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Novel bifunctional sulfonamides catalyze an enantioselective conjugate addition

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ABSTRACT

A new bifunctional organocatalyst with a novel structural and functional motif has been developed. This bifunctional sulfonamide organocatalyst was used in the conjugate addition of 1,3-dicarbonyl compounds (**13**) to β-nitrostyrenes (**12**). Yields up to 91% and enantiomeric excesses up to 79% were obtained in this reaction. This catalyst activates both **13** via its basic moiety and **12** through hydrogen bonding.

1. Introduction

The use of non-transition metal-based organocatalysts has gained increasing popularity in recent years due both to a mounting desire to use more environmentally benign catalysts and to the expanding scope of organocatalytic reactions.[1] More specifically, organocatalysts that act as relatively weak hydrogen bond donors or as stronger, Brønsted acids have proven effective in a variety of transformations.[2] Within this class of organocatalysts, there are numerous examples of thioureas[3–6] of type **1** (Fig. 1) and several examples of cinchona alkaloids[7] (**2**) and bis-phenols[8] (**3**). These organocatalysts each contain two hydrogen bond donors, and act by coordinating one or both of them to electrophiles. Moreover, they are considered bifunctional, because they contain a basic tertiary amine and can activate the nucleophilic reaction partner as well.

In the search for new structural and functional motifs for organocatalysts of this type, the strategy of adapting anion receptors that bind anions through the donation of multiple hydrogen bonds for this purpose was employed. Bissulfonamide **4** (Fig. 2) met this criterion and was particularly attractive for several reasons.[9] First, Crabtree and co-workers demonstrated that **4** could catalyze an organic reaction (i.e., imine formation) and proposed that double hydrogen bond donation of **4** to the electrophile was the mode of activation.[10] Second, it was recently revealed that chiral bissulfonamides (**5**) could act as hydrogen bonding organocatalysts.[11] Enantiomeric excesses (ee's) of up to 87% in a hetero Diels–Alder reaction were obtained using these organocatalysts.[11c] Finally, since there can be a correlation between acidity and hydrogen bond donor ability,[12] it was postulated that incorporating the more acidic sulfonamide functional group as a hydrogen bond donor in bifunctional catalysts of the type illustrated in Figure 1 could be favorable.

While there is no facile way to modify **5** to incorporate an appropriately situated tertiary amine moiety, the 1,3-benzenedisulfonyl scaffold of **4** would allow for ready incorporation of a broad structural array of chiral amines. This would enable the development of the first bifunctional bissulfonamide organocatalysts, of type **6**, which contain both a tertiary amine and two sulfonamides, each capable of forming a discrete hydrogen bond with the substrate.[13]

2. Results and discussion

It was first necessary to assess the catalytic potential of these bissulfonamides in organic reactions that generate a chiral center. Toward this end, compounds **4** and **7** (Fig. 3) were examined in the conjugate addition of a 1,3-dicarbonyl compound to β-nitrostyrene (Table 1),[14] a transformation in which bifunctional thioureas of type **1** have been successfully employed.[3a,4a,5b,6b,c] Pleasingly, **4** and **7** produced 2.2- and 2.4-fold rate accelerations, respectively (entries 1–3, Table 1). This suggested that chiral variants of **4** that incorporate both acidic bissulfonamide protons and a basic tertiary amine, could be effective catalysts for an enantioselective conjugate addition.

Chiral amines that have been successfully employed in bifunctional thiourea catalysts were selected for incorporation into bissulfonamide catalysts.[3–6,15] A variety of catalysts were

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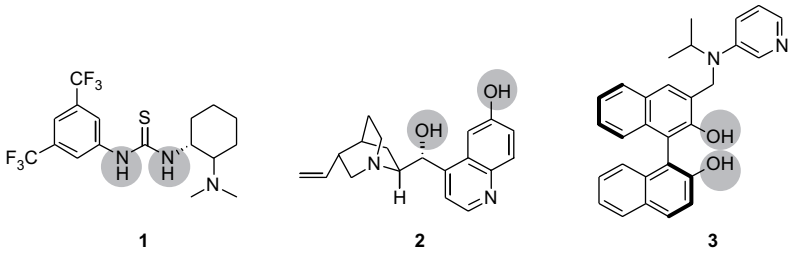


Figure 1. Bifunctional organocatalysts with two H-bond donors.

synthesized[16] to independently test the effect of acidity of the sulfonamide protons (**6b**, **6c**) and of the chiral moieties (**6a**, **6b**, **6d**) on reaction yield and ee. Additionally, C_2-symmetric catalyst **8** was synthesized from commercially available 1,3-benzenedisulfonyl chloride. Among the catalysts, the bissulfonamide derived from 1,2-diphenylethylenediamine generated the product in the highest yield (entry 4), but lowest ee. The bissulfonamides derived from 1,2-cyclohexanediamine all afforded products in similar, reduced yields but with improved, yet varying, ee's (entries 5, 6, and 8). The bissulfonamide (**6d**) derived from a sterically demanding, aryl amine did not catalyze the reaction (entry 7). Tethering the tertiary amine to the bissulfonamide appears to lower the reaction rate (for example, entry 6 vs 3; vida infra).[17] These initial studies led to the selection of catalyst **6c** for further studies despite the low yield.

Optimization of other reaction conditions ensued using catalyst **6c**. A solvent study revealed that non-polar solvents, such as toluene and Et_2O, resulted in higher product yields relative to more polar solvents, such as THF and CH_2Cl_2 (entries 2–5, Table 2). The most polar solvent, acetonitrile, gave the product in the lowest yield (entry 1). Moderate to good enantiomeric excesses were achieved in all solvents with the exception of THF. The reduced ee obtained using THF may be related to the enhanced background reaction observed in this solvent (vida infra). The highest ee's were attained in non-coordinating solvents, such as toluene and CH_2Cl_2. The reaction could also be run using solvent-free conditions, which generated products in significantly improved yields, but with only moderate ee's (entries 6 and 7). Thus, toluene, being both non-polar and non-coordinating, was identified as the optimal solvent for this reaction.

Next, several other variables were examined. Tripling the catalyst loading more than doubled the yield, but resulted in a loss of enantioselectivity (entry 8 vs 2). Alternatively, either doubling the reaction concentration or doubling the equivalents of **13a** increased the reaction yield to a similar, lesser degree, but resulted in a less pronounced decrease in ee (entries 9 and 10 vs 5). In longer reaction times, doubling the equivalents of **13a** produced comparable ee's and a more dramatic improvement in yield (entry 11 vs 5). Running the reaction at 0 °C produced a minimal increase in ee, but halved the yield (entry 12 vs 11). There was no difference in yield and only slight differences in ee when the equivalents of **13a** were increased further at room temperature (entries 13 and 14 vs 11). Increasing the reaction time further led to a greater than 4-fold improvement in yield and an insignificant drop in ee relative to initial reaction conditions (entry 15), as the ee of the reaction increased slightly over time. Finally, running the reaction at elevated temperatures for extended reaction times led to still greater product yields, but slightly lower enantioselectivities (entry 16). Since obtaining useful product yields had been an impediment with this catalyst, these last conditions were identified as the optimal reaction conditions.

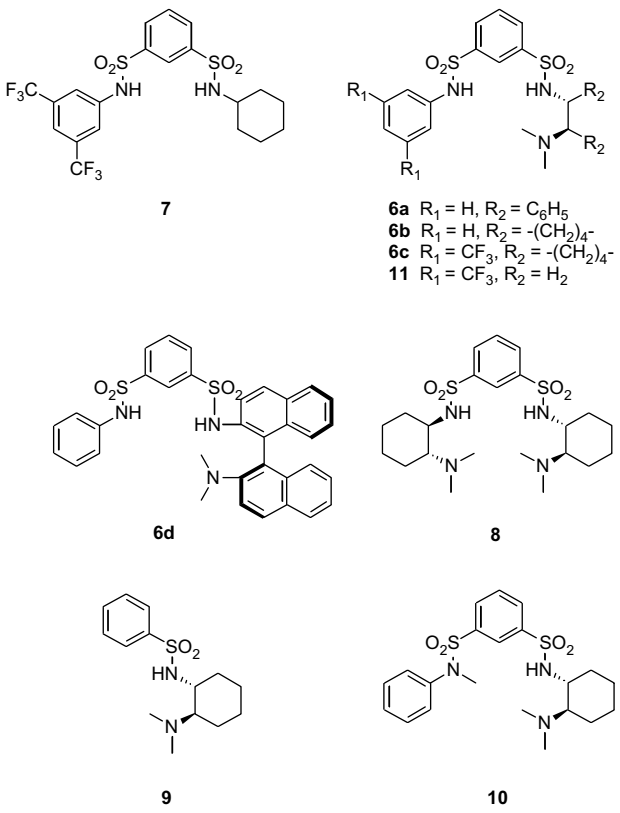


Figure 3. Novel bissulfonamide organocatalysts.

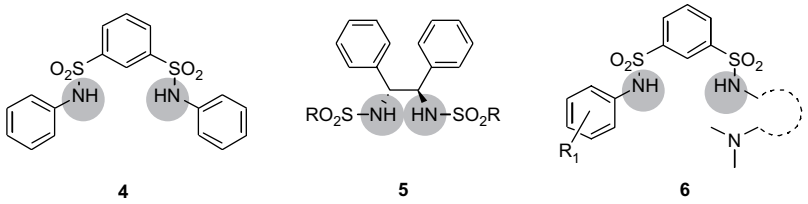
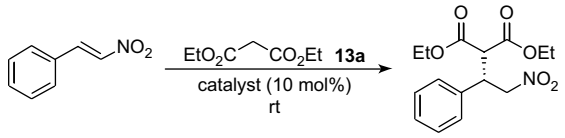


Figure 2. Bissulfonamide organocatalysts with two H-bond donors.

Table 1
Optimization of organocatalyst structure



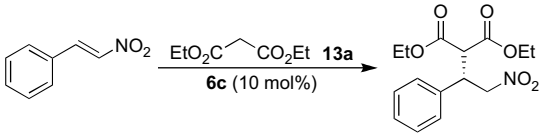
12a (*R*)-**14a**

Entry	Catalyst	Solvent	Time (h)	% Yield[a]	% ee[b,c]
1	Et_3N	Et_2O	144	26	—
2	**4**+Et_3N	Et_2O	144	56	—
3	**7**+Et_3N	Et_2O	144	62	—
4	**6a**	Et_2O	72	15	20
5	**6b**	CH_2Cl_2	72	5	50[d]
6	**6c**	CH_2Cl_2	72	7	72
7	**6d**	CH_2Cl_2	72	Trace	—
8	**8**	CH_2Cl_2	72	8	53

Reactions conditions: **12a** (1 equiv), **13a** (2 equiv), catalyst (0.1 equiv), solvent, rt.
[a] Isolated yield.
[b] Enantiomeric excess was determined by chiral HPLC analysis.
[c] Absolute configuration was determined by comparison of the specific rotation of **14a** with the literature value.[18a]
[d] Similar ee's for this catalyst were obtained in Et_2O.

These optimized reaction conditions were used in an exploration of the substrate scope of this reaction. More reactive β-nitrostyrenes (i.e., those substituted with electron-withdrawing groups) generated reduced yields of the desired product at elevated temperatures (entry 2, Table 3). This was due to the formation of byproducts arising from the incorporation of multiple β-nitrostyrene units. When reactions using these substrates were instead run at room temperature, byproduct formation was not observed, and yields up to 75% and ee's up to 79% were obtained (entries 1, 3, and 4). While substitution of the β-nitrostyrenes at the meta and

Table 2
Optimization of reaction conditions

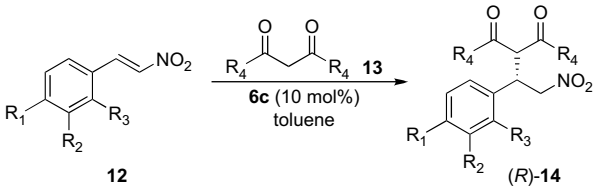


12a (*R*)-**14a**

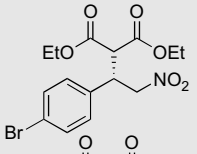
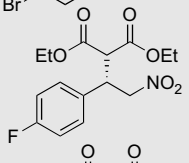
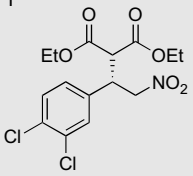
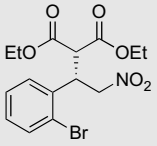
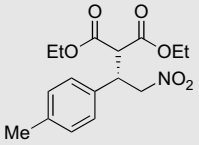
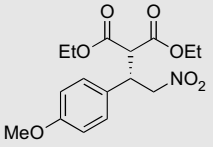
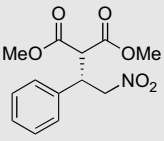
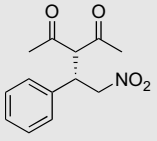
Entry	Solvent	Equiv **13a**	Time (h)	Temp (°C)	% Yield[a]	% ee[b,c]
1	MeCN	2	72	rt	4	47
2	CH_2Cl_2	2	72	rt	7	72
3	THF	2	72	rt	7	27
4	Et_2O	2	72	rt	15	65
5	Toluene	2	72	rt	13	70
6	—	2	72	rt	68	49
7	—	2	72	0	42	53
8	CH_2Cl_2	2	72	rt	16	60[d]
9	Toluene	2	72	rt	22	62[e]
10	Toluene	4	72	rt	20	66
11	Toluene	4	168	rt	45	68
12	Toluene	4	240	0	22	70
13	Toluene	6	168	rt	45	65
14	Toluene	10	168	rt	45	66
15	Toluene	4	240	rt	57	69
16	Toluene	2	168	50	66	64

Reactions conditions: **12a** (1 equiv), **13a**, **6c** (0.1 equiv), solvent, rt.
[a] Isolated yield.
[b] Enantiomeric excess was determined by chiral HPLC analysis.
[c] Absolute configuration was determined by comparison of the specific rotation of **14a** with the literature value.[18a]
[d] Compound **6c** (0.3 equiv) was used.
[e] Reaction concentration doubled.

Table 3
Investigation of substrate scope



12 (*R*)-**14**

Entry	**14**	Condition	Yield[a]	ee[b]
1	**14b** 	A	69	69[c]
2	**14b**	B	60	62
3	**14c** 	A	64	79[e]
4	**14d** 	A	75	77[d]
5	**14e** 	A	70	57[d]
6	**14f** 	B	51	66[c]
7	**14g** 	B	56	64[c]
8	**14h** 	B	69	63[c]
9	**14i** 	A	91	49[c]

Reactions conditions A: **12** (1 equiv), **13** (4 equiv), **6c** (0.1 equiv), toluene, rt, 240 h.
Reaction conditions B: **12** (1 equiv), **13** (2 equiv), **6c** (0.1 equiv), toluene, 50 °C, 168 h.
[a] Isolated yield.
[b] Enantiomeric excess was determined by chiral HPLC analysis.
[c] Absolute configuration was determined by comparison of the specific rotation of the products with the literature value.[18]
[d] Absolute configuration was not determined.
[e] Absolute configuration was *S* by comparison of the specific rotation of **14c** with the literature value.[18a]

para positions was well tolerated, ortho substitution resulted in a loss of enantioselectivity (entry 5). Reactions of more electron-rich β-nitrostyrenes also provided products in good ee, but slightly reduced yields (entries 6 and 7). The addition of **13a** to even less reactive, alkyl-substituted nitroalkenes, using either reaction condition A or B, led to product formation in up to 58% ee, but in yields no greater than 12%.[19] The conjugate addition of dimethyl malonate to β-nitrostyrene afforded the desired product in a good yield and ee (entry 8). Analogous to what was observed with more reactive electrophiles, the more reactive 2,4-pentanedione generated reduced yields of the desired product due to the formation of byproducts at elevated temperatures.[19] When this reaction was instead run at room temperature, the product was obtained in 91% yield, but only moderate ee (entry 9).

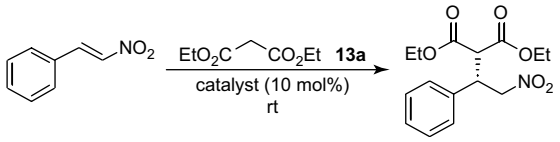
Although the design of these organocatalysts was derived from bissulfonamide **4**, the former do not necessarily function like the latter (i.e., as double hydrogen bond donors). To gain insight into the role of the catalysts' sulfonamide protons in this reaction, the interaction of **7** with **12a** was examined in titration experiments using ^{1}H NMR. Bissulfonamide **7** was chosen for investigation because it incorporates a mixed aryl/alkyl sulfonamide system similar to that of the optimal catalyst, and its two sulfonamide protons have distinct chemical shifts. Using rigorously dried deuterated solvent, in the absence of **12a**, the *N*-aryl sulfonamide proton appeared as a sharp singlet at 7.50 ppm and the *N*-alkyl sulfonamide proton appeared as a sharp doublet at 4.82 ppm (entry 1, Table 4). With an increasing ratio of **12a** to **7**, the *N*-aryl sulfonamide proton gradually shifted downfield and broadened, while the *N*-alkyl sulfonamide proton remained unchanged. When the ratio of **12a** to **7** was 4:1, the *N*-aryl sulfonamide proton appeared as a broad singlet at 7.55 ppm (entry 2, Table 4). This subtle shift downfield, in combination with peak broadening, is consistent with hydrogen bond donation of the *N*-aryl sulfonamide moiety and is comparable to what Takemoto and co-workers observed with C_2-symmetric aryl thioureas in the presence of β-nitrostyrene.[4a]

Further evidence in support of a role for hydrogen bonding in this reaction was provided by synthetic experimental data, both already acquired and new. By comparing entries 5 and 6 in Table 1, enhancing the acidity of the sulfonamide N–H bond appears to improve the chiral induction of the catalyst. A correlation between catalyst acidity and reaction enantioselectivity has been observed in other hydrogen bonding organocatalysts.[12b] Additionally, the fact that the highest yields and ee's were obtained in non-polar and non-coordinating solvents, respectively, is consistent with a neutrally charged, hydrogen bonding transition state (entries 1–5, Table 2). Furthermore, when methanol was the reaction solvent, the products were generated in a 2.7-fold increased yield, but as a nearly racemic mixture (entry 1, Table 5 vs entry 6, Table 1). Presumably, methanol accelerated the reaction through hydrogen bond donation to β-nitrostyrene; this interfered with the interaction of this substrate with the catalyst that is necessary for the enantioselectivity of this reaction. Moreover, catalysts **9** and **10**, which lack a second N–H bond, generated products in substantially diminished yields and reduced enantioselectivies (entries 2 and 3, Table 5 vs entries 5, 6, and 8, Table 1). Thus, the acidic *N*-aryl sulfonamide appears to be necessary for both reaction yield and maximum ee's.

Table 4
^{1}H NMR mechanistic investigations

Entry	Catalyst	^{1}H NMR (CH_2Cl_2, 0.13 M)	Equiv **12a**
1	**7**	7.50 (s, 1H, N_{ARYL}–H) 4.82 (d, J=7.8 Hz, 1H, N_{AKLYL}–H)	0
2	**7**	7.55 (br s, 1H, N_{ARYL}–H) 4.82 (d, J=7.8 Hz, 1H, N_{AKLYL}–H)	4
3	**6c**	6.50 (br s, 2H, N_{ARYL}–H and N_{ALKYL}–H)	0

Table 5
Synthetic mechanistic investigations



12a (*R*)-**14a**

Entry	Catalyst	Solvent	Time (h)	% Yield[a]	% ee[b,c]
1	**6c**	MeOH	72	35	5
2	**9**	CH_2Cl_2	72	<2	41
3	**10**	CH_2Cl_2	72	<2	nd
4	**7**	THF	144	nr	—
5	Et_3N	THF	144	48	—
6	Et_3N+**7**	THF	144	69	—
7	**11**	THF	144	21	—

Reactions conditions: **12a** (1 equiv), **13a** (2 equiv), catalyst (0.1 equiv), solvent, rt.
[a] Isolated yield.
[b] Enantiomeric excess was determined by chiral HPLC analysis.
[c] Absolute configuration was determined by comparison of the specific rotation of **14a** with the literature value.[18a]

In addition to the acidic *N*-aryl sulfonamide, the basic moiety is also necessary for reaction yield, as hydrogen bonding alone does not promote this reaction (entry 4, Table 5). Interestingly, however, catalyst **11** provided the product in reduced yields relative to both the bissulfonamide that was not tethered to a tertiary amine as well as to the uncatalyzed reaction (entries 5–7, Table 5). It is possible that this is the result of sterics, and that tethering the tertiary amine to the catalyst hinders the association with β-nitrostyrene. It is also plausible that there is an intramolecular hydrogen bond, or a formal proton transfer, between the sulfonamides and the tertiary amine. Indeed, there is a pronounced difference in the chemical shifts and peak shapes of the *N*-alkyl and *N*-aryl sulfonamide protons of catalyst **7**, where such intramolecular interactions are not possible, and those of catalyst **6c** (entries 1 vs 3, Table 4). Moreover, the fact that both sulfonamide protons are chemically equivalent in **6c** suggests that they are both tied up in an intramolecular interaction with the tertiary amine, which may be hampering catalytic activity.

3. Conclusion

In conclusion, a novel sulfonamide organocatalyst, **6c**, has been developed. The data suggests this catalyst is indeed bifunctional, using at least its most acidic proton to activate **12** through hydrogen bonding, and using its basic moiety to activate **13**. The data also suggests it might be possible to improve upon the activity of this catalyst system by altering the tether length, or type, of the basic moiety. These investigations are presently underway.

The novel catalyst systems described herein serve to demonstrate that new structural and functional motifs can be employed in bifunctional hydrogen bonding catalysts. Ultimately, expanding the structural and functional motifs used in this class of catalysts may further enhance their utility in organic synthesis.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR data use the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets, td=triplet of doublets, dt=doublet of triplets. Enantiomer

ratios were determined using an HPLC with Daicel Chemical Industries, LTD. Chiralpak AD-H (0.46×25 cm) and Chiralpak OD-H (0.46×25 cm) columns. Chromatography was carried out with Merck, grade 9385, 230–400 mesh, 600 Å silica gel and with Merck, silica 60F_{254} on glass, 250 um layer TLC plates with fluorescent indicator. Solvents were dried and kept air free in a solvent purification unit. Solvents were evaporated using a standard rotovapor and a high vacuum. All reactions were carried out in oven dried glassware and conducted under an argon atmosphere.

4.2. Preparation of catalysts

Catalysts were prepared according to a modified procedure.[16]

4.2.1. N^1,N^3-Diphenylbenzene-1,3-disulfonamide **4**[9]

Yellow amorphous solid; ^{1}H NMR (400 MHz, CD_3CN) δ 8.13 (m, 1H), 8.02 (br s, 2H), 7.86 (dt, J=2.3, 7.8 Hz, 2H), 7.57 (td, J=2.4, 7.8 Hz, 1H), 7.27–7.20 (m, 4H), 7.13 (m, 2H), 7.00 (m, 4H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 141.5, 137.6, 132.2, 131.3, 130.4, 126.7, 126.6, 122.7 ppm.

4.2.2. N^1-((1R,2R)-2-(Dimethylamino)-1,2-diphenylethyl)-N^3-phenylbenzene-1,3-disulfonamide **6a**

Colorless amorphous; $[\alpha]_D^{28}$ +128.5 (c 1.03, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (t, J=1.8 Hz, 1H), 7.61 (d, J=7.8 Hz, 1H), 7.49 (d, J=7.8 Hz, 1H), 7.31–7.23 (m, 2H), 7.23–7.12 (m, 5H), 7.08–7.03 (m, 2H), 7.00–6.94 (m, 2H), 6.89–6.76 (m, 5H), 4.76 (d, J=11.1 Hz, 1H), 3.57 (d, J=11.1 Hz, 1H), 2.16 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 139.9, 137.0, 136.1, 131.3, 130.9, 130.3, 129.9, 129.6, 129.1, 128.7, 128.0, 128.0, 127.6, 126.3, 126.1, 122.2, 73.1, 57.6, 40.3 ppm; IR (film) ν 3256, 2933, 2790, 1593, 1348, 1176, 1148 cm^{-1}; HRMS calcd for $C_{28}H_{29}N_3O_4S_2$ (M^+) 535.1600, obsd 535.1608.

4.2.3. N^1-((1R,2R)-2-(Dimethylamino)cyclohexyl)-N^3-phenylbenzene-1,3-disulfonamide **6b**

Colorless amorphous; $[\alpha]_D^{28}$ −61.6 (c 1.03, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.95 (d, J=7.1 Hz, 1H), 7.83 (s, J=7.1 Hz, 1H), 7.47 (t, J=7.3 Hz, 1H), 7.19–6.95 (m, 5H), 6.52 (s, 2H), 2.53 (m, 1H), 2.11 (m, 1H), 2.03 (t, J=11.1 Hz, 1H), 1.77 (s, 6H), 1.63 (m, 2H), 1.50 (m, 1H), 1.02 (m, 3H), 0.84 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 140.6, 136.1, 131.4, 131.0, 129.9, 129.6, 126.3, 126.0, 122.1, 66.4, 54.4, 39.7, 32.7, 25.0, 24.3, 21.2 ppm; IR (film) ν 2925, 2852, 1597, 1454, 1344, 1180, 1152, 1111, 1082 cm^{-1}; HRMS calcd for $C_{20}H_{27}N_3O_4S_2$ (M^+) 437.1443, obsd 437.1450.

4.2.4. N^1-(3,5-Bis(trifluoromethyl)phenyl)-N^3-((1R,2R)-2-(dimethylamino)cyclohexyl)benzene-1,3-disulfonamide **6c**

Colorless amorphous; $[\alpha]_D^{27}$ −32.4 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.07 (d, J=7.8 Hz, 1H), 7.97 (d, J=7.8 Hz, 1H), 7.58 (t, J=7.8 Hz, 1H), 7.55 (s, 2H), 7.35 (s, 1H), 7.32 (br s, 2H), 3.04 (m, 1H), 2.74 (m, 1H), 2.32 (s, 6H), 1.81 (m, 1H), 1.69 (m, 2H), 1.37 (m, 1H), 1.18–0.85 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 145.4, 135.4, 135.1, 134.7, 134.4, 133.7, 132.2, 132.1, 128.8, 126.8, 124.0, 122.5, 117.1, 66.6, 52.8, 38.1, 30.4, 21.9, 21.7, 19.4 ppm; IR (film) ν 2921, 2852, 1609, 1466, 1381, 1176, 1131, 1012 cm^{-1}; HRMS calcd for $C_{22}H_{25}F_6N_3O_4S_2$ (M^+) 573.1191, obsd 573.1202.

4.2.5. (R)-N^1-(2′-(Dimethylamino)-1,1′-binaphthyl-2-yl)-N^3-phenylbenzene-1,3-disulfonamide **6d**

White crystals; mp 194–197 °C; $[\alpha]_D^{27}$ −207.2 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.99 (s, 2H), 7.91 (m, 2H), 7.74 (m, 1H), 7.66 (d, J=8.1 Hz, 1H), 7.47 (d, J=9.1 Hz, 1H), 7.43 (t, J=7.6 Hz, 1H), 7.18 (t, J=7.8 Hz, 1H), 7.13 (t, J=7.3 Hz, 1H), 7.07–6.94 (m, 5H), 6.88 (d, J=7.8 Hz, 1H), 6.82 (m, 2H), 6.63 (t, J=7.8 Hz, 1H), 6.38 (s, 1H), 6.35 (t, J=7.8 Hz, 1H), 6.02 (d, J=8.8 Hz, 1H), 2.61 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 140.9, 138.9, 135.8, 133.8, 133.7, 132.3, 131.3, 130.8, 130.2, 129.5, 129.5, 129.4, 129.2, 128.8, 128.5, 128.4, 127.9, 127.2, 126.9, 126.7, 125.9, 125.6, 125.1, 124.9, 124.0, 123.6, 122.5, 122.2, 118.0, 43.7 ppm; IR (film) ν 3264, 3060, 2843, 2795, 1589, 1348, 1180, 1156 cm^{-1}; HRMS calcd for $C_{34}H_{29}N_3O_4S_2$ (M^+) 607.1600, obsd 607.1599.

4.2.6. N^1-(3,5-Bis(trifluoromethyl)phenyl)-N^3-cyclohexylbenzene-1,3-disulfonamide **7**

Colorless amorphous; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (t, J=1.5 Hz, 1H), 8.12 (dt, J=1.5, 7.8 Hz, 1H), 7.89 (dt, J=1.5, 7.8 Hz, 1H), 7.63 (t, J=7.8 Hz, 1H), 7.61 (s, 3H), 5.27 (d, J=7.6 Hz, 1H), 3.17 (m, 1H), 1.74–1.45 (m, 5H), 1.31–1.04 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 140.1, 138.1, 133.7, 133.3, 133.0, 132.7, 131.7, 131.0, 130.3, 125.9, 120.9, 119.1, 53.4, 33.9, 25.1, 24.6 ppm; IR (film) ν 3277, 2933, 2856, 1377, 1279, 1136 cm^{-1}; HRMS calcd for $C_{20}H_{20}F_6N_2O_4S_2$ (M^+) 530.0769, obsd 530.0765.

4.2.7. N^1,N^3-Bis((1R,2R)-2-(dimethylamino)cyclohexyl)benzene-1,3-disulfonamide **8**

White crystals; mp 167–170 °C; $[\alpha]_D^{27}$ −144.0 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (t, J=1.8 Hz, 1H), 7.99 (dd, J=1.8, 7.8 Hz, 2H), 7.58 (t, J=7.8 Hz, 1H), 6.03 (br s, 2H), 2.59 (m, 2H), 2.23 (m, 2H), 2.05 (td, J=3.0, 11.9 Hz, 2H), 1.97 (s, 12H), 1.66 (m, 4H), 1.54 (m, 2H), 1.18–0.98 (m, 6H), 0.97–0.83 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 130.9, 129.7, 126.1, 66.3, 54.3, 39.7, 32.6, 25.0, 24.2, 21.1 ppm; IR (film) ν 3191, 2993, 2860, 2782, 1454, 1344, 1180, 1157, 1086, 1042 cm^{-1}; HRMS calcd for $C_{22}H_{38}N_4O_4S_2$ (M^+) 486.2335, obsd 486.2342.

4.2.8. N-((1R,2R)-2-(Dimethylamino)cyclohexyl)-benzenesulfonamide **9**

White crystals; mp 77–82 °C; $[\alpha]_D^{27}$ −118.4 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.56–7.42 (m, 3H), 5.99 (br s, 1H), 2.56 (td, J=4.0, 10.6 Hz, 1H), 2.35 (m, 1H), 2.09 (td, J=3.8, 10.4 Hz, 1H), 1.85 (s, 6H), 1.68 (m, 2H), 1.58 (m, 1H), 1.30–1.01 (m, 3H), 0.93 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 132.5, 129.0, 127.4, 66.4, 54.2, 39.7, 32.8, 25.2, 24.3, 21.1 ppm; IR (film) ν 3199, 2933, 2860, 2786, 1720, 1446, 1340, 1164, 1091 cm^{-1}; HRMS calcd for $C_{14}H_{22}N_2O_2S$ (M^+) 282.1402, obsd 282.1407.

4.2.9. N^1-((1R,2R)-2-(Dimethylamino)cyclohexyl)-N^3-methyl-N^3-phenylbenzene-1,3-disulfonamide **10**

Colorless amorphous; $[\alpha]_D^{27}$ −79.4 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (t, J=1.5 Hz, 1H), 8.09 (dt, J=1.5, 7.6 Hz, 1H), 7.64 (dt, J=1.5, 7.6 Hz, 1H), 7.58 (t, J=7.6 Hz, 1H), 7.38–7.27 (m, 3H), 7.07 (m, 2H), 3.21 (s, 3H), 2.66 (td, J=4.0, 10.4 Hz, 1H), 2.26 (m, 1H), 2.13 (td, J=4.0, 10.4 Hz, 1H), 1.95 (s, 6H), 1.74 (m, 2H), 1.62 (m, 1H), 1.39–0.75 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 141.0, 138.3, 131.4, 131.2, 129.6, 129.3, 127.9, 126.8, 126.6, 66.4, 54.4, 39.7, 38.6, 32.6, 25.1, 24.3, 21.1 ppm; IR (film) ν 2933, 2860, 2782, 1491, 1450, 1356, 1185, 1152, 1074 cm^{-1}; HRMS calcd for $C_{21}H_{29}N_3O_4S_2$ (M^+) 451.1600, obsd 451.1609.

4.2.10. N^1-(3,5-Bis(trifluoromethyl)phenyl)-N^3-(2-(dimethylamino)ethyl)benzene-1,3-disulfonamide **11**

White crystals; mp 158–162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (m, 1H), 8.04 (d, J=7.8 Hz, 1H), 7.94 (d, J=7.8 Hz, 1H), 7.63 (s, 2H), 7.60 (t, J=7.8 Hz, 1H), 7.52 (s, 1H), 5.83 (br s, 2H), 3.06 (t, J=5.8 Hz, 2H), 2.62 (t, J=5.8 Hz, 2H), 2.32 (s, 6H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 144.4, 143.4, 142.3, 133.3, 133.0, 132.7, 132.3, 131.8, 131.6, 131.4, 126.4, 122.2, 116.8, 58.2, 44.8, 40.6 ppm; IR (film) ν 1610, 1642, 1373, 1274, 1168, 1127, 1021 cm^{-1}; HRMS calcd for $C_{18}H_{19}F_6N_3O_4S_2$ (M^+) 519.0721, obsd 519.0723.

4.3. General procedure for enantioselective catalysis of Michael addition of 1,3-dicarbonyl compounds to nitroolefins and characterization

4.3.1. Condition A

To an oven dried flask under an argon atmosphere were added dicarbonyl **13** (2.0 mmol), toluene (1.0 mL), and β-nitrostyrene **12** (0.5 mmol) at room temperature. The disulfonamide catalyst (0.05 mmol, 28.7 mg) was added and reaction was allowed to stir at room temperature for 240 h. The reaction mixture was purified via column chromatography on silica gel (petroleum ether/EtOAc 9:1 as eluent) to give the desired product **14**.

4.3.2. Condition B

To an oven dried flask under an argon atmosphere were added dicarbonyl **13** (1.0 mmol), toluene (1.0 mL), and β-nitrostyrene **12** (0.5 mmol) at room temperature. The disulfonamide catalyst (0.05 mmol, 28.7 mg) was added and reaction was allowed to stir in an oil bath at 50 °C for 168 h. The reaction mixture was cooled to room temperature and purified via column chromatography on silica gel (petroleum ether/EtOAc 9:1 as eluent) to give the desired product **14**.

4.3.3. (R)-Diethyl 2-(2-nitro-1-phenylethyl)malonate ***14a*** [18a]

Colorless oil; $[\alpha]_D^{27}$ −4.6 (*c* 1.00, $CHCl_3$, 69% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.21 (m, 5H), 4.90 (m, 2H), 4.23 (m, 3H), 4.01 (q, *J*=7.1 Hz, 2H), 3.83 (d, *J*=9.4 Hz, 1H), 1.27 (t, *J*=7.1 Hz, 3H), 1.05 (t, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 166.9, 136.5, 129.1, 128.5, 128.2, 77.8, 62.2, 62.0, 55.2, 43.1, 14.1, 13.8 ppm; HPLC [Chiralcel AD-H, hexane/ethanol=95:5, 1.0 mL/min, λ=254 nm, retention times: (*R*) (major) 14.4 min, (*S*) (minor) 18.8 min].

4.3.4. (R)-Diethyl 2-(1-(4-bromophenyl)-2-nitroethyl)-malonate ***14b*** [18c]

White solid; mp 56–57 °C; $[\alpha]_D^{28}$ −6.8 (*c* 1.00, $CHCl_3$, 69% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J*=8.6 Hz, 2H), 7.13 (d, *J*=8.6 Hz, 2H), 4.86 (m, 2H), 4.22 (m, 3H), 4.04 (q, *J*=7.1 Hz, 2H), 3.77 (d, *J*=9.4 Hz, 1H), 1.27 (t, *J*=7.1 Hz, 3H), 1.09 (t, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 166.7, 135.5, 132.2, 129.9, 122.5, 77.4, 62.3, 62.1, 54.8, 42.5, 14.0, 13.8 ppm; HPLC [Chiralcel AD-H, hexane/2-propanol=90:10, 1.0 mL/min, λ=254 nm, retention times: (*R*) (major) 21.7 min, (*S*) (minor) 57.3 min].

4.3.5. (S)-Diethyl 2-(1-(4-fluorophenyl)-2-nitroethyl)-malonate ***14c*** [18a]

Colorless oil; $[\alpha]_D^{28}$ −4.9 (*c* 1.00, $CHCl_3$, 79% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 2H), 7.01 (t, *J*=8.6 Hz, 2H), 4.87 (m, 2H), 4.23 (m, 3H), 4.03 (q, *J*=7.1 Hz, 2H), 3.78 (d, *J*=9.3 Hz, 1H), 1.27 (t, *J*=7.3 Hz, 3H), 1.08 (t, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 166.8, 130.0, 129.9, 116.1, 115.9, 77.8, 62.3, 62.1, 55.1, 42.5, 14.1, 13.9 ppm; HPLC [Chiralcel AD-H, hexane/ethanol=95:5, 1.0 mL/min, λ=254 nm, retention times: (S) (major) 21.0 min, (*R*) (minor) 31.8 min].

4.3.6. Diethyl 2-(1-(3,4-dichlorophenyl)-2-nitroethyl)malonate ***14d***

White solid; mp 59–60 °C; $[\alpha]_D^{28}$ 1.1 (*c* 1.00, $CHCl_3$, 77% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J*=8.3 Hz, 1H), 7.36 (d, *J*=2.0 Hz, 1H), 7.11 (dd, *J*=2.0, 8.3 Hz, 1H), 4.87 (m, 2H), 4.22 (m, 3H), 4.08 (q, *J*=7.3 Hz, 2H), 3.76 (d, *J*=8.8 Hz, 1H), 1.27 (t, *J*=7.1 Hz, 3H), 1.13 (t, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 166.6, 136.8, 133.3, 132.9, 131.0, 130.4, 127.6, 77.2, 62.5, 62.3, 54.8, 42.2, 14.1, 13.9 ppm; IR (film) ν 3412, 2983, 2929, 1728, 1552, 1471, 1176, 1152, 1033 cm^{-1}; HRMS calcd for $C_{15}H_{17}Cl_2NO_6$ (M^+) 377.0433, obsd 377.0441; HPLC [Chiralcel AD-H, hexane/2-propanol=90:10, 1.0 mL/min, λ=254 nm, retention times: (major) 20.8 min, (minor) 27.9 min].

4.3.7. Diethyl 2-(1-(2-bromophenyl)-2-nitroethyl)malonate ***14e*** [4a]

Orange oil; $[\alpha]_D^{28}$ −5.5 (*c* 1.00, $CHCl_3$, 57% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J*=7.8 Hz, 1H), 7.28–7.12 (m, 3H), 5.12 (m, 1H), 4.94 (dd, *J*=4.3, 13.6 Hz, 1H), 4.75 (m, 1H), 4.32–4.01 (m, 5H), 1.24 (t, *J*=7.1 Hz, 3H), 1.13 (t, *J*=7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 166.9, 135.7, 134.0, 129.8, 128.7, 128.0, 125.0, 75.9, 62.2, 62.2, 53.5, 41.7, 14.1, 13.9 ppm; HPLC [Chiralcel OD-H, hexane/2-propanol=95:5, 1.0 mL/min, λ=254 nm, retention times: (minor) 15.4 min, (major) 21.8 min].

4.3.8. (R)-Diethyl 2-(2-nitro-1-p-tolylethyl)malonate ***14f*** [18c]

Colorless oil; $[\alpha]_D^{28}$ −3.3 (*c* 1.00, $CHCl_3$, 66% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 4H), 4.86 (m, 2H), 4.21 (m, 3H), 4.02 (q, *J*=7.1 Hz, 2H), 3.80 (d, *J*=9.4 Hz, 1H), 2.30 (s, 3H), 1.26 (t, *J*=7.6 Hz, 3H), 1.07 (t, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 167.0, 138.1, 133.4, 129.7, 128.0, 77.9, 62.1, 61.9, 55.2, 42.8, 21.12, 14.1, 13.8 ppm; HPLC [Chiralcel AD-H, hexane/2-propanol=95:5, 1.0 mL/min, λ=254 nm, retention times: (*R*) (major) 20.8 min, (*S*) (minor) 53.1 min].

4.3.9. (R)-Diethyl 2-(1-(4-methoxyphenyl)-2-nitroethyl)-malonate ***14g*** [18c]

Yellow oil; $[\alpha]_D^{28}$ −4.9 (*c* 1.00, $CHCl_3$, 64% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J*=8.6 Hz, 2H), 6.83 (d, *J*=8.6 Hz, 2H), 4.85 (m, 2H), 4.20 (m, 3H), 4.02 (q, *J*=7.1 Hz, 2H), 3.77 (m, 4H), 1.27 (t, *J*=7.1 Hz, 3H), 1.08 (t, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 167.0, 159.6, 129.3, 128.2, 114.4, 78.0, 62.2, 61.9, 55.3, 55.3, 42.5, 14.1, 13.9 ppm; HPLC [Chiralcel AD-H, hexane/ethanol=90:10, 1.0 mL/min, λ=254 nm, retention times: (*R*) (major) 21.8 min, (*S*) (minor) 34.0 min].

4.3.10. (R)-Dimethyl 2-(2-nitro-1-phenylethyl)malonate ***14h*** [18a]

White solid; mp 53–54 °C; $[\alpha]_D^{28}$ −4.6 (*c* 1.00, $CHCl_3$, 63% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.2 (m, 5H), 4.91 (m, 2H), 4.25 (td, *J*=5.3, 8.8 Hz, 1H), 3.87 (d, *J*=9.1 Hz, 1H), 3.76 (s, 3H), 3.56 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 167.3, 136.3, 129.1, 128.5, 128.0, 77.5, 54.9, 53.0, 52.8, 43.0 ppm; HPLC [Chiralcel AD-H, hexane/2-propanol=95:5, 1.0 mL/min, λ=254 nm, retention times: (*R*) (major) 26.2 min, (*S*) (minor) 40.8 min].

4.3.11. (R)-3-(2-Nitro-1-phenylethyl)pentane-2,4-dione ***14i*** [18b]

White solid; mp 110–111 °C; $[\alpha]_D^{28}$ −95.4 (*c* 1.00, $CHCl_3$, 49% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.27 (m, 3H), 7.19 (m, 2H), 4.63 (m, 2H), 4.37 (d, *J*=10.9 Hz, 1H), 4.24 (m, 1H), 2.30 (s, 3H), 1.94 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 201.1, 136.3, 129.5, 128.7, 128.1, 78.3, 70.9, 43.0, 30.5, 29.7 ppm; HPLC [Chiralcel AD-H, hexane/2-propanol=95:5, 1.0 mL/min, λ=254 nm, retention times: (*S*) (minor) 18.2 min, (*R*) (major) 25.6 min].

4.4. NMR experiments

Measurements were carried out using a Bruker 400 MHz NMR Spectrometer. CD_2Cl_2 99.9% D was dried over molecular sieves, 4 Å, 1.6 mm pellets in a glove box for 4–5 days. Samples were prepared in a glove box with both vacuum dried catalyst and β-nitrostyrene using oven dried glassware and needles. NMR samples (0.5 mL) were prepared from a 13.4 mM catalyst stock solution to which were added a proportionate amount of β-nitrostyrene.[4a]

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.11.027.

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