.4. (*S*)-2-((*R*)-1-(2-Trifluoromethanephenyl)-2-nitroethyl)cyclohexanone 2d.[11b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, $J = 7.6$ Hz, 1H), 7.56 (t, $J = 7.6$ Hz, 1H), 7.39 (dd, $J = 16.4$ and 10.0 Hz, 2H), 5.02 (dd, $J = 12.0$ and 6.8 Hz, 1H), 4.76 (dd, $J = 12.0$ and 4.0 Hz, 1H), 4.13–4.05 (m, 1H), 3.06–2.96 (m, 1H), 2.54–2.40 (m, 3H), 2.18–2.08 (m, 1H), 1.84–1.52 (m, 4H), 1.38–1.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.5, 137.1, 132.4, 128.0, 127.8, 126.6 (q, $J = 20.8$ Hz, 1C), 125.5, 122.7, 78.5, 52.5, 43.0, 39.1, 33.5, 28.7, 25.5; $[\alpha]_D^{20} = -15.7$ (*c* 0.64, CH_2Cl_2); *syn*/*anti* = 99/1; ee = 95%; HPLC (Chiralpak AD, *i*-propanol/hexane = 10/90, flow rate 0.5 mL/min, $\lambda = 254$ nm): $t_{minor} = 13.4$ min, $t_{major} = 18.3$ min.

4.2.5. (*S*)-2-((*R*)-1-(4-Bromophenyl)-2-nitroethyl)cyclohexanone 2e.[10a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, $J = 6.8$ and 1.6 Hz, 2H), 7.06 (dd, $J = 6.8$ and 1.6 Hz, 2H), 4.92 (dd, $J = 12.4$ and 4.4 Hz, 1H), 4.60 (dd, $J = 12.4$ and 10.0 Hz, 1H), 3.74 (dt, $J = 9.6$ and 4.4 Hz, 1H), 2.70–2.60 (m, 1H), 2.52–2.32 (m, 2H), 2.14–2.04 (m, 1H), 1.84–1.52 (m, 4H), 1.30–1.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.4, 136.8, 132.1, 129.9, 121.7, 78.5, 52.3, 43.4, 42.7, 33.1, 28.4, 25.0; $[\alpha]_D^{20} = -14.2$ (*c* 0.40, CH_2Cl_2); *syn*/*anti* = 94/6; ee = 94%; HPLC (Chiralpak AS-H, *i*-propanol/hexane = 10/90, flow rate 1 mL/min, $\lambda = 254$ nm): $t_{minor} = 18.2$ min, $t_{major} = 32.7$ min.

4.2.6. (*S*)-2-((*R*)-2-Nitro-(2-nitrophenyl)ethyl)cyclohexanone 2f.[9] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, $J = 8.0$ Hz, 1H), 7.59 (t, $J = 8.0$ Hz, 1H), 7.48–7.42 (m, 2H), 4.98–4.87 (m, 2H), 4.32 (dt, $J = 8.8$ and 4.8 Hz, 1H), 2.99–2.91 (m, 1H), 2.52–2.32 (m, 2H), 2.16–2.08 (m, 1H), 1.88–1.78 (m, 2H), 1.72–1.40 (m, 4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.0, 150.8, 133.1, 132.8, 129.3, 128.6, 124.9, 77.6, 52.2, 42.8, 38.7, 33.2, 28.3, 25.3; $[\alpha]_D^{20} = -148.3$ (*c* 0.65, CH_2Cl_2); *syn*/*anti* = 99/1; ee = 93%; HPLC (Chiralpak AD, *i*-propanol/hexane = 5/95, flow rate 1 mL/min, $\lambda = 238$ nm): $t_{minor} = 32.3$ min, $t_{major} = 48.0$ min.

4.2.7. (*S*)-2-((*R*)-1-(2,4-Dichlorophenyl)-2-nitroethyl)cyclohexanone 2g.[9] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, $J = 2.0$ Hz, 1H), 7.28–7.14 (m, 2H), 4.95–4.80 (m, 2H), 4.25 (dt, $J = 9.6$ and 4.8 Hz, 1H), 2.93–2.82 (m, 1H), 2.52–2.32 (m, 2H), 2.16–2.07 (m, 1H), 1.87–1.50 (m, 4H), 1.40–1.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3, 135.2, 134.1, 130.1, 127.7, 51.6, 42.8, 40.6, 33.1, 28.4, 25.3; $[\alpha]_D^{20} = -40.7$ (*c* 0.71, CH_2Cl_2); *syn*/*anti* = 98/2; ee = 96%; HPLC (Chiralpak AS-H, *i*-propanol/hexane = 5/95, flow rate 1 mL/min, $\lambda = 238$ nm): $t_{minor} = 16.0$ min, $t_{major} = 29.9$ min.

4.2.8. (*S*)-2-((*R*)-1-(2-Chlorophenyl)-2-nitroethyl)cyclohexanone 2h.[10a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, $J = 6.8$ Hz, 2H), 7.30–7.28 (m, 3H), 4.90 (d, $J = 2.0$ Hz, 1H), 4.89 (s, 1H), 4.35–4.25 (m, 1H), 2.98–2.86 (m, 1H), 2.52–2.34 (m, 2H), 2.16–2.06 (m, 1H), 1.86–1.54 (m, 4H), 1.40–1.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6, 135.4, 134.5, 130.3, 129.4, 128.9, 127.3, 77.2, 51.7, 42.8, 41.0, 33.0, 28.5, 25.2; $[\alpha]_D^{20} = -49.2$ (*c* 0.50, $CHCl_3$); *syn*/*anti* = 99/1; ee = 95%; HPLC (Chiralpak AD, *i*-propanol/hexane = 5/95, flow rate 1 mL/min, $\lambda = 254$ nm): $t_{minor} = 13.0$ min, $t_{major} = 18.9$ min.

4.2.9. (*R*)-Tetrahydro-3-((*R*)-2-nitro-1-phenylethyl)pyran-4-one 2i.[11b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 3H), 7.21–7.16 (m, 2H), 4.96 (dd, $J = 12.4$ and 4.8 Hz, 1H), 4.64 (dd, $J = 12.4$ and 10.0 Hz, 1H), 4.20–4.10 (m, 1H), 3.87–3.68 (m, 2H), 3.70 (dd, $J = 11.2$ and 5.2 Hz, 1H), 3.27 (dd, $J = 11.2$ and 10.0 Hz, 1H), 2.93–2.83 (m, 1H), 2.73–2.61 (m, 1H), 2.60–2.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3, 136.2, 129.2, 128.3, 127.9, 78.7, 71.6, 69.0, 53.3, 42.9, 41.3; $[\alpha]_D^{20} = -17.7$ (*c* 0.44, CH_2Cl_2); *syn*/*anti* = 98/2; ee = 92%; HPLC (Chiralpak AS-H, *i*-propanol/hexane = 40/60, flow rate 0.5 mL/min, $\lambda = 254$ nm): $t_{minor} = 22.3$ min, $t_{major} = 29.0$ min.

4.2.10. (*R*)-Tetrahydro-3-((*R*)-2-nitro-1-phenylethyl)pyran-4-one 2j.[11b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 3H), 7.21–7.16 (m, 2H), 4.96 (dd, $J = 12.4$ and 4.8 Hz, 1H), 4.64 (dd, $J = 12.4$ and 10.0 Hz, 1H), 4.20–4.10 (m, 1H), 3.87–3.68 (m, 2H), 3.70 (dd, $J = 11.2$ and 5.2 Hz, 1H), 3.27 (dd, $J = 11.2$ and 10.0 Hz, 1H), 2.93–2.83 (m, 1H), 2.73–2.61 (m, 1H), 2.60–2.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3, 136.2, 129.2, 128.3, 127.9, 78.7, 71.6, 69.0, 53.3, 42.9, 41.3; $[\alpha]_D^{20} = -27.9$ (*c* 0.45, CH_2Cl_2); *syn*/*anti* = 91/9; ee = 93%; HPLC (Chiralpak AS-H, *i*-propanol/hexane = 50/50, flow rate 0.5 mL/min, $\lambda = 254$ nm): $t_{minor} = 20.7$ min, $t_{major} = 25.8$ min.

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12. The (*S*)-pyrrolidine trifluoromethanesulfonamide (20 mol %) catalyzed Michael addition of *trans*-β-nitro-2-(trifluoromethyl)styrene with cyclohexanone at 0 °C resulted in 70% yield and 88% ee (see Ref. 11b).