Asymmetric Direct Michael Reactions of Cyclohexanone with Aromatic Nitroolefins in Water Catalyzed by Novel Axially Unfixed Biaryl-Based Bifunctional Organocatalysts

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Abstract: A new family of axially unfixed biaryl-based water-compatible bifuctional organocatalysts were designed and synthesized for the asymmetric direct Michael reaction of cyclohexanone with various nitroolefins in water. One of the organocatalysts incorporates pyrrolidine and arylsulfonamide motifs as active organocatalytic sites, and axially unfixed biaryl as a skeleton; with this organocatalyst, the direct Michael reactions proceeded readily, furnishing the desired Michael adducts in high yields (up to 99% yield) with high levels of stereocontrol (up to >99:1 dr and 94% ee).

Key words: biaryl compounds, aqueous chemistry, organocatalysts, asymmetric Michael reaction, stereoselectivity

The asymmetric organocatalytic direct Michael reaction represents one of the most efficient and powerful methods for the formation of C–C or C–heteroatom bonds, and has been widely used to generate enantioenriched organic compounds in the context of drug discovery and organic synthesis of natural products and heterocycles.[1] Since the seminal works of List and Barbas, many efficient and highly stereoselective organocatalysts have been developed for the asymmetric direct Michael reactions.[2] To the best of our knowledge, most of the reports deal with such reactions in organic solvents. In view of the clear advantages of performing organocatalytic direct Michael reactions in water, many recent efforts have been devoted to the development of highly efficient water-compatible organocatalysts.[3] The main challenges with the development of such catalysts stem from interference in the transition state by water, which reduces the reactivity and level of stereocontrol of the organocatalysts.[4] Encouraged by the pioneering findings of Barbas, a number of water-compatible organocatalysts has been devised for the direct Michael additions of ketones or aldehydes to nitroolefins in water with high yields and levels of stereocontrol.[5] It has been demonstrated that the success of these water-compatible organocatalysts in the direct Michael reactions in water depends significantly on the fact that they can assemble with the Michael donors and acceptors, and sequester water from the transition states of the direct Michael reactions in water efficiently through hydrophobic interactions. Evidently, sufficient hydrophobicity of the water-compatible organocatalysts is necessary to achieve high levels of stereocontrol in direct Michael reactions in water. The appropriate hydrophobicity of the water-compatible organocatalysts can be afforded by the introduction of a bulky hydrophobic group into the architecture of the organocatalysts. To date, through the choice of different bulky hydrophobic scaffolds,[6] several tens of highly efficient water-compatible organocatalysts have already been developed to perform direct Michael reactions in water. However, so far, there have been no reports on the development of hydrophobic axially unfixed chiral biphenyl- or bipyridyl-based water-compatible organocatalysts for the direct Michael reactions in water. Accordingly, the development of novel water-compatible organocatalysts that catalyze such reactions efficiently through the use of hydrophobic axially unfixed chiral biphenyl or bipyridyl as scaffolds is described herein.

In this paper we describe the design, synthesis and asymmetric catalysis of novel axially unfixed biaryl-based organocatalysts **2a**–**c** in direct Michael reactions in water (Scheme 1). The designed organocatalysts involve biaryl, pyrrolidine and arylsulfonamide fragments, and their behavior is assumed to stem from their bifunctional nature. It was envisioned that in our organocatalytic systems, the Michael donors would be activated through enamine formation, and the Michael acceptors would be activated by the formation of double hydrogen bonds. Moreover, the biaryl group present in the organocatalysts can function as a fundamental scaffold unit that adjusts the spatial orientation of arylsulfonamide and pyrrolidine catalytic sites more freely. In particular, the presence of the hydrophobic biaryl moiety of the organocatalysts can ensure the organocatalysts have sufficient hydrophobicity to aggregate with the hydrophobic reactants and exclude water efficiently from the transition states by means of the hydrophobic interactions, thus yielding high reactivities and levels of stereocontrol.

Starting from organocatalysts **1a**–**c**, which showed excellent reactivities and stereoselectivities in organocatalytic direct aldol reactions in water in our recently published

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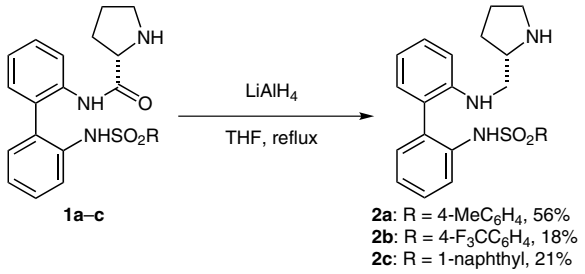


Scheme 1 Synthesis of novel organocatalysts **2a–c**

work,[7] a series of novel organocatalysts **2a–c** with C_1-symmetry were prepared in 18–56% yields according to the strategy shown in Scheme 1. Conversion of **1a–c** into **2a–c**, respectively, was easily accomplished upon treatment with $LiAlH_4$ in anhydrous in tetrahydrofuran (THF) at reflux. In addition, to investigate the structure–reactivity relationships of organocatalysts **2a–c**, organocatalyst **1a**, with C_1-symmetry, and **3**/**4**, bearing C_2-symmetry, as shown in Figure 1 were also synthesized in a straightforward manner according to our developed procedures.[7,8]

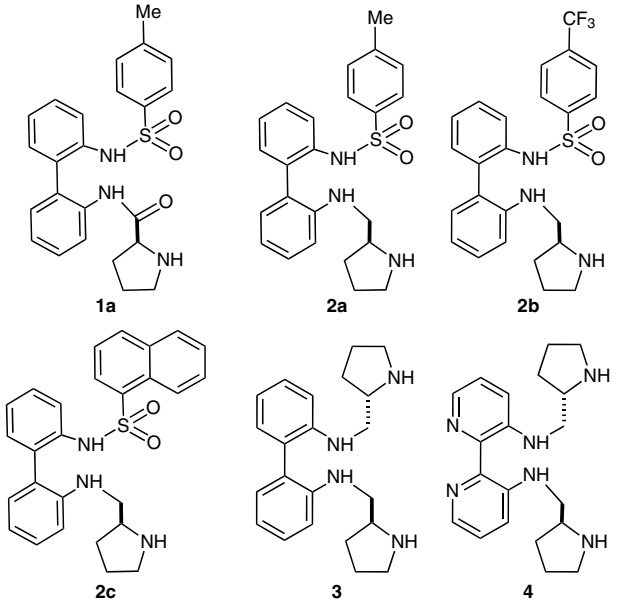
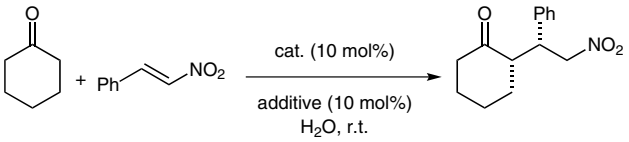


Figure 1 Organocatalysts examined in this work

With organocatalysts **1a**, **2a–c** (Scheme 1), **3** and **4** (Figure 1) in hand, we started to evaluate their reactivities and levels of stereocontrol in the Michael reaction (Table 1). The organocatalytic Michael additions of cyclohexanone to nitroolefin proceeded smoothly in favor of the *syn* diastereoisomers, and delivered comparable diastereoselectivities in most cases. The chemical yields and enantioselectivities of the Michael additions changed significantly depending on the chemical structure of the organocatalyst used. Known catalysts **3** and **4**, with C_2-symmetry, tended to furnish the Michael products with up to 93% ee and up to 95:5 dr, albeit with rather low chemical yields (15–21%; Table 1, entries 7–10). In comparison to catalysts **3** and **4**, catalysts **2a–c** exhibited much superior reactivities and slightly lower enantioselectivities under the same reaction conditions (Table 1, entries 2, 5 and 6 vs. 7 and 9). In the series of catalysts **2a–c**, similar diastereoselectivities and enantioselectivities in the Michael additions were found; however, significantly different reactivities were identified (Table 1, entries 2, 5 and 6). For instance, organocatalyst **2a** enabled the Michael addition to reach completion in 12 hours; in contrast, the same reaction went to completion in 17 hours under catalysis by **2b**. Noticeably, it was found that in the presence of **2c** as catalyst, the Michael addition proceeded very sluggishly, and reached completion in 30 hours.

Table 1 Screening of Biaryl Organocatalysts[a]



Entry	Cat.	Time (h)	Yield (%)[b]	dr (*syn*/*anti*)[c]	ee (%) (*syn*)[c]
1	**1a**	36	69	96:4	–11
2	**2a**	12	85	97:3	89
3[d]	**2a**	14	85	96:4	85
4[d,e]	**2a**	36	–	–	–
5	**2b**	17	81	97:3	89
6	**2c**	30	81	97:7	87
7	**3**	48	18	93:7	90
8[f]	**3**	48	15	95:5	91
9	**4**	48	15	94:6	93
10[f]	**4**	48	21	95:5	92
11[g]	**2a**	24	88	96:4	87
12[h]	**2a**	30	73	96:4	86
13[i]	**2a**	48	42	96:4	86

[a] Reaction conditions: nitroolefin (0.1 mmol), cyclohexanone (104 μL, 1.0 mmol), catalyst (10 mol%), $PhCO_2H$ (10 mol%), H_2O (0.5 mL), r.t.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Brine was used as solvent.
[e] $NaHCO_3$ was used as additive.
[f] $C_{17}H_{35}CO_2H$ (20 mol%) was used.
[g] Molar ratio of cyclohexanone to nitroolefin: 5:1.
[h] Molar ratio of cyclohexanone to nitroolefin: 2:1.
[i] Molar ratio of cyclohexanone to nitroolefin: 1:1.

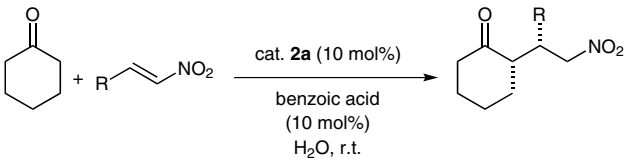
Furthermore, under catalysis of **2a**, it was revealed that the use of brine instead of water as the reaction medium slightly reduced the enantioselectivity and diastereoselectivity of the Michael reaction; however, the chemical

yield remained at the same level (Table 1, entries 2 vs. 3). Even worse, when the reaction was catalyzed with **2a**, no Michael addition took place at all when brine was chosen as reaction solvent and $NaHCO_3$ as additive (Table 1, entry 4). Moreover, to our surprise it was noted that catalyst **1a** showed much inferior reactivity and levels of enantioselectivity compared with those of catalyst **2a** (Table 1, entries 1 vs. 2). Accordingly, by considering reactivities and levels of stereocontrol in the organocatalyzed Michael additions mentioned above, catalyst **2a** was identified as the most efficient organocatalyst examined. Moreover, when the reaction was catalyzed by 10 mol% **2a**, it was noted that the reaction rate of the Michael addition accelerated significantly with an increased ratio of cyclohexanone to nitroolefin; however, the stereoselectivity of the reaction did not change drastically (Table 1, entries 2 and 11–13).

Subsequently, by using **2a** as catalyst (10 mol%), the effects of various catalytic loadings, acidic additives and organic solvents on the asymmetric organocatalytic Michael reactions in water were evaluated (see the Supporting Information), and optimal reaction conditions were established as **2a** (10 mol%)/$PhCO_2H$ (10 mol%)/H_2O/r.t. As summarized in Table 2, under the optimized reaction conditions, the scope of the Michael reaction was extended by using a variety of aromatic nitroolefins. In most cases, the Michael reactions proceeded smoothly, delivering the desired Michael adducts in excellent yields with excellent levels of diastereoselectivity and good levels of enantioselectivity (Table 2, entries 2–7, 9, 11 and 12). In general, aromatic nitroolefins containing an electron-withdrawing group on the benzene ring tended to give the corresponding products in excellent levels of diastereoselectivity and good levels of enantioselectivity (Table 2, entries 2–8). Moreover, heteroaromatic nitroolefins also showed similar levels of stereocontrol in the Michael reactions (Table 2, entries 11 and 12 vs. 2–8). Meanwhile, it should be noted that a nitroolefin bearing a methyl group at the 4-position on the benzene ring also produced the Michael adduct in 98% yield with 95:5 dr and 87% ee. In contrast, use of a nitroolefin bearing a methoxy group at the 4-position on the benzene continued to deliver the desired Michael adduct in excellent yield and diastereoselectivity, but the enantiomeric excess decreased to a certain degree (Table 2, entries 9 vs. 10). Generally, compared with the aromatic nitroolefins, aliphatic nitroolefins also delivered the desired Michael adducts with comparable levels of stereoselectivity, but with rather low chemical yields (Table 2, entries 1–12 vs. 13–14).

Furthermore, the Michael addition of a variety of Michael donors involving aliphatic aldehydes and ketones to nitroolefin was carried out by using catalyst **2a** as shown in Table 3. Catalyzed by **2a**, the Michael addition of acetone to nitroolefin did not take place at all within 62 hours (Table 3, entry 1). Similarly, the choice of cyclopentanone and butan-2-one as Michael donors did not afford the desired Michael adducts after a reaction time of 62 hours (Table 3, entries 2 and 3). In the case of Michael addition

Table 2 Extension of the Scope of Nitroolefins at Room Temperature[a]



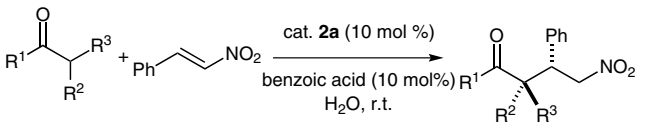
Entry	R	Time (h)	Yield (%)[b]	dr (*syn*/*anti*)[c]	ee (%) (*syn*)[c]
1	Ph	12	85	97:3	89
2	4-FC_6H_4	6	99	96:4	89
3	4-ClC_6H_4	6	96	96:4	89
4	4-BrC_6H_4	4	92	96:4	85
5	4-$O_2NC_6H_4$	5	99	97:3	89
6	3-$O_2NC_6H_4$	8	95	95:5	88
7	2-$O_2NC_6H_4$	4	99	>99:1	84
8	4-$F_3CC_6H_4$	7	80	94:6	91
9	4-MeC_6H_4	6	98	95:5	88
10	4-$MeOC_6H_4$	18	96	93:7	77
11	2-furyl	5	96	95:5	87
12	2-thienyl	5	90	92:8	86
13	cyclohexyl	92	5	>99:1	94
14	isopropyl	92	24	92:8	89

[a] Reaction conditions: nitroolefin (0.1 mmol), cyclohexanone (104 μL, 1.0 mmol), catalyst **2a** (10 mol%), $PhCO_2H$ (10 mol%), H_2O (0.5 mL), r.t.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

of pentan-3-one to nitroolefin, the Michael adducts were achieved in 26% yield with 96:4 dr (*syn*/*anti*) and 89% ee (Table 3, entry 4). Moreover, aliphatic aldehydes such as propionaldehyde and isobutyraldehyde were examined as Michael donors in the Michael additions with the use of **2a** as catalyst. When propionaldehyde was tested as a Michael donor, the addition reaction gave rise to the Michael adduct in 98% yield with 91:9 dr (*syn*/*anti*) and 25% ee (*syn*). When the branched isobutyraldehyde served as a Michael donor, the desired adduct was isolated in 32% yield with 77% ee.

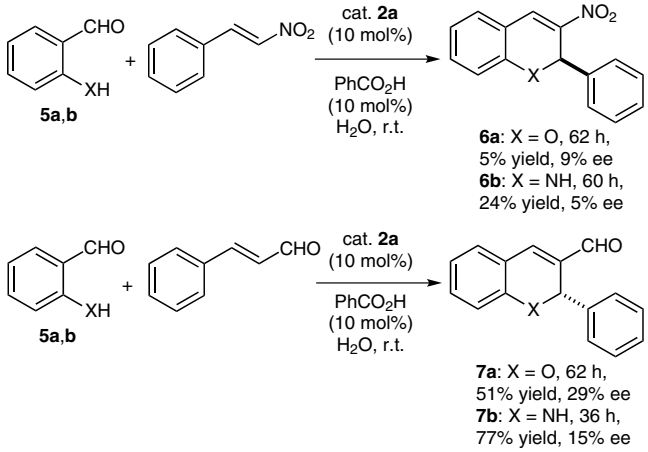
Finally, the catalytic efficiency of **2a** was also evaluated in a series of cascade cyclization reactions initiated by aza- or oxa-Michael addition as shown in Scheme 2. The Michael addition of 2-hydroxybenzaldehyde (**5a**) to nitroolefin delivered the Michael adduct **6a** in 5% yield with 9% ee; in contrast, use of 2-aminobenzaldehyde (**5b**) as Michael donor gave the desired Michael adduct **6b** in 24% yield with 5% ee. When nitroolefin was replaced by α,β-unsaturated aldehyde as Michael acceptor, use of **5a** or **5b**

Table 3 Scope of the Reaction with Michael Donors[a]



Entry	R^1	R^2	R^3	Time (h)	Yield (%)[b]	dr (*syn*/*anti*)[c]	ee (%) (*syn*)[c]
1	Me	H	H	62	–	–	–
2	-$(CH_2)_3$-		–	62	–	–	–
3	Me	Me	H	62	–	–	–
4	Et	Me	H	62	26	96:4	89
5	H	Me	H	62	98	91:9	25
6	H	Me	Me	62	32	–	77

[a] Reaction conditions: nitroolefin (0.1 mmol), Michael donor (1.0 mmol), catalyst **2a** (10 mol%), benzoic acid (10 mol%).
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.



Scheme 2 Cascade cyclization reactions catalyzed by **2a** initiated by aza- or oxa-Michael addition

furnished the desired Michael adducts **7a** in 51% yield (29% ee) and **7b** in 77% yield (15% ee), respectively.

To account for the stereochemical outcome observed with organocatalyst **2a**, the organocatalytic transition state depicted in Figure 2 was proposed. In this model, catalyst **2a** behaves as a bifunctional organocatalyst. The activation of cyclohexanone as a Michael donor was accomplished through the formation of an enamine with the aid of the acidic additive; acting as a Michael acceptor, nitroolefin was simultaneously activated through double hydrogen bonding interactions. Subsequent attack of the enamine generated in situ on the *Re* face of the well-oriented nitroolefin led to the formation of the desired Michael adduct with high stereocontrol.

In conclusion, a class of novel water-compatible organocatalysts with an axially unfixed biaryl unit as skeleton has been designed and synthesized for the asymmetric organocatalytic direct Michael reactions in water.[9] Under the optimal reaction conditions, organocatalyst **2a** performed with high efficiency and delivered high enantioselectivities and diastereoselectivities in Michael reactions performed in water. Further studies on the mechanisms and the utility of the water-compatible bifunctional organocatalyst in other asymmetric transformations in water are in progress in our laboratory, and will be reported in due course.

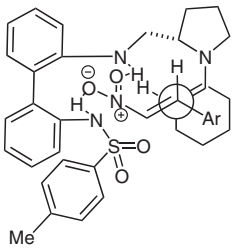


Figure 2 Proposed transition state for the Michael addition under catalysis of **2a**

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

References and Notes

(1) For selected reviews on applications of organocatalytic Michael additions in organic synthesis, see: (a) Bhanja, C.; Jena, S.; Nayak, S.; Mohapatra, S. *Beilstein J. Org. Chem.* **2012**, *8*, 1668. (b) Marcia de Figueiredo, R.; Christmann, M. *Eur. J. Org. Chem.* **2007**, 2575. (c) Marques-Lopez, E.; Herrera, R. P.; Christmann, M. *Nat. Prod. Rep.* **2010**, *27*, 1138.

(2) For selected reviews on asymmetric organocatalytic Michael additions, see: (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (c) Nising, C. F.; Brase, S. *Chem. Soc. Rev.* **2008**, *37*, 1218. (d) Zhang, Y.; Wang, W. *Catal. Sci. Technol.* **2012**, *2*, 42. (e) Enders, D.; Wang, C.; Liebich, J. X. *Chem. Eur. J.* **2009**, *15*, 11058. (f) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (g) Nising, C. F.; Brase, S. *Chem. Soc. Rev.* **2012**, *41*, 988. (h) Enders, D.; Lüttgen, K.; Narine, A. A. *Synthesis* **2007**, 959. (i) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, 2065. (j) Krishna, P. R.; Sreeshailam, A.; Srinivas, R. *Tetrahedron* **2009**, *65*, 9657. (k) Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299.

(3) For selected reviews on asymmetric organocatalytic Michael additions in water, see: (a) Gruttadauria, M.; Giacalone, F.;

Noto, R. *Adv. Synth. Catal.* **2009**, *351*, 33. (b) Paradowska, J.; Stodulski, M.; Mlynarski, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 4288. (c) Raj, M.; Singh, V. K. *Chem. Commun.* **2009**, 6687. (d) Mase, N.; Barbas, C. F. *Org. Biomol. Chem.* **2010**, *8*, 4043. (e) Bhowmick, S.; Bhowmick, K. C. *Tetrahedron: Asymmetry* **2011**, *22*, 1945.

(4) (a) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209. (b) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751.

(5) For recent examples on organocatalytic Michael addition of ketones and aldehydes to nitroolefins in water, see: (a) Vishnumaya Singh, V. K. *Org. Lett.* **2007**, *9*, 1117. (b) Karthikeyan, T.; Sankararaman, S. *Tetrahedron: Asymmetry* **2008**, *19*, 2741. (c) Zheng, Z.; Perkins, B. L.; Ni, B. *J. Am. Chem. Soc.* **2010**, *132*, 50. (d) Lo, C.-M.; Chow, H.-F. *J. Org. Chem.* **2009**, *74*, 5181. (e) Wu, J.; Ni, B.; Headley, A. D. *Org. Lett.* **2009**, *11*, 3354. (f) Xiao, J.; Xu, F.-X.; Lu, Y.-P.; Loh, T.-P. *Org. Lett.* **2010**, *12*, 1220. (g) Chuan, Y.; Chen, G.; Peng, Y. *Tetrahedron Lett.* **2009**, *50*, 3054. (h) Moon, H. W.; Kim, D. Y. *Tetrahedron Lett.* **2010**, *51*, 2906. (i) Bae, H. Y.; Some, S.; Oh, J. S.; Lee, Y. S.; Song, C. E. *Chem. Commun.* **2011**, *47*, 9621. (j) Jia, Y.; Mao, Z.; Wang, R. *Tetrahedron: Asymmetry* **2011**, *22*, 2018. (k) Qiao, Y.; He, J.; Ni, B.; Headley, A. D. *Adv. Synth. Catal.* **2012**, *354*, 2849. (l) Singh, S.; Chimni, S. S. *Tetrahedron: Asymmetry* **2012**, *23*, 1068. (m) Chen, Q.; Qiao, Y.; Ni, B. *Synlett* **2013**, *24*, 839.

(6) (a) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F. *J. Am. Chem. Soc.* **2006**, *128*, 4966. (b) Zu, L.; Wang, J.; Li, H.; Wang, W. *Org. Lett.* **2006**, *8*, 3077. (c) Palomo, C.; Landa, A.; Mielgo, A.; Oiarbide, M.; Puente, Á.; Vera, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 8431. (d) Luo, C.; Du, D.-M. *Synthesis* **2011**, 1968. (e) Zhu, S.; Yu, S.; Ma, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 545. (f) Ma, A.; Zhu, S.; Ma, D. *Tetrahedron Lett.* **2008**, *49*, 3075. (g) Maltsev, O. V.; Kucherenko, A. S.; Zlotin, S. G. *Eur. J. Org. Chem.* **2009**, 5134. (h) Mager, I.; Zeitler, K. *Org. Lett.* **2010**, *12*, 1480.

(7) Zhao, H.-W.; Yue, Y.-Y.; Li, H.-L.; Song, X.-Q.; Sheng, Z.-H.; Yang, Z.; Meng, W.; Yang, Z. *Synlett* **2013**, *24*, 2160.

(8) Zhao, H.-W.; Li, H.-L.; Yue, Y.-Y.; Sheng, Z.-H. *Eur. J. Org. Chem.* **2013**, 1740.

(9) **Asymmetric Michael Addition; General Procedure:** A suspension of catalyst **2a** (4.2 mg, 0.01 mmol), $PhCO_2H$ (1.2 mg, 0.01 mmol) and cyclohexanone (104 μL, 1.0 mmol) in water (0.5 mL) was stirred at r.t. for 30 min. Nitroolefin (0.1 mmol) was added and the mixture was stirred for the time indicated in the tables. The mixture was extracted with CH_2Cl_2 (2 × 5 mL) and the organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. A mixture of *syn*- and *anti*-Michael products was obtained through flash chromatography on silica gel (petroleum–EtOAc, 5:1). The dr and ee values were determined by chiral HPLC analysis [Chiralcel AS-H; hexane–2-propanol, 85:15; 1.0 mL/min; λ = 210 nm; t_R = 13.91 (minor), 23.41 (major) min]. **(*S*)-2-[(*R*)-2-Nitro-1-phenylethyl]cyclohexanone (Table 2, entry 1):** Reaction time: 12 h. Yield: 85%; dr = 97:3 (*syn*/*anti*); ee = 89% (*syn*).^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.32 (m, 3 H), 7.16–7.17 (m, 2 H), 4.94 (dd, *J* = 12.4, 4.0 Hz, 1 H), 4.60–4.66 (m, 1 H), 3.76 (d, *J* = 4.0 Hz, 1 H), 2.69 (s, 1 H), 2.38–2.49 (m, 2 H), 2.07 (d, *J* = 3.2 Hz, 1 H), 1.55–1.80 (m, 4 H), 1.19–1.28 (m, 1 H).

