Highly Enantioselective Michael Addition of Ketones and an Aldehyde to Nitroalkenes Catalyzed by a Binaphthyl Sulfonimide in Water

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Abstract: A binaphthyl sulfonimide organocatalyst was used to promote highly enantioselective and diastereoselective Michael addition reactions of ketones to nitroalkenes in water. In most cases, the products were obtained in good yields with excellent enantioselectivities and diastereoselectivities (93–97% ee, up to >99:1 dr). The catalyst could also be used in an asymmetric Michael addition of isobutyraldehyde to nitroalkenes to give the desired products in moderate yields and moderate enantioselectivities (up to 83% ee).

Key words: asymmetric catalysis, organocatalysis, Michael additions, nitroalkenes, sulfonimides

Asymmetric organocatalysis of Michael addition reaction is, without doubt, one of the most general and versatile methods for the construction of C–C bonds in organic synthesis.[1] As a result, this reaction has attracted the interest of many organic chemists who have produced some good results.[2] Recently, asymmetric Michael reactions that take place in environmentally clean, safe, and cheap solvents, such as water,[3] brine,[4] or ionic liquids,[5] have been the subject of considerable development. Compared with typical organic solvents, water as a solvent for this reaction has many advantages in that it is nontoxic, environmentally benign, cheap, and can be safely handled. Organic reactions in aqueous media have been reviewed by Li, with particular attention to the formation of C–C bonds.[6] Despite the excellent results reported in this area, the design and development of organocatalytic enantioselective reactions that take place in water remain as major challenges.

We recently prepared the L-proline-based binaphthyl sulfonimides and sulfonamides **1a–d** (Figure 1) as highly efficient and stereoselective organocatalysts for the asymmetric Michael addition of ketones to nitroalkenes in the presence of benzoic acid in organic solvents.[7] With regard to asymmetric organocatalysis of Michael addition reaction in aqueous media, Lin has reported several new types of organocatalysts bearing sulfide or sulfone functions that are suitable for highly stereoselective Michael addition of ketones to nitroalkenes in water.[3e] He speculated that the oxygen of the sulfone functionality in combination with a protic solvent, such as water, provides a hydrogen-bonding interaction that leads to an improvement in both reactivity and stereoselectivity in the asymmetric Michael addition. Singh hypothesized that when the reaction is performed in an aqueous medium, hydrophobic hydration should be enhanced by a binaphthyl group and, because of the aromatic nature of this group, that this should also work in an organic medium.[4b] We therefore hypothesized that catalysts **1a–d** should also act as water-soluble organocatalysts, and we attempted to apply them in catalyzing the Michael addition of ketones to nitroalkenes in water.

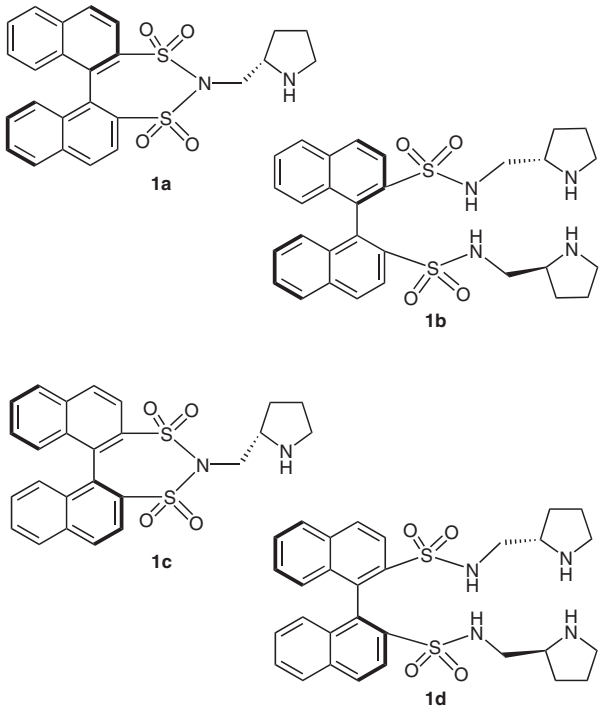

Figure 1 Binaphthyl sulfonimide and sulfonamide organocatalysts **1a–d**

To our surprise, the (*R*)-1,1′-binaphthyl-derived catalyst **1a** showed interesting results in the catalytic asymmetric Michael addition of cyclohexanone (**2**) with [(*E*)-2-nitrovinyl]benzene (**3a**) in water. Cyclohexanone (**2**) (1.0 mmol) reacted with [(*E*)-2-nitrovinyl]benzene (**3a**) (0.2 mmol) in the presence of the catalyst **1a** (10 mol%) in water (0.2 mL at room temperature to give the desired adduct **4a** in 95% yield with 95% ee and 99:1 dr within 12 hours (Table 1, entry 1).

Encouraged by these results, we attempted to optimize the reaction conditions. With the catalyst **1a–d** in hand, the

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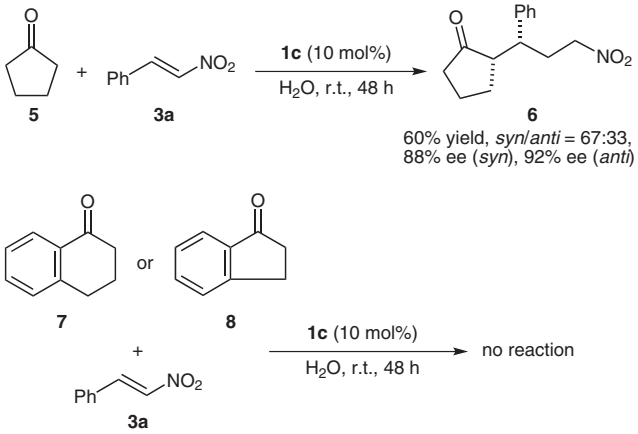
effects of the solvent, additive, and reaction time on the outcome of the reaction were thoroughly investigated, and the results are summarized in Table 1. Initially, the reaction was performed by using 10 mol% of **1a** in water or brine. It has been reported that the addition of an acid to the Michael reaction system can improve chemical yields by accelerating the formation of the enamine.[8] However, the reaction rate, yield, and enantiomeric excess were decreased when acids such as 2-nitrobenzoic acid (entry 7; 93% ee, 98:2 dr), 4-toluenesulfonic acid (entry 3; 91% ee, 97:3 dr), or benzoic acid (entry 4; 93% ee, 98:2 dr) was added. No product was obtained in the presence of trifluoroacetic acid (entry 2). Furthermore, the results of the reaction were not improved by using brine instead of water (entries 1 and 6). Therefore, the other chiral catalysts **1b–d** were screened by using water as solvent without an additive (entries 8–10). Catalysts **1a–d** facilitated the asymmetric Michael addition reaction with good-to-excellent stereoselectivities and yields. Sulfonimides **1a** and **1c** produced slight higher enantioselectivities than did sulfonamides **1b** and **1d**. Catalyst **1c** gave the best results, with a 96% yield and 96% ee (entry 9) of the *syn* diastereomer (99:1 dr).

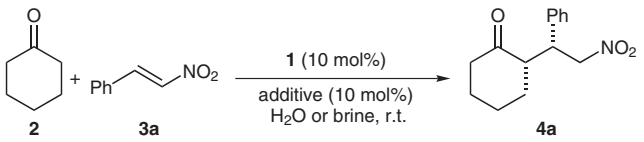
The excellent catalytic ability of the organocatalyst **1c** was confirmed by further studies, and the results are summarized in Table 2. They show that various aromatic nitroalkenes **3a–l** react smoothly with cyclohexanone (**2**) in the presence of catalyst **1c** (10 mol%) in water, leading to the corresponding adducts **4a–l** in moderate-to-excellent yields and excellent diastereoselectivities and enantioselectivities. A slight influence on the reactivity was observed in the reactions of cyclohexanone (**2**) and nitroalkenes with a *para*-oriented electron-withdrawing or electron-donating substituents on the aromatic rings, such as **3f**, which afforded the corresponding adduct **4f** within 48 hours. Interestingly, the rate and enantioselectivity of this this reaction were better in water than in organic solvents.[7]

The reactions of other ketones (cyclopentanone, 1-tetralone, indan-1-one, and acetone) were also carried out in the presence of catalyst **1c** (Scheme 1). The reaction of cyclopentanone with [(*E*)-2-nitrovinyl]benzene (**3a**) in water gave the corresponding product **6** in a higher yield



Scheme 1 Further studies on the scope of substrates for the Michael addition of ketones to (*E*)-2-nitrovinyl]benzene (**3a**)

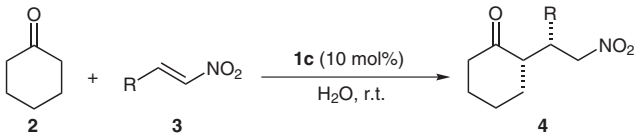
Table 1 Optimization of Solvents, Additives, and Catalysts



Entry[a]	Catalyst	Additive	Solvent	Time (h)	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%)
1	**1a**	–	H_2O	12	95	99:1	95
2	**1a**	CF_3CO_2H	H_2O	24	0	–	–
3	**1a**	TsOH	H_2O	12	90	97:3	91
4	**1a**	$PhCO_2H$	H_2O	12	94	98:2	93
5	**1a**	$PhCO_2H$	brine	12	94	98:2	93
6	**1a**	–	brine	12	90	97:3	93
7	**1a**	$2\text{-}O_2NC_6H_4CO_2H$	H_2O	12	93	98:2	93
8	**1b**	–	H_2O	12	92	97:3	92
9	**1c**	–	H_2O	12	96	99:1	96
10	**1d**	–	H_2O	12	90	98:2	94

[a] All reactions were carried out by using cyclohexanone (**2**; 98 mg, 1.0 mmol), the additive (10 mol%), and catalyst **1** (10 mol%) in H_2O or brine (0.2 mL). The mixture were stirred at r.t. for 15 min, then [(*E*)-2-nitrovinyl]benzene (**3a**; 29.8 mg, 0.20 mmol) was added.
[b] Yield of the isolated product after chromatography on silica gel.
[c] Determined by chiral HPLC on a Chiracel AS-H column with hexane and *i*-PrOH as eluents.
[d] Determined by chiral HPLC analysis.

Table 2 Catalytic Asymmetric Michael Addition of Cyclohexanone to Nitroalkenes



Entry[a]	R	Time (h)	Product	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%)
1	Ph	12	**4a**	96	99:1	96
2	2-$MeOC_6H_4$	24	**4b**	94	96:4	95
3	2-ClC_6H_4	24	**4c**	91	>99:1	97
4	4-ClC_6H_4	24	**4d**	88	>99:1	96
5	4-FC_6H_4	24	**4e**	80	98:2	97
6	4-MeC_6H_4	48	**4f**	85	>99:1	97
7	4-BrC_6H_4	24	**4g**	90	99:1	95
8	3-$O_2NC_6H_4$	24	**4h**	85	98:2	97
9	3-BrC_6H_4	24	**4i**	85	97:3	96
10	3,4-$(MeO)_2C_6H_3$	48	**4j**	60	98:2	93
11	2-thienyl	48	**4k**	65	>99:1	94
12	2-furyl	48	**4l**	68	98:2	95

[a] All the reactions were carried out by using cyclohexanone (**2**; 100 mg, 1.0 mmol) and catalyst **1c** (10 mol%) in H_2O (0.2 mL). The mixture was stirred at r.t. for 15 min, then nitroalkene **3** (0.20 mmol) was added.
[b] Yield of the isolated product after chromatography on silica gel.
[c] Determined by chiral HPLC.
[d] Determined by chiral HPLC analysis; the configuration was assigned according to the literature.[2]

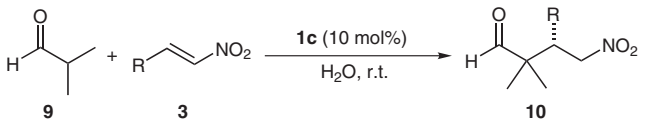
(60%) and better enantioselectivity (88% ee) than in dichloromethane (21% yield and 73% ee).[7] Unfortunately, as shown in Scheme 1, the reactions of 1-tetralone, indan-1-one, and acetone with [(*E*)-2-nitrovinyl]benzene (**3a**) in water failed to give the corresponding products.

On the basis of the configuration of the product, we propose the putative transition state for the **1c**-catalyzed asymmetric Michael addition of a ketone to a nitroalkene shown in Figure 2. The pyrrolidine ring first reacts with the carbonyl compound to form an enamine. Subsequently, the oxygen atom of the sulfonimide group, through a hydrogen bond with water, directs the nitro group so that the enamine attacks the nitroalkene from the *Re* face opposite the binaphthyl group of **1c** to give the product with a high enantio- and diastereoselectivity.

In an attempt to extend the application of the catalyst, we next examined the Michael addition of an aldehyde to nitroalkenes under the optimized conditions. As expected, the catalyst can also be applied to enolizable aldehydes, such as isobutyraldehyde, and the results are summarized in Table 3. Isobutyraldehyde gave the desired products **10** in moderate yields (63–86%) and moderate enantioselectivities (55–83% ee). In these cases, catalyst **1c** showed a similar reactivity and selectivity for a range of nitroalkenes.

In conclusion, we used the water-soluble L-proline-based binaphthyl sulfonimides and sulfonamides **1a–d** as highly efficient and stereoselective organocatalysts in the asym-

Table 3 Catalytic Asymmetric Michael Addition of Isobutyraldehyde to Nitroalkenes



Entry[a]	R	Time (h)	Product	Yield[b] (%)	ee[c] (%)
1	Ph	72	**10a**	80	83
2	4-FC_6H_4	48	**10b**	73	67
3	4-ClC_6H_4	48	**10c**	76	69
4	4-BrC_6H_4	48	**10d**	63	72
5	4-Tol	96	**10e**	67	55
6	3-$O_2NC_6H_4$	48	**10f**	86	79

[a] All reactions were carried out by using aldehyde **9** (72 mg, 1.0 mmol) and catalyst **1c** (10 mol%) in H_2O (0.2 mL). The mixture was stirred at r.t. for 15 min, then nitroalkene **3** (0.20 mmol) was added.
[b] Yield of the isolated product after chromatography on silica gel.
[c] Determined by chiral HPLC analysis; the configuration was assigned according to the literature.[8]

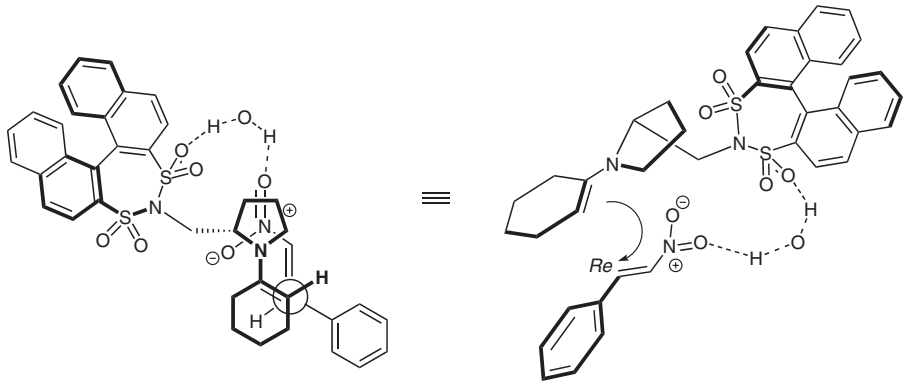


Figure 2 A proposed transition state

metric Michael addition of cyclohexanone to nitroalkenes. The corresponding products were obtained in good yields and excellent enantioselectivities and diastereoselectivities (93–97% ee, up to >99:1 dr). The catalyst **1c** was also effective in the asymmetric Michael addition of isobutyraldehyde to nitroalkenes, and the desired products were obtained in moderate yields and enantioselectivities (up to 83% ee). Syntheses of derivatives of these organocatalysts as well as studies on their applications in other organic reactions are currently under way in our group.

Commercially available compounds were used without further purification. Column chromatography was carried out on silica gel (200–300 mesh). Melting points were measured with a XT-4 melting point apparatus. The ^{1}H NMR spectra were recorded on a Varian Mercury-plus 400 M spectrometer. Optical rotations were measured with a WZZ–3 polarimeter. The enantiomeric excesses of the products were determined by chiral HPLC analysis using an Agilent HP 1200 instrument with hexane–*i*-PrOH as the eluent.

(2*S*)-2-[(1*R*)-2-Nitro-1-phenylethyl]cyclohexanone (4a); Typical Procedure

The organocatalyst **1c** (9.8 mg, 0.02 mmol) was added to cyclohexanone (**2**; 98 mg, 1.0 mmol) in H_2O (0.2 mL) at r.t. Nitroalkene **3a** (29.8 mg, 0.2 mmol) was added, and the resulting mixture was stirred at r.t. until the reaction was complete (TLC). The product was isolated by flash chromatography (silica gel, PE–EtOAc) as a white solid; yield: 96%; mp 122–124 °C; $[\alpha]_D^{20}$ –18.0 (*c* 0.5, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.34 (m, 3 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 4.95 (dd, *J* = 4.4, 12.8 Hz, 1 H), 4.64 (dd, *J* = 10.4, 12.4 Hz, 1 H), 3.76 (dt, *J* = 4.4, 10.0 Hz, 1 H), 2.66–2.73 (m, 1 H), 2.36–2.51 (m, 2 H), 2.07–2.11 (m, 1 H), 1.67–1.81 (m, 2 H), 1.55–1.62 (m, 2 H), 1.22–1.29 (m, 1 H).

HPLC [Chiralpak AS-H, hexane–*i*-PrOH (85:15), flow rate 1 mL/min, detection at 230 nm]: t_R (minor) = 13.5 min, t_R (major) = 21.1 min; *syn*/*anti* = 99:1, 96% ee.

Compounds **4b–l** and **6** were similarly prepared.

(2*S*)-2-[(1*R*)-1-(2-Methoxyphenyl)-2-nitroethyl]cyclohexanone (4b)

White solid; yield: 94%; mp 96–99 °C; $[\alpha]_D^{20}$ –34.0 (*c* 0.5, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.27 (m, 1 H), 7.08 (dd, *J* = 1.2, 7.2 Hz, 1 H), 6.88 (t, *J* = 7.2 Hz, 2 H), 4.82–4.85 (m, 2 H), 3.93–4.00 (m, 1 H), 3.84 (s, 3 H), 2.95–3.02 (m, 1 H), 2.38–2.45 (m, 2 H), 2.06–2.10 (m, 1 H), 1.74–1.79 (m, 1 H), 1.55–1.69 (m, 3 H), 1.15–1.25 (m, 1 H).

HPLC [Chiralpak AS-H, hexane–*i*-PrOH (85:15), flow rate 1 mL/min, detection at 230 nm]: t_R (minor) = 16.2 min, t_R (major) = 19.0 min; *syn*/*anti* = >96:4, 95% ee.

(2*S*)-2-[(1*R*)-1-(2-Chlorophenyl)-2-nitroethyl]cyclohexanone (4c)

Colorless oil; yield: 91%; $[\alpha]_D^{20}$ –42.0 (*c* 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.39 (m, 1 H), 7.19–7.25 (m, 3 H), 4.89 (d, *J* = 7.2 Hz, 2 H), 4.27–4.33 (m, 1 H), 2.88–2.96 (m, 1 H), 2.35–2.50 (m, 2 H), 2.08–2.13 (m, 1 H), 1.79–1.83 (m, 1 H), 1.55–1.75 (m, 3 H), 1.25–1.38 (m, 1 H).

HPLC [Chiralpak IA, hexane–*i*-PrOH (90:10), flow rate 1 mL/min, detection at 254 nm]: t_R (minor) = 8.0 min, t_R (major) = 10.5 min; *syn*/*anti* = > 99:1, 97% ee.

(2*S*)-2-[(1*R*)-1-(4-Chlorophenyl)-2-nitroethyl]cyclohexanone (4d)

White solid; yield: 88%; mp 93–95 °C; $[\alpha]_D^{20}$ –34.4 (*c* 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (dd, *J* = 5.2, 8.8 Hz, 2 H), 6.99–7.03 (m, 2 H), 4.96 (dd, *J* = 4.8, 12.8 Hz, 1 H), 4.60 (dd, *J* = 10.4, 12.8 Hz, 1 H), 3.78 (dt, *J* = 4.4, 10.0 Hz, 1 H), 2.62–2.70 (m, 1 H), 2.33–2.48 (m, 2 H), 2.06–2.11 (m, 1 H), 1.55–1.81 (m, 4 H), 1.17–1.27 (m, 1 H).

HPLC [Chiralpak AS-H, hexane–*i*-PrOH (85:15), flow rate 1 mL/min, detection at 230 nm]: t_R (minor) = 13.9 min, t_R (major) = 24.8 min; *syn*/*anti* = 99:1, 96% ee.

(2*S*)-2-[(1*R*)-1-(4-Fluorophenyl)-2-nitroethyl]cyclohexanone (4e)

White solid; yield: 80%; mp 64–65 °C; $[\alpha]_D^{20}$ –34.0 (*c* 0.5, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.16 (dd, *J* = 5.2 and 8.8 Hz, 2 H), 6.99–7.03 (m, 2 H), 4.96 (dd, *J* = 4.8, 12.8 Hz, 1 H), 4.60 (dd, *J* = 10.4, 12.8 Hz, 1 H), 3.79 (dt, *J* = 4.4, 10.0 Hz, 1 H), 2.62–2.75 (m, 1 H), 2.37–2.48 (m, 2 H), 2.07–2.11 (m, 1 H), 1.58–1.81 (m, 4 H), 1.17–1.27 (m, 1 H).

HPLC [Chiralpak AS H, hexane–*i*-PrOH (90:10), flow rate 1.0 mL/min, detection at 254 nm]: t_R (minor) = 21.6 min, t_R (major) = 36.6 min; *syn*/*anti* = 98:2, 97% ee.

(2*S*)-2-[(1*R*)-1-(4-Methylphenyl)-2-nitroethyl]cyclohexanone (4f)

White solid; yield: 85%; mp 124–126 °C; $[\alpha]_D^{20}$ –14.0 (*c* 1.0, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.12 (d, *J* = 8.0 Hz, 2 H), 7.04 (d, *J* = 8.0 Hz, 2 H), 4.92 (dd, *J* = 4.4, 12.4 Hz, 1 H), 4.60 (dd, *J* = 10.0, 12.0 Hz, 1 H), 3.72 (dt, *J* = 4.4, 10.0 Hz, 1 H), 2.63–2.70 (m, 1 H), 2.34–2.49 (m, 2 H), 2.31 (s, 3 H), 2.05–2.10 (m, 1 H), 1.55–1.80 (m, 4 H), 1.18–1.27 (m, 1 H).

HPLC [Chiralpak AS-H, hexane–*i*-PrOH (90:10), flow rate 1.0 mL/min, detection at 230 nm]: t_R (minor) = 10.5 min, t_R (major) = 17.5 min; *syn*/*anti* = > 99:1, 97% ee.

(2*S*)-2-[(1*R*)-1-(4-Bromophenyl)-2-nitroethyl]cyclohexanone (4g)

White solid; yield: 90%; mp 119–121 °C; $[\alpha]_D^{20}$ –33.6 (*c* 0.5, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 6.0, 8.4 Hz, 2 H), 7.15 (d, *J* = 8.4 Hz, 1 H), 7.07 (d, *J* = 8.4 Hz, 1 H), 4.94 (dd, *J* = 4.4, 12.4 Hz, 1 H), 4.59 (dd, *J* = 10.4, 12.8 Hz, 1 H), 3.75 (dt, *J* = 4.4, 10.0 Hz, 1 H), 2.61–2.73 (m, 1 H), 2.34–2.47 (m, 2 H), 2.02–2.10 (m, 1 H), 1.54-1.76 (m, 4 H), 1.17–1.27 (m, 1 H).

HPLC [Chiralpak AS-H, hexane–*i*-PrOH (90:10), flow rate = 1.0 mL/min, detection at 254 nm]: t_R (minor) = 19.0 min, t_R (major) = 35.9 min; *syn*/*anti* = 99:1, 95% ee.

(2*S*)-2-[(1*R*)-2-Nitro-1-(3-nitrophenyl)ethyl]cyclohexanone (4h)

Colorless oil; yield: 85%; $[\alpha]_D^{20}$ –30.2 (*c* 1.0, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.10–8.17 (m, 2 H), 7.52–7.60 (m, 2 H), 5.03 (dd, *J* = 4.4, 13.2 Hz, 1 H), 4.71 (dd, *J* = 10.4, 13.2 Hz, 1 H), 3.95 (dt, *J* = 4.4, 9.6 Hz, 1 H), 2.73–2.88 (m, 1 H), 2.40–2.51 (m, 2 H), 2.11–2.15 (m, 1 H), 1.60–1.73 (m, 4 H), 1.24–1.33 (m, 1 H).

HPLC [Chiralpak IA, hexane–*i*-PrOH (98:2), flow rate = 1.0 mL/min, detection at 254 nm]: t_R (minor) = 60.7 min, t_R (major) = 74.0 min; *syn*/*anti* = 98:2, 97% ee.

(2*S*)-2-[(1*R*)-1-(3-bromophenyl)-2-nitroethyl]cyclohexanone (4i)

Colorless oil; yield: 85%; $[\alpha]_D^{20}$ –28.8 (*c* 0.5, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33–7.41 (m, 2 H), 7.11–7.22 (m, 2 H), 4.95 (dd, *J* = 4.4, 12.8 Hz, 1 H), 4.60 (dd, *J* = 10.0, 12.8 Hz, 1 H), 3.75 (dt, *J* = 4.4, 9.6 Hz, 1 H), 2.62–2.75 (m, 1 H), 2.37–2.46 (m, 2 H), 2.08–2.11 (m, 1 H), 1.60–1.73 (m, 4 H), 1.22–1.29 (m, 1 H).

HPLC [Chiralpak AS-H, hexane–*i*-PrOH (90:10), flow rate 1.0 mL/min, detection at 230 nm]: t_R (minor) = 21.1 min, t_R (major) = 41.7 min; *syn*/*anti* = 97:3, 96% ee.

(2*S*)-2-[(1*R*)-1-(3,4-Dimethoxyphenyl)-2-nitroethyl]cyclohexanone (4j)

White solid; yield: 60%; mp 133–135 °C; $[\alpha]_D^{20}$ –13.6 (*c* 0.5, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.81 (d, *J* = 8.4 Hz, 1 H), 6.71 (dd, *J* = 62.0, 8.4 Hz, 1 H), 6.66 (d, *J* = 2.0 Hz, 1 H), 4.91 (dd, *J* = 4.8, 12.4 Hz, 1 H), 4.62 (dd, *J* = 10.0, 12.0 Hz, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.71 (dt, *J* = 4.8, 10.0 Hz, 1 H), 2.62–2.69 (m, 1 H), 2.35–2.50 (m, 2 H), 2.07–2.11 (m, 1 H), 1.59–1.82 (m, 4 H), 1.20–1.29 (m, 1 H).

HPLC [Chiralpak AS-H, hexane–*i*-PrOH (75:25), flow rate 1.0 mL/min, detection at 230 nm]: t_R (minor) = 17.5 min, t_R (major) = 38.9 min; *syn*/*anti* = 98:2, 93% ee.

(2*S*)-2-[(1*S*)-2-Nitro-1-(2-thienyl)ethyl]cyclohexanone (4k)

Brown solid; yield: 65%; mp 82–84 °C; $[\alpha]_D^{20}$ –30.4 (*c* 0.5, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.23 (d, *J* = 4.8 Hz, 1 H), 6.93 (dd, *J* = 3.6, 5.2 Hz, 1 H), 6.87 (d, *J* = 3.6 Hz, 1 H), 4.89 (dd, *J* = 4.4, 12.4 Hz, 1 H), 4.65 (dd, *J* = 9.6, 12.4 Hz, 1 H), 4.13 (dt, *J* = 4.4, 8.8 Hz, 1 H), 2.65–2.72 (m, 1 H), 2.37–2.47 (m, 2 H), 2.08–2.13 (m, 1 H), 1.83–1.93 (m, 2 H), 1.60–1.70 (m, 2 H), 1.30–1.34 (m, 1 H).

HPLC [Chiralpak IA, hexane–*i*-PrOH (98:2), flow rate 1.0 mL/min, detection at 230 nm]: t_R (minor) = 26.3 min, t_R (major) = 33.9 min; *syn*/*anti* = 99:1, 94% ee.

(2*S*)-2-[(1*S*)-1-(2-Furyl)-2-nitroethyl]cyclohexanone (4l)

Brown oil; yield: 68%; $[\alpha]_D^{20}$ –12.8 (*c* 0.5, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35 (d, *J* = 2.0 Hz, 1 H), 6.29 (dd, *J* = 2.0, 3.2 Hz, 1 H), 6.18 (d, *J* = 3.2 Hz, 1 H), 4.79 (dd, *J* = 4.8, 12.4 Hz, 1 H), 4.67 (dd, *J* = 9.6, 12.4 Hz, 1 H), 3.98 (dt, *J* = 4.8, 9.2 Hz, 1 H), 2.72–2.79 (m, 1 H), 2.33–2.48 (m, 2 H), 2.08–2.13 (m, 1 H), 1.72–1.86 (m, 2 H), 1.62–1.67 (m, 2 H), 1.26–1.30 (m, 1 H).

HPLC [Chiralpak AS-H, hexane–*i*-PrOH (85:15), flow rate 1.0 mL/min, detection at 230 nm]: t_R (minor) = 15.6 min, t_R (major) = 18.2 min; *syn*/*anti* = 98:2, 95% ee.

(2*S*)-2-[(1*R*)-2-Nitro-1-phenylethyl]cyclopentanone (6)

White solid; yield: 60%; mp 115–117 °C; $[\alpha]_D^{20}$ –16.6 (*c* 1.0, CH_2Cl_2).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.29–7.32 (m, 3 H), 7.15–7.18 (m, 2 H), 5.34 (dd, *J* = 5.6, 12.8 Hz, 1 H), 4.71 (dd, *J* = 9.9, 12.8 Hz, 1 H), 3.66–3.74 (m, 1 H), 2.31–2.44 (m, 2 H), 2.08–2.20 (m, 1 H), 1.84–1.94 (m, 2 H), 1.64–1.76 (m, 1 H), 1.48–1.56 (m, 1 H).

HPLC [Chiralpak IA, hexane–*i*-PrOH (95:5), flow rate 1.0 mL/min, detection at 230 nm]: t_R (major, *anti*) = 10.8 min, t_R (minor, *anti*) = 12.5 min, t_R(minor, *syn*) = 13.6 min, t_R (major, *syn*) = 19.8 min; *syn*/*anti* = 67:33, 88% ee (*syn*), 92% ee (*anti*).

Sulfonimide 1c-Catalyzed Asymmetric Michael Addition of Isobutyraldehyde to Nitroalkenes; General Procedure

Organocatalyst **1c** (9.8 mg, 0.02 mmol) was added to isobutyraldehyde (**9**) (72 mg, 1.0 mmol) in H_2O (0.2 mL) at r.t. Nitroalkene **3** (0.2 mmol) was then added and the resulting mixture was stirred at r.t. until the reaction was complete (TLC). The product was isolated by flash chromatography (silica gel, PE–EtOAc).

(3*R*)-2,2-Dimethyl-4-nitro-3-phenylbutanal (10a)

Colorless oil; yield: 80%; $[\alpha]_D^{20}$ +9.6 (*c* 0.5, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.53 (s, 1 H), 7.26–7.35 (m, 3 H), 7.19–7.21 (m, 2 H), 4.86 (dd, *J* = 11.2, 13.2 Hz, 1 H), 4.69 (dd, *J* = 4.4, 13.2 Hz, 1 H), 3.78 (dd, *J* = 4.4, 11.2 Hz, 1 H), 1.13 (s, 3 H), 1.00 (s, 3 H).

HPLC [Chiralpak IB, hexane–*i*-PrOH (80:20), flow rate 0.8 mL/min, detection at 254 nm]: t_R (major) = 11.6 min, t_R (minor) = 14.8 min; 83% ee.

(3*R*)-3-(4-Fluorophenyl)-2,2-dimethyl-4-nitrobutanal (10b)

Brown oil; yield: 73%; $[\alpha]_D^{20}$ +1.2 (*c* 0.48, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.5 (s, 1 H), 7.17–7.21 (m, 2 H), 7.01–7.05 (m, 2 H), 4.83 (dd, *J* = 11.4, 13.0 Hz, 1 H), 4.69 (dd, *J* = 4.2, 13.0 Hz, 1 H), 3.77 (dd, *J* = 4.2, 11.4 Hz, 1 H), 1.12 (s, 3 H), 1.01 (s, 3 H).

HPLC [Chiralpak IB, hexane–*i*-PrOH (85:15), flow rate 0.8 mL/min, detection at 254 nm]: t_R (major) = 10.5 min, t_R (minor) = 16.0 min; 67% ee.

(3*R*)-3-(4-Chlorophenyl)-2,2-dimethyl-4-nitrobutanal (10c)

Brown oil; yield: 76%; $[\alpha]_D^{20}$ +1.7 (*c* 0.45, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.50 (s, 1 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 7.15 (*J* = 8.4 Hz, 2 H), 4.82 (dd, *J* = 11.6, 13.2 Hz, 1 H), 4.69 (dd, *J* = 4.0, 13.2 Hz, 1 H), 3.77 (dd, *J* = 4.0, 11.6 Hz, 1 H), 1.12 (s, 3 H), 1.01 (s, 3 H).

HPLC [Chiralpak IB, hexane–*i*-PrOH (80:20), flow rate 0.8 mL/min, detection at 254 nm]: t_R (major) = 9.9 min, t_R (minor) = 13.8 min; 69% ee.

(3*R*)-3-(4-Bromophenyl)-2,2-dimethyl-4-nitrobutanal (10d)

Brown oil; yield: 63%; $[\alpha]_D^{20}$ +1.1 (*c* 0.42, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.50 (s, 1 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.09 (d, *J* = 8.4 Hz, 2 H), 4.82 (dd, *J* = 11.6, 13.2 Hz, 1 H), 4.69 (dd, *J* = 4.0, 13.2 Hz, 1 H), 3.76 (dd, *J* = 4.0, 11.6 Hz, 1 H), 1.12 (s, 3 H), 1.01 (s, 3 H).

HPLC [Chiralpak IB, hexane–*i*-PrOH (80:20), flow rate 0.8 mL/min, detection at 230 nm]: t_R (major) = 13.4 min, t_R (minor) = 17.8 min; 72% ee.

(*R*)-2,2-Dimethyl-3-(4-methylphenyl)-4-nitrobutanal (10e)

Colorless oil; yield: 67%; $[\alpha]_D^{20}$ +2.5 (*c* 0.38, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.53 (s, 1 H), 7.13 (d, *J* = 8.0 Hz, 1 H), 7.07 (d, *J* = 8.0 Hz, 1 H), 4.82 (dd, *J* = 11.2, 12.8 Hz, 1 H), 4.67 (dd, *J* = 4.2, 12.8 Hz, 1 H), 3.74 (dd, *J* = 4.2, 11.2 Hz, 1 H), 2.32 (s, 3 H), 1.12 (s, 3 H), 1.00 (s, 3 H).

HPLC [Chiralpak IB, hexane–*i*-PrOH (80:20), flow rate 0.8 mL/min, detection at 230 nm]: t_R (major) = 10.0 min, t_R (minor) = 12.6 min; 55% ee.

(*R*)-2,2-Dimethyl-4-nitro-3-(3-nitrophenyl)butanal (10f)

Brown oil; yield: 86%; $[\alpha]_D^{20}$ +4.4 (*c* 0.55, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.51 (s, 1 H), 8.13–8.21 (m, 2 H), 7.53–7.61 (m, 2 H), 4.93 (dd, *J* = 11.4, 13.4 Hz, 1 H), 4.77 (dd,

J = 3.8, 13.4 Hz, 1 H), 3.94 (dd, J = 3.8, 11.4 Hz, 1 H), 1.18 (s, 3 H), 1.06 (s, 3 H).

HPLC [Chiralpak AS-H, hexane–*i*-PrOH (90:10), flow rate = 1.0 mL/min, detection at 254 nm]: t_R (minor) = 49.2 min, t_R (major) = 53.4 min; 79% ee.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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References

(1) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138.

(2) For recent reviews on asymmetric Michael additions, see: (a) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877. (b) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933. (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (d) Sulzer-Mosse, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123. For selected examples of asymmetric Michael additions of ketones to nitroalkenes, see: (e) Yang, Z. G.; Liu, J.; Liu, X. H.; Wang, Z.; Feng, X. M.; Su, Z. S.; Hu, C. W. *Adv. Synth. Catal.* **2008**, *350*, 2001. (f) Li, P. H.; Wang, L.; Wang, M.; Zhang, Y. C. *Eur. J. Org. Chem.* **2008**, 1157. (g) Tan, B.; Zeng, X. F.; Lu, Y. P.; Chua, P. J.; Zhong, G. F. *Org. Lett.* **2009**, *11*, 1927. (h) Belot, S.; Quintard, A.; Krause, N.; Alexakis, A. *Adv. Synth. Catal.* **2010**, *352*, 667. (i) Lu, A. D.; Wu, R. H.; Wang, Y. M.; Zhou, Z. H.; Wu, G. P.; Fang, J. X.; Tang, C. C. *Eur. J. Org. Chem.* **2010**, 2057. (j) Lv, G. H.; Jin, R. H.; Mai, W. P.; Gao, L. X. *Tetrahedron: Asymmetry* **2008**, *19*, 2568. (k) Sato, A.; Yoshida, M.; Hara, S. *Chem. Commun.* **2008**, 6242.

(3) For asymmetric Michael reactions in water, see: (a) Luo, S.; Mi, X.; Liu, S.; Xu, H.; Cheng, J.-P. *Chem. Commun.* **2006**, 3687. (b) Zu, L.; Wang, J.; Li, H.; Wang, W. *Org. Lett.* **2006**, *8*, 3077. (c) Yan, Z.-Y.; Niu, Y.-N.; Wei, H.-L.; Wu, L.-Y.; Zhao, Y.-B.; Liang, Y.-M. *Tetrahedron: Asymmetry* **2006**, *17*, 3288. (d) Cao, Y.-J.; Lai, Y.-Y.; Wang, X.; Li, Y.-J.; Xiao, W.-J. *Tetrahedron Lett.* **2007**, *48*, 21. (e) Syu, S.-E.; Kao, T.-T.; Lin, W. *Tetrahedron* **2010**, *66*, 891. (f) Palomo, C.; Landa, A.; Mielgo, A.; Oiarbide, M.; Puente, A.; Vera, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 8431. (g) Zhu, S.; Yu, S.; Ma, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 545. (h) Alza, E.; Cambeiro, X. C.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2007**, *9*, 3717.

(4) For asymmetric Michael reactions in brine, see: (a) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F. III *J. Am. Chem. Soc.* **2006**, *128*, 4966. (b) Vishnumaya Singh, V. K. *Org. Lett.* **2007**, *9*, 1117. (c) Wu, J.; Ni, B.; Headley, A. D. *Org. Lett.* **2009**, *11*, 3354.

(5) For asymmetric Michael reactions in ionic liquids, see: Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Angew. Chem. Int. Ed.* **2006**, *45*, 3093.

(6) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095.

(7) Ban, S. R.; Du, D.-M.; Liu, H.; Yang, W. *Eur. J. Org. Chem.* **2010**, 5160.

(8) He, T.; Gu, Q.; Wu, X. Y. *Tetrahedron* **2010**, *66*, 3195.