One-Pot Catalytic Enantioselective Synthesis of Functionalized Tetrahydroquinolines by Aza-Michael/Michael Cascade Reactions of N-Protected 2-Aminophenyl α,β-Unsaturated Esters with Nitroolefins

Ki-Tae Kang, Sung-Gon Kim*

Department of Chemistry, College of Natural Science, Kyonggi University, 154-42 Gwanggyosan-ro, Yeongtong-gu, Suwon, 443-760, Republic of Korea
Fax +82(31)2531165; E-mail: sgkim123@kyonggi.ac.kr

Received: 08.07.2014; Accepted after revision: 06.08.2014

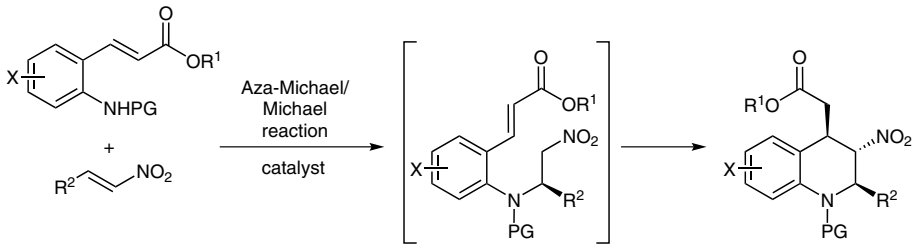
Abstract: A highly enantioselective synthesis of functionalized tetrahydroquinolines with useful biological properties has been developed by means of asymmetric organocatalytic aza-Michael/Michael cascade reactions of nitroolefins with N-protected 2-aminophenyl α,β-unsaturated esters in the presence of a chiral thiourea catalyst. The reaction gave the corresponding highly functionalized tetrahydroquinolines in good yields, excellent diastereoselectivities (>30:1 dr), and high enantioselectivities (≤99% ee).

Key words: organocatalysis, Michael additions, cascade reactions, asymmetric synthesis, tetrahydroquinolines

The tetrahydroquinoline core is a characteristic structural motif in many biologically active natural products and pharmacologically relevant therapeutic agents.[1] In particular, chiral functionalized tetrahydroquinolines form the structural cores of many natural products and pharmaceuticals that exhibit a broad range of biological activities, such as anti-HIV, antibacterial, antifungal, antimalarial, antitumor, and cardiovascular effects.[2] Consequently, the asymmetric synthesis of functionalized tetrahydroquinolines has been investigated intensively, and numerous stereoselective methodologies have been developed.[3] In particular, highly functionalized tetrahydroquinolines with chiral centers at the 2-, 3-, and 4-positions have received considerable attention and, as a result, there is an increasing demand for the development of new methods for their efficient asymmetric synthesis. A number of successful examples that use *ortho*-amino aromatic compounds as nucleophiles to react with a diverse range of electrophiles to give highly functionalized tetrahydroquinolines have been reported.[4] For example, Masson and co-workers successfully developed a three-component enantioselective Povarov reaction for the efficient synthesis of 2,3,4-trisubstituted tetrahydroquinolines from anilines, aldehydes, and ene carbamates as precursors.[4c]

Organocatalytic[5] enantioselective domino/cascade reactions[6] have also been identified as potential methods for the asymmetric synthesis of functionalized tetrahydroquinolines. In particular, many organocatalytic reactions catalyzed by bifunctional thiourea derivatives of cinchona alkaloids have been described.[7] Recently, Xu and co-workers reported an aza-Michael/Michael cascade reaction of 2-aminophenyl α,β-unsaturated ketones with nitroolefins to give 2,3,4-trisubstituted tetrahydroquinolines in high yields and excellent enantioselectivities, but with only moderate to good diastereoselectivities.[4a] Because of the limited success of this approach, there is still a need to develop an efficient enantioselective synthetic method for preparing highly functionalized tetrahydroquinolines. Recently, our group and Du and co-workers independently reported an organocatalyzed aza-Michael/Michael cascade reaction for the synthesis of chiral highly functionalized tetrahydroquinolines by using 2-(tosylamino)phenyl α,β-unsaturated ketones and nitroolefins as the starting materials to give the desired products in good yields and excellent diastereoselectivities and enantioselectivities.[8]

To develop these findings further, we surmised that the use of 2-(tosylamino)phenyl α,β-unsaturated esters in the aza-Michael/Michael cascade reaction might give chiral highly functionalized tetrahydroquinolines possessing greater synthetic versatility, as the ester functional group can be readily transformed into various other functional



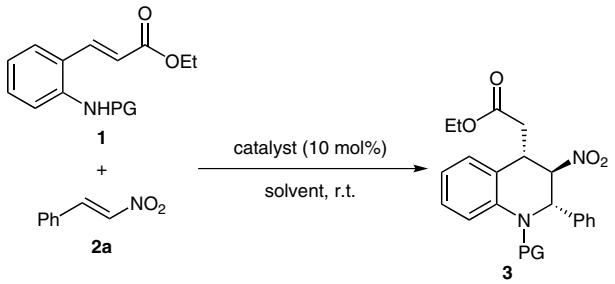
Scheme 1 Organocatalytic aza-Micheal/Micheal cascade reaction of N-protected 2-aminophenyl α,β-unsaturated esters with nitroalkenes

SYNTHESIS 2014, 46, 3365–3373
Advanced online publication: 10.09.2014
DOI: 10.1055/s-0034-1379044; Art ID: ss-2014-f0428.eps

groups, such as carboxylic acid, aldehyde, or alcohol groups (Scheme 1).[9]

We began our studies by evaluating the cascade reaction of N-protected-2-aminophenyl α,β-unsaturated ethyl esters **1** with β-nitrostyrene (**2a**) using thiourea cinchona alkaloid **Ia** as the catalyst in dichloromethane at room temperature (Table 1 and Figure 1).

Table 1 Exploration of the Aza-Michael/Michael Reactions of N-Protected 2-Aminophenyl α,β-Unsaturated Esters with β-Nitrostyrene[a]



Entry	PG	Catalyst	Solvent	Time (h)	Yield (%)[b]	dr[c]	ee[d] (%)
1	CO_2Et	**Ia**	CH_2Cl_2	48	–[e]	nd[f]	nd
2	Boc	**Ia**	CH_2Cl_2	48	–[e]	nd	nd
3	Cbz	**Ia**	CH_2Cl_2	48	–[e]	nd	nd
4	Ts	**Ia**	CH_2Cl_2	40	85	>30:1	92
5	Ts	**Ib**	CH_2Cl_2	30	57	>30:1	93
6	Ts	**Ic**	CH_2Cl_2	36	53	>30:1	92
7	Ts	**Id**	CH_2Cl_2	30	85	24:1	96
8	Ts	**IIa**	CH_2Cl_2	30	66	>30:1	92
9	Ts	**IIb**	CH_2Cl_2	24	86	>30:1	98
10	Ts	**IIIa**	CH_2Cl_2	36	91	10:1	94
11	Ts	**IIIb**	CH_2Cl_2	48	8	nd	nd
12	Ts	**IIb**	CH_2Cl_2	24	88	>30:1	97
13	Ts	**IIb**	DCE	52	71	>30:1	97
14	Ts	**IIb**	toluene	24	85	>30:1	99
15	Ts	**IIb**	MeCN	52	15	25:1	95
16	Ts	**IIb**	THF	52	5	nd	nd
17	Ts	**IIb**	MeOH	52	5	nd	nd
18	Ts	**IIb**	DMF	52	–[e]	nd	nd

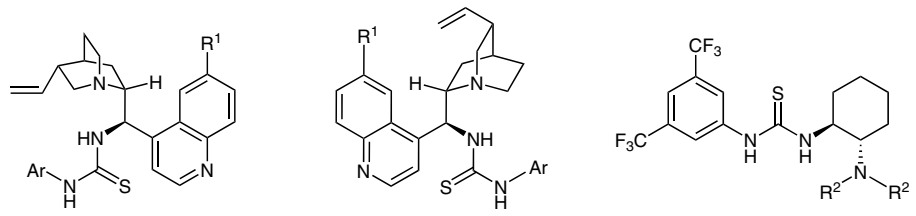
[a] All of the reactions were carried out in the appropriate solvent (0.3 M) with **1** (0.15 mmol) and β-nitrostyrene (**2a**, 0.30 mmol) in the presence of the catalyst (10 mol%) at r.t.
[b] Isolated yield after chromatographic purification.
[c] Determined by ^1H NMR analysis.
[d] Determined by chiral-phase HPLC analysis.
[e] No reaction.
[f] Not determined.

The choice of protecting group on the nitrogen atom of the phenyl α,β-unsaturated ethyl ester significantly affected the reactivity of the substrate in the aza-Michael/Michael reaction. No reaction was observed when ethoxycarbonyl, *tert*-butoxycarbonyl, or benzyloxycarbonyl protecting groups were used (Table 1, entries 1–3). However, the reaction proceeded smoothly to give the desired tetrahydroquinoline **3aa** in good yield, excellent diastereoselectivity (>30:1 dr), and good enantioselectivity (92% ee) when a more strongly electron-withdrawing tosyl group was used as the protecting group in ester **1** (Table 1, entry 4).

Under analogous conditions, the cinchona alkaloid-based catalysts **Ib**, **Ic**, and **IIa** gave similar results to catalyst **Ia**, affording **3aa** in moderate yield with excellent diastereoselectivity (>30:1 dr) and good enantioselectivity (entries 5, 6, and 8). Of the cinchona alkaloids tested, the thiourea cinchona alkaloid **IIb** was found to be the optimal catalyst in terms of the reactivity and stereoselectivity of the reaction (entry 9). The Takemoto catalysts **IIIa** and **IIIb**[10] gave inferior results to catalyst **IIb** (entries 5–8). Next, we examined various solvents to optimize the reaction further. The reaction medium had a marked effect on the conversion efficiency of the reaction. Protic solvents gave reduced reaction efficiencies (entries 15–18), probably due to a reduction in the activity of the catalyst because the aza-Michael/Michael reaction occurs through substrate activation by the thiourea catalyst through hydrogen-bonding interactions. The solvent-screening studies identified toluene as the optimal solvent for the reaction (entry 14); however, we chose dichloromethane as the solvent for further evaluation of this reaction, because most of the substrates that we tested showed poor solubility in toluene.

Having identified the optimal reactions conditions [**1** (1 equiv), **2** (2 equiv), catalyst **IIb** (10 mol%), CH_2Cl_2], we examined the scope of the reaction with various substrates. First, we examined the reaction of various 2-(tosylamino)phenyl α,β-unsaturated esters **1a**–**j** with β-nitrostyrene (**2a**; Table 2). The reaction proved insensitive to the type of ester moiety and it proceeded smoothly to give the corresponding tetrahydroquinolines **3aa**–**da** in good yields and excellent diastereo- and enantioselectivities. Furthermore, the sterically bulky *tert*-butyl ester **1d** presented no problems, and gave tetrahydroquinoline **3da** with >30:1 dr and 98% ee, albeit with a reduced yield (entry 4). The electronic nature, bulk, and position of the substituent in the phenyl ring of the 2-(tosylamino)phenyl α,β-unsaturated ethyl esters had no obvious effect on the efficiency, diastereoselectivity, or enantioselectivity of the reaction (entries 5–10).

We also evaluated the catalytic aza-Michael/Michael cascade reactions of various nitroolefins **2b**–**m** (Table 3). The electronic nature of nitroolefin **2** had little effect on the reactivity or stereoselectivity of the reaction. Aromatic nitroolefins with either electron-donating (Table 3, entries 1–5) or electron-withdrawing substituents (entries 6–10) on the phenyl ring participated in the reaction with high efficiency, regardless of the substitution pattern. All prod-



Ia R^1 = H, Ar = 3,5-$(F_3C)_2C_6H_3$
Ib R^1 = H, Ar = Ph
Ic R^1 = OMe, Ar = 3,5-$(F_3C)_2C_6H_3$
Id R^1 = OMe, Ar = Ph

IIa R^1 = OMe, Ar = 3,5-$(F_3C)_2C_6H_3$
IIb R^1 = OMe, Ar = Ph

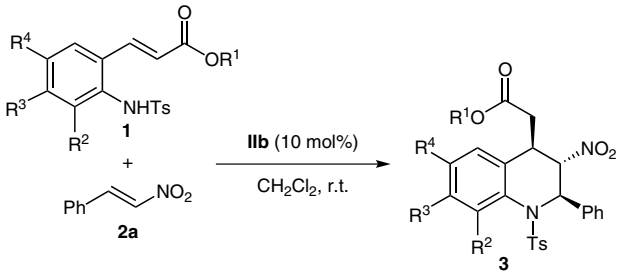
IIIa R^2 = Me
IIIb R^2 = H

Figure 1 Evaluated chiral organocatalysts

ucts were obtained in good yield with excellent diastereoselectivities (from 25:1 to >30:1 dr) and enantioselectivities (94–99% ee). Much to our delight, the hetaryl nitroolefin **2l** was also tolerated and gave the highly functionalized tetrahydroquinoline **3al** in 83% yield with >30:1 d.r. and 98% ee (entry 11). In addition, the aliphatic nitroolefin **2m** also gave the desired product **3am** in excellent yield and diastereoselectivity, albeit with a slightly diminished enantioselectivity (entry 12).

To determine the absolute configuration of the products, we prepared single crystals suitable for X-ray crystallographic analysis from the tetrahydroquinoline **3ae**. The absolute stereochemistry of **3ae** was unambiguously as-

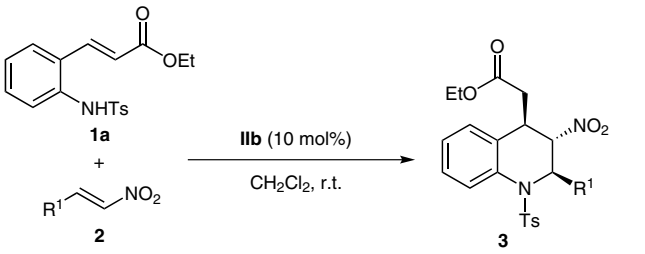
Table 2 Enantioselective Aza-Michael/Michael Reactions of 2-(Tosylamino)phenyl α,β-Unsaturated Esters **1a–j** with β-Nitrostyrene (**2a**) Catalyzed by Thiourea **IIb**[a]



Entry	R^1	R^2	R^3	R^4	Product	Time (h)	Yield (%)[b]	dr[c]	ee[d] (%)
1	Et	H	H	H	**3aa**	24	91	>30:1	98
2	Me	H	H	H	**3ba**	24	82	>30:1	94
3	Bn	H	H	H	**3ca**	24	98	>30:1	98
4	*t*-Bu	H	H	H	**3da**	48	45	>30:1	98
5	Et	H	H	Me	**3ea**	36	79	>30:1	97
6	Et	Me	H	H	**3fa**	36	63	>30:1	98
7	Et	H	OCH_2O		**3ga**	28	72	>30:1	94
8	Et	H	H	Cl	**3ha**	28	83	>30:1	96
9	Et	H	Cl	H	**3ia**	36	80	>30:1	97
10	Et	H	H	Br	**3ja**	36	64	25:1	94

[a] All of the reactions were carried out in CH_2Cl_2 (0.3 M) with **1** (0.15 mmol) and β-nitrostyrene (**2a**, 0.30 mmol) in the presence of catalyst **IIb** (10 mol%) at r.t.
[b] Isolated yield after chromatographic purification.
[c] Determined by ^1H NMR analysis.
[d] Determined by chiral-phase HPLC analysis.

Table 3 Enantioselective Aza-Michael/Michael Reactions of 2-(Tosylamino)phenyl α,β-Unsaturated Ethyl Ester (**1a**) with Nitroalkenes **2b–m** Catalyzed by Thiourea **IIb**[a]



Entry	R^1	Product	Time (h)	Yield (%)[b]	dr[c]	ee%[d]
1	4-$MeOC_6H_4$	**3ab**	24	52	>30:1	94
2	3-$MeOC_6H_4$	**3ac**	24	88	>30:1	96
3	2-$MeOC_6H_4$	**3ad**	24	61	>30:1	95
4	3,4-$(MeO)_2C_6H_3$	**3ae**	24	73	>30:1	99
5	4-MeC_6H_4	**3af**	24	78	>30:1	97
6	4-ClC_6H_4	**3ag**	24	72	28:1	96
7	2-ClC_6H_4	**3ah**	24	92	>30:1	97
8	2-BrC_6H_4	**3ai**	24	74	>30:1	97
9	4-FC_6H_4	**3aj**	24	80	28:1	96
10	4-$O_2NC_6H_4$	**3ak**	24	76	25:1	94
11	2-thienyl	**3al**	24	83	>30:1	98
12	*i*-Pr	**3am**	24	94	>30:1	70

[a] All of the reactions were carried out in CH_2Cl_2 (0.3 M) with **1** (0.15 mmol) and nitroalkene **2** (0.30 mmol) in the presence of catalyst **IIb** (10 mol%) at r.t.
[b] Isolated yield after chromatographic purification.
[c] Determined by ^1H NMR analysis.
[d] Determined by chiral-phase HPLC analysis.

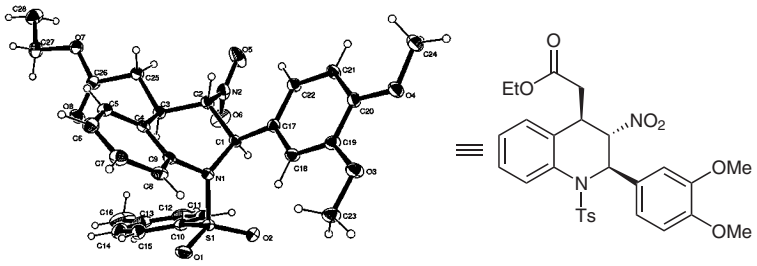
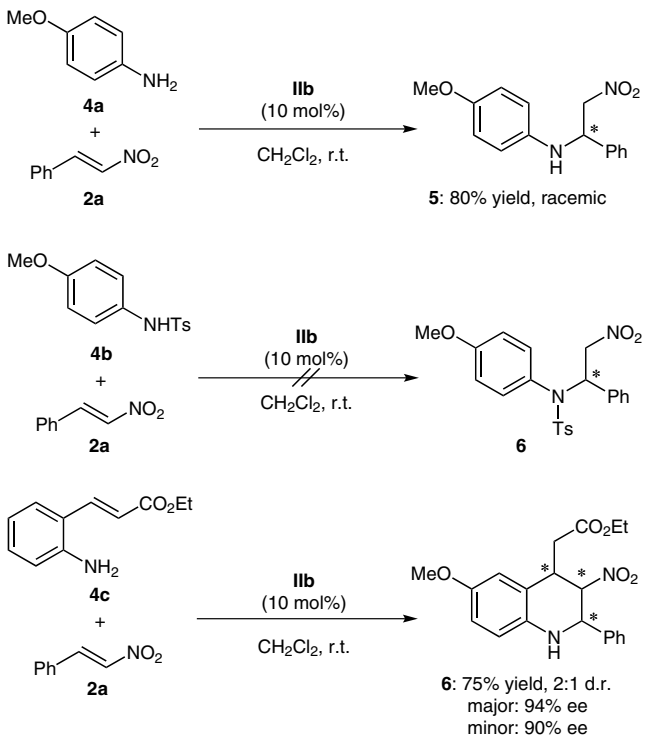


Figure 2 X-ray crystal structure of compound **3ae**

signed as (2*R*,3*S*,4*R*) by means of single-crystal X-ray diffraction (Figure 2).[11] By analogy, the other products were assumed to have the same configuration.

Finally, to confirm the role of the tosyl group and the α,β-unsaturated ester moiety, as well as their combined effect, we examined the catalytic reactions of 4-methoxyaniline (**4a**), 4-methoxy-*N*-tosylaniline (**4b**), and the 2-aminophenyl α,β-unsaturated ethyl ester **4c** with β-nitrostyrene (**2a**) in the presence of the thiourea cinchona alkaloid catalyst **IIb** under our optimized reaction conditions (Scheme 2). The reaction of 4-methoxyaniline (**4a**) gave the desired product **5** in 80% yield but as a racemate, indicating that the α,β-unsaturated ester moiety is a key feature for chiral induction in the aza-Michael/Michael cascade reaction. Notably, no reaction was observed when 4-methoxy-*N*-tosylaniline (**4b**) was used, whereas the 2-aminophenyl α,β-unsaturated ethyl ester **4c** gave the desired product **6** in good yield and high enantioselectivity (94% ee for the major isomer), but with moderate diastereoselectivity (2:1 dr). From these results, we surmise that the presence of a tosyl group is important for achieving a high level of diastereoselectivity, although it decreases the observed reactivity.

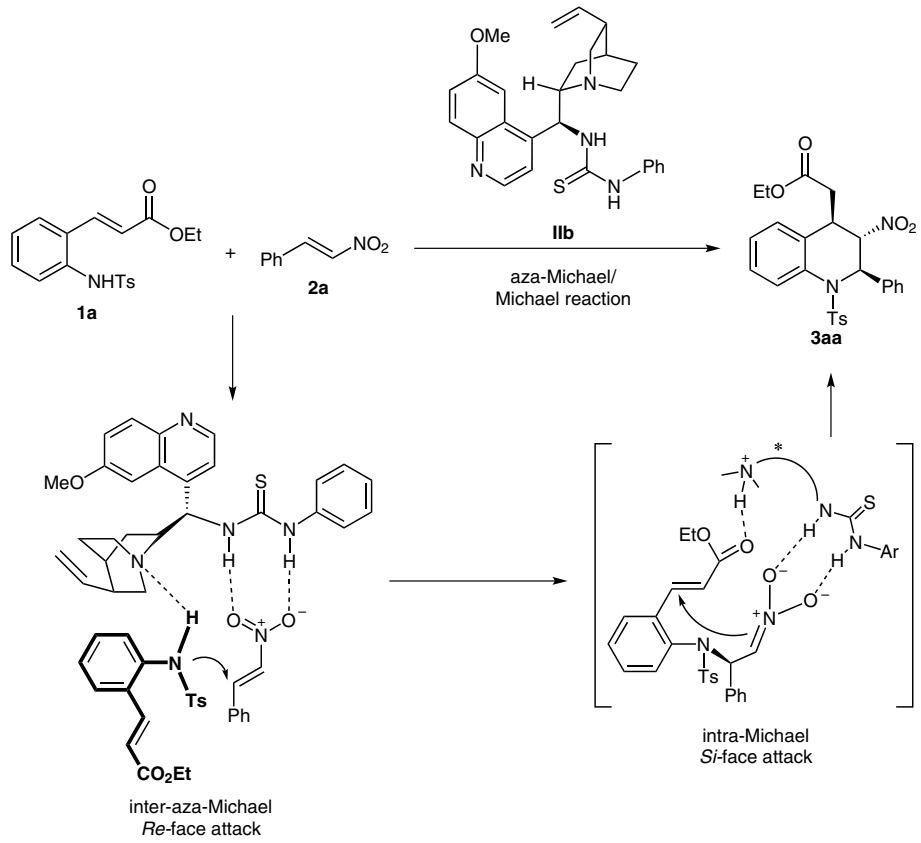


Scheme 2 The effects of tosyl and α,β-unsaturated ester functional groups in organocatalytic aza-Micheal/Micheal reactions

From our experimental results and a dual-activation model,[12] we propose a simplified but plausible mechanism that account for the observed stereoselectivity of the reaction (Scheme 3). Initially, the nitroolefin **2a** is activated by hydrogen bonding, including an interaction between the carbonyl and thiourea moieties of the bifunctional catalyst **IIb**. Meanwhile, the tertiary amine moiety present in the catalyst acts as a base and activates the tosylated amine in compound **1a**. The amine in the 2-(tosylamino)phenyl α,β-unsaturated ethyl ester attacks activated β-nitrostyrene (**2a**) preferentially from the *Re* face, resulting in an intermediate with an *R*-configuration. The resulting α-carbon derived from the nitroalkene approaches the α,β-unsaturated ester group by an intramolecular Michael reaction to give the (2*R*,3*S*,4*R*)-product **3**.

In conclusion, a highly diastereo- and enantioselective catalytic aza-Michael/Michael cascade reaction of 2-(tosylamino)phenyl α,β-unsaturated ketones with nitroolefins in the presence of a cinchona alkaloid-derived thiourea was developed for the efficient preparation of highly functionalized tetrahydroquinoline derivatives. The cascade reaction proceeded well with a wide range of nitroolefins and 2-(tosylamino)phenyl α,β-unsaturated esters, and provided efficient access to a variety of highly functionalized tetrahydroquinolines in good yields and excellent diastereo- and enantioselectivities (up to >30:1 dr, 99% ee).

All reactions were performed in flame- or oven-dried glassware under an atmosphere of dry N_2. Organic solvents were distilled before use. Organic solutions were concentrated under reduced pressure using a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32–64 mesh silica gel 63. TLC was performed on 0.25 mm silica gel 60-F plates (EM Reagents, Darmstadt). Developed chromatograms were visualized by fluorescence quenching and by staining with anisaldehyde. ^{1}H NMR spectra were recorded at 400 or 700 MHz and ^{13}C NMR spectra were recorded at 100 MHz or 176 MHz on Bruker Avance II 400 or Avance III 700 spectrometers. The NMR spectra were internally referenced to residual nondeuterated solvent signals. Optical rotations were measured with a Perkin-Elmer P241 polarimeter with a sodium lamp (589 nm) and a 1.0 dm cell. High-resolution mass spectra were recorded by using a SYNAPT G2 Q-TOF mass spectrometer. HPLC analysis was performed



Scheme 3 A proposed mechanism for the asymmetric aza-Micheal/Micheal reaction

on a Hewlett-Packard 1100 Series chromatograph by using an AD-H (25 cm) column and an AD-H guard (5 cm) column.

Alkyl [(2*R*,3*S*,4*R*)-3-Nitro-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl]acetates 3; General Procedure

A 2-dram amber vial equipped with a magnetic stirrer bar was charged at r.t. with catalyst **IIb** (0.015 mmol, 10 mol%) and enoate **1** (0.15 mmol, 1.0 equiv), followed by toluene (0.5 mL) The solution was stirred for 5 min and then nitroalkene **2** (0.30 mmol, 2.0 equiv) was added. The mixture was stirred at r.t. until enoate **1** was completely consumed (TLC). The mixture was then directly purified by chromatography (silica gel, 20% EtOAc–hexane).

Ethyl [(2*R*,3*S*,4*R*)-3-Nitro-2-phenyl-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl]acetate (3aa)

White solid; yield: 68 mg (91%); mp 147–148 °C; $[\alpha]_D^{26}$ –8.0 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (dd, *J* = 5.2, 8.0 Hz, 1 H), 7.57 (d, *J* = 8.4 Hz, 2 H), 7.44 (t, *J* = 7.6 Hz, 1 H), 7.20–7.36 (m, 8 H), 7.03 (d, *J* = 8.0 Hz, 1 H), 6.02 (d, *J* = 7.2 Hz, 1 H), 4.82 (dd, *J* = 7.2, 10.8 Hz, 1 H), 4.11 (dq, *J* = 2.0, 7.2 Hz, 2 H), 2.74 (ddd, *J* = 4.0, 8.8, 12.0 Hz, 1 H), 2.56 (dd, *J* = 8.4, 17.2 Hz, 1 H), 2.43 (s, 3 H), 2.37 (dd, *J* = 4.0, 17.2 Hz, 1 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 144.5, 139.7, 135.8, 135.5, 131.4, 129.9, 129.1, 128.7, 128.5, 127.7, 127.4, 127.2, 126.2, 125.0, 94.7, 62.8, 61.0, 36.5, 32.5, 21.6, 14.1.

HRMS (ESI): *m*/*z* calcd for $C_{26}H_{26}N_2NaO_6S$ $[M + Na]^+$: 517.1409; found: 517.1403.

HPLC: Chiralpak AD-H column and AD-H guard column (10% *i*-PrOH–hexanes, 1.0 mL/min flow, λ = 254 nm); minor isomer: t_R = 13.3 min; major isomer: t_R = 24.2 min; 98% ee.

Methyl [(2*R*,3*S*,4*R*)-3-Nitro-2-phenyl-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl]acetate (3ba)

White solid; yield: 59 mg (82%); mp 148–150 °C; $[\alpha]_D^{20}$ –16.1 (*c* 1.4, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 7.6 Hz, 1 H), 7.57 (d, *J* = 8.0 Hz, 2 H), 7.44 (t, *J* = 7.6 Hz, 1 H), 7.20–7.36 (m, 8 H), 7.02 (d, *J* = 8.0 Hz, 1 H), 6.02 (d, *J* = 7.2 Hz, 1 H), 4.79 (dd, *J* = 7.2, 10.8 Hz, 1 H), 3.64 (s, 3 H), 2.70–2.77 (m, 1 H), 2.58 (dd, *J* = 8.4, 17.2 Hz, 1 H), 2.44 (s, 3 H), 2.36 (dd, *J* = 3.6, 17.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 144.5, 139.6, 135.8, 135.5, 131.4, 129.9, 129.1, 128.8, 128.5, 127.8, 127.5, 127.2, 126.2, 124.9, 94.8, 62.8, 52.1, 36.5, 32.3, 21.7.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{24}N_2NaO_6S$: 503.1253; found: 503.1252.

HPLC: Chiralpak AD-H column and AD-H guard column (10% *i*-PrOH–hexanes, 1.0 mL/min flow, λ = 254 nm); minor isomer: t_R = 21.5 min; major isomer: t_R = 26.4 min; 94% ee.

Benzyl [(2*R*,3*S*,4*R*)-3-Nitro-2-phenyl-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl]acetate (3ca)

Colorless gum; yield: 82 mg (98%); $[\alpha]_D^{22}$ –19.0 (*c* 1.03, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.0 Hz, 1 H), 7.56 (d, *J* = 8.4 Hz, 2 H), 7.43 (t, *J* = 7.6 Hz, 1 H), 7.19–7.39 (m, 13 H), 6.97 (d, *J* = 7.6 Hz, 1 H), 6.03 (d, *J* = 6.8 Hz, 1 H), 5.09 (dd, *J* = 12.0, 20.4 Hz, 2 H), 4.83 (dd, *J* = 7.2, 10.8 Hz, 1 H), 2.77 (ddd, *J* = 4.0, 8.8, 11.6 Hz, 1 H), 2.61 (dd, *J* = 8.4, 17.2 Hz, 1 H), 2.38–2.58 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 144.6, 139.6, 135.8, 135.4, 135.3, 131.2, 129.9, 129.1, 128.8, 128.6, 128.5, 128.4, 128.3, 127.7, 127.3, 127.2, 126.2, 125.1, 94.6, 66.8, 62.7, 36.5, 32.6, 21.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{31}H_{28}N_2NaO_6S$: 579.1566; found: 579.1565.

HPLC: Chiralpak AD-H column and AD-H guard column (10% *i*-PrOH–hexanes, 1.0 mL/min flow, λ = 220 nm); minor isomer: t_R = 19.5 min; major isomer: t_R = 34.0 min; 98% ee.

tert-Butyl [(2*R*,3*S*,4*R*)-3-Nitro-2-phenyl-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl]acetate (3da)

Colorless gum; yield: 36 mg (45%); $[\alpha]_D^{22}$ –17.9 (*c* 1.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (dd, *J* = 0.8, 8.0 Hz, 1 H), 7.55 (d, *J* = 8.4 Hz, 2 H), 7.43 (t, *J* = 7.6 Hz, 1 H), 7.20–7.35 (m, 8 H), 7.08 (d, *J* = 8.0 Hz, 1 H), 6.01 (d, *J* = 7.2, 10.8 Hz, 1 H), 4.84 (dd, *J* = 7.2, 10.8 Hz, 1 H), 2.66 (ddd, *J* = 4.0, 8.8, 10.8 Hz, 1 H), 2.45 (dd, *J* = 8.0, 17.2 Hz, 1 H), 2.42 (s, 3 H), 2.30 (dd, *J* = 4.0, 17.2 Hz, 1 H), 1.39 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 144.5, 139.8, 135.8, 135.3, 131.7, 129.8, 129.1, 128.6, 128.4, 127.5, 127.2, 127.1, 126.2, 125.2, 94.6, 81.6, 62.8, 36.7, 33.5, 27.9, 21.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{30}N_2NaO_6S$: 545.1722; found: 545.1719.

HPLC: Chiralpak AD-H column and AD-H guard column (10% *i*-PrOH–hexanes, 1.0 mL/min flow, λ = 254 nm); minor isomer: t_R = 9.02 min; major isomer: t_R = 14.1 min; 98% ee.

Ethyl [(2*R*,3*S*,4*R*)-6-Methyl-3-nitro-2-phenyl-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl]acetate (3ea)

White solid; yield: 60 mg (79%); mp 136–138 °C; $[\alpha]_D^{25}$ +16.7 (*c* 0.98, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.0 Hz, 1 H), 7.58 (d, *J* = 8.4 Hz, 2 H), 7.21–7.37 (m, 8 H), 6.83 (s, 1 H), 6.00 (d, *J* = 6.8 Hz, 1 H), 4.80 (dd, *J* = 2.8, 6.8 Hz, 1 H), 4.11 (q, *J* = 7.2 Hz, 2 H), 2.69–2.76 (m, 1 H), 2.55 (dd, *J* = 8.4, 17.2 Hz, 1 H), 2.43 (s, 3 H), 2.32–2.39 (m, 4 H), 1.23 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 144.3, 139.8, 137.3, 135.6, 133.2, 131.2, 129.8, 129.4, 129.1, 128.4, 127.5, 127.2, 126.2, 125.5, 94.8, 62.8, 60.9, 36.5, 32.6, 21.6, 21.4, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{28}N_2NaO_6S$: 531.1566; found: 531.1569.

HPLC: Chiralpak AD-H column and AD-H guard column (10% EtOH–hexanes, 1.0 mL/min flow, λ = 254 nm); minor isomer: t_R = 8.9 min; major isomer: t_R = 10.8 min; 97% ee.

Ethyl [(2*R*,3*S*,4*R*)-8-Methyl-3-nitro-2-phenyl-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl]acetate (3fa)

White solid; yield: 56 mg (63%); mp 77–78 °C; $[\alpha]_D^{24}$ –40.9 (*c* 0.49, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.0 Hz, 2 H), 7.28–7.39 (m, 7 H), 7.05 (dd, *J* = 3.6, 7.6 Hz, 2 H), 6.94 (d, *J* = 7.2 Hz, 1 H), 5.80 (d, *J* = 7.6 Hz, 1 H), 4.79 (dd, *J* = 7.6, 12.0 Hz, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 2.71–2.79 (m, 1 H), 2.57 (dd, *J* = 4.0, 17.2 Hz, 1 H), 2.40–2.51 (m, 7 H), 1.25 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 144.7, 139.7, 139.3, 135.6, 134.8, 134.5, 131.4, 130.0, 129.0, 128.6, 128.2, 127.9, 126.7, 122.4, 94.7, 63.8, 60.9, 36.9, 32.1, 21.6, 19.5, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{28}N_2NaO_6S$: 531.1566; found: 531.1566.

HPLC: Chiralpak AD-H column and AD-H guard column (5% EtOH–hexanes, 1.0 mL/min flow, λ = 254 nm); minor isomer: t_R = 8.5 min; major isomer: t_R = 10.4 min; 98% ee.

Ethyl {(6*R*,7*S*,8*R*)-7-Nitro-6-phenyl-5-tosyl-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]quinolin-8-yl}acetate (3ga)

White solid; yield: 58 mg (72%); mp 171–173 °C; $[\alpha]_D^{25}$ +82.4 (*c* 0.86, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 6.4 Hz, 2 H), 7.29–7.37 (m, 6 H), 7.22 (dd, *J* = 2.0, 8.0 Hz, 2 H), 6.50 (s, 2 H), 6.05 (dd, *J* = 1.2, 12.0 Hz, 2 H), 5.96 (d, *J* = 6.8 Hz, 1 H), 4.75 (dd, *J* = 7.2, 10.8 Hz, 1 H), 4.10 (q, *J* = 7.2 Hz, 2 H), 2.34–2.56 (m, 6 H), 1.23 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 147.6, 147.2, 144.5, 139.8, 135.4, 129.9, 129.6, 129.1, 128.5, 127.2, 126.2, 125.6, 109.6, 104.7, 102.0, 95.3, 63.0, 61.1, 36.7, 32.4, 21.6, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{26}N_2NaO_8S$: 561.1308; found: 561.1304.

HPLC: Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ = 254 nm); minor isomer: t_R = 10.2 min; major isomer: t_R = 23.5 min; 94% ee.

Ethyl [(2*R*,3*S*,4*R*)-6-Chloro-3-nitro-2-phenyl-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl]acetate (3ha)

White solid; yield: 66 mg (83%); mp 131–133 °C; $[\alpha]_D^{24}$ +33.3 (*c* 1.1, $CHCl_3$).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 9.1 Hz, 1 H), 7.59 (d, *J* = 7.7 Hz, 2 H), 7.40 (dd, *J* = 1.4, 8.4 Hz, 1 H), 7.28–7.37 (m, 5 H), 7.20 (d, *J* = 7.0 Hz, 2 H), 7.03 (s, 1 H), 6.04 (d, *J* = 7.0 Hz, 1 H), 4.89 (dd, *J* = 6.3, 10.5 Hz, 1 H), 4.13 (q, *J* = 7.0 Hz, 2 H), 2.72–2.78 (m, 1 H), 2.51 (dd, *J* = 7.7, 17.5 Hz, 1 H), 2.44 (s, 3 H), 2.34 (dd, *J* = 7.7, 16.8 Hz, 1 H), 1.24 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 169.5, 144.8, 139.1, 135.2, 134.4, 133.0, 130.0, 129.2 (two peaks overlapping), 128.9, 128.6, 128.5, 127.2, 126.2, 125.6, 93.8, 62.6, 61.2, 36.4, 32.5, 21.7, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{25}ClN_2NaO_6S$: 551.1020; found: 551.1024.

HPLC: Chiralpak AD-H column and AD-H guard column (20% EtOH, 1.0 mL/min flow, λ = 254 nm); minor isomer: t_R = 6.6 min; major isomer: t_R = 8.0 min; 96% ee.

Ethyl [(2*R*,3*S*,4*R*)-7-Chloro-3-nitro-2-phenyl-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl]acetate (3ia)

White solid; yield: 63 mg (80%); mp 109–110 °C; $[\alpha]_D^{25}$ +27.8 (*c* 0.96, $CHCl_3$).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 1.4 Hz, 1 H), 7.61 (d, *J* = 8.4 Hz, 2 H), 7.29–7.38 (m, 5 H), 7.26 (dd, *J* = 1.4, 7.7 Hz, 1 H), 7.21 (d, *J* = 7.0 Hz, 2 H), 6.97 (d, *J* = 8.4 Hz, 1 H), 6.08 (d, *J* = 7.0 Hz, 1 H), 4.89 (dd, *J* = 7.0, 10.5 Hz, 1 H), 4.10 (dq, *J* = 2.1, 7.0 Hz, 2 H), 2.78–2.83 (m, 1 H), 2.51 (dd, *J* = 7.7, 17.5 Hz, 1 H), 2.44 (s, 3 H), 2.32 (dd, *J* = 4.9, 17.5 Hz, 1 H), 1.22 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 169.7, 144.9, 139.0, 136.9, 135.2, 134.3, 130.0, 129.3, 129.2, 128.7, 127.3, 127.2, 126.8, 126.4, 126.2, 93.6, 62.5, 61.2, 36.1, 32.9, 21.7, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{25}ClN_2NaO_6S$: 551.1020; found: 551.1019.

HPLC: Chiralpak AD-H column and AD-H guard column (5% EtOH–hexanes, 1.0 mL/min flow, λ = 254 nm); major isomer: t_R = 14.3 min; minor isomer: t_R = 17.6 min; 97% ee.

Ethyl [(2*R*,3*S*,4*R*)-6-Bromo-3-nitro-2-phenyl-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl]acetate (3ja)

White solid; yield: 55 mg (64%); mp 128–130 °C; $[\alpha]_D^{25}$ +49.9 (*c* 0.96, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 8.0 Hz, 1 H), 7.59 (d, *J* = 8.0 Hz, 2 H), 7.54 (dd, *J* = 1.6, 7.6 Hz, 1 H), 7.28–7.37 (m, 5 H), 7.19–7.23 (m, 3 H), 6.05 (d, *J* = 6.8 Hz, 1 H), 4.91 (dd, *J* = 6.4, 10.0 Hz, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 2.76–2.83 (m, 1 H), 2.51 (dd, *J* = 8.0, 17.2 Hz, 1 H), 2.44 (s, 3 H), 2.33 (dd, *J* = 1.2, 17.2 Hz, 1 H), 1.25 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 144.8, 139.1, 135.3, 135.0, 133.1, 131.8, 130.0, 129.2, 129.1, 128.7, 128.6, 127.2, 126.2, 120.7, 93.7, 62.5, 61.2, 36.3, 32.7, 21.6, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{25}BrN_2NaO_6S$: 595.0514; found: 595.0517.

HPLC: Chiralpak AD-H column and AD-H guard column (5% EtOH–hexanes, 1.0 mL/min flow, λ = 254 nm); minor isomer: t_R = 12.0 min; major isomer: t_R = 15.8 min; 94% ee.

Ethyl [(2*R*,3*S*,4*R*)-2-(4-Methoxyphenyl)-3-nitro-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl]acetate (3ab)
White solid; yield: 41 mg (52%); mp 124–125 °C; $[\alpha]_D^{26}$ –0.13 (*c* 0.71, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (dd, *J* = 0.8, 8.0 Hz, 1 H), 7.56 (d, *J* = 8.4 Hz, 2 H), 7.42 (t, *J* = 7.7 Hz, 1 H), 7.11–7.19 (m, 3 H), 7.12 (d, *J* = 7.6 Hz, 2 H), 7.03 (dd, *J* = 0.8, 7.6 Hz, 1 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 5.95 (d, *J* = 6.8 Hz, 1 H), 4.76 (dd, *J* = 7.2, 8.4 Hz, 1 H), 4.10 (dq, *J* = 2.0, 7.6 Hz, 2 H), 3.79 (s, 3 H), 2.73 (ddd, *J* = 4.0, 8.4, 10.8 Hz, 1 H), 2.56 (dd, *J* = 8.0, 17.2 Hz, 1 H), 2.43 (s, 3 H), 2.38 (dd, *J* = 4.0, 17.2 Hz, 1 H), 1.22 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 159.6, 144.4, 135.8, 135.5, 131.8, 131.5, 129.8, 128.7, 127.7, 127.6, 127.3, 127.2, 124.9, 114.4, 94.8, 62.5, 61.0, 55.3, 36.5, 32.5, 21.6, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{28}N_2NaO_7S$: 547.1515; found: 547.1513.

HPLC: Chiralpak AD-H column and AD-H guard column (10% EtOH–hexanes, 1.0 mL/min flow, λ = 254 nm); minor isomer: t_R = 21.5 min; major isomer: t_R = 26.4 min; 94% ee.

Ethyl [(2*R*,3*S*,4*R*)-2-(3-Methoxyphenyl)-3-nitro-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl]acetate (3ac)
White solid; yield: 69 mg (88%); mp 95–97 °C; $[\alpha]_D^{27}$ –16.8 (*c* 0.99, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (dd, *J* = 0.8, 8.0 Hz, 1 H), 7.57 (d, *J* = 8.0 Hz, 2 H), 7.43 (t, *J* = 8.0 Hz, 1 H), 7.21–7.32 (m, 4 H), 7.04 (d, *J* = 8.0 Hz, 1 H), 6.75–6.87 (m, 3 H), 6.02 (d, *J* = 7.2 Hz, 1 H), 4.82 (dd, *J* = 6.8, 10.8 Hz, 1 H), 4.11 (dq, *J* = 1.6, 7.2 Hz, 2 H), 3.76 (s, 3 H), 2.73–2.81 (m, 1 H), 2.56 (dd, *J* = 8.4, 17.2 Hz, 1 H), 2.43 (s, 3 H), 2.37 (dd, *J* = 4.0, 17.2 Hz, 1 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 160.0, 144.5, 141.2, 135.9, 135.5, 131.3, 130.2, 129.8, 128.7, 127.5, 127.3, 127.2, 125.0, 118.4, 113.9, 111.9, 94.6, 62.6, 61.0, 55.2, 36.5, 32.6, 21.6, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{28}N_2NaO_7S$: 547.1515; found: 547.1515.

HPLC: Chiralpak AD-H column and AD-H guard column (10% *i*-PrOH–hexanes, 1.0 mL/min flow, λ = 220 nm); minor isomer: t_R = 19.5 min; major isomer: t_R = 34.0 min; 96% ee.

Ethyl [(2*R*,3*S*,4*R*)-2-(2-Methoxyphenyl)-3-nitro-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl]acetate (3ad)
White solid; yield: 48 mg (61%); mp 116–117 °C; $[\alpha]_D^{27}$ –100.9 (*c* 0.35, $CHCl_3$).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.4 Hz, 1 H), 7.61 (d, *J* = 8.4 Hz, 2 H), 7.41 (t, *J* = 7.7 Hz, 1 H), 7.21–7.29 (m, 5 H), 6.99 (d, *J* = 7.7 Hz, 1 H), 6.87 (d, *J* = 7.7 Hz, 1 H), 6.82 (d, *J* = 7.7 Hz, 1 H), 6.34 (d, *J* = 7.0 Hz, 1 H), 4.78 (dd, *J* = 6.3, 9.8 Hz, 1 H), 4.06 (dq, *J* = 3.5, 7.0 Hz, 2 H), 3.62 (s, 3 H), 2.49–2.52 (m, 1 H), 2.52 (dd, *J* = 8.4, 16.8 Hz, 1 H), 2.40 (s, 3 H), 2.33 (dd, *J* = 3.5, 16.8 Hz, 1 H), 1.18 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 170.0, 156.0, 144.3, 136.8, 135.8, 130.8, 129.7, 129.6, 128.4, 127.9, 127.7, 127.3, 127.1, 126.8, 125.0, 120.8, 110.6, 93.4, 60.9, 59.3, 54.7, 36.7, 33.1, 21.6, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{28}N_2NaO_7S$: 547.1515; found: 547.1514.

HPLC: Chiralpak AD-H column and AD-H guard column (10% *i*-PrOH–hexanes, 1.0 mL/min flow, λ = 254 nm); minor isomer: t_R = 16.2 min; major isomer: t_R = 19.7 min; 95% ee.

Ethyl [(2*R*,3*S*,4*R*)-2-(3,4-Dimethoxyphenyl)-3-nitro-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl]acetate (3ae)
White solid; yield: 61 mg (73%); mp 87–89 °C; $[\alpha]_D^{27}$ +26.0 (*c* 0.33, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 7.6 Hz, 1 H), 7.57 (d, *J* = 8.4 Hz, 2 H), 7.41 (t, *J* = 8.4 Hz, 1 H), 7.24–7.32 (m, 3 H), 7.05 (d, *J* = 7.6 Hz, 1 H), 6.68–6.81 (m, 3 H), 6.00 (d, *J* = 6.8 Hz, 1 H), 4.87 (dd, *J* = 6.8, 10.8 Hz, 1 H), 4.10 (q, *J* = 7.2 Hz, 2 H), 3.85 (s, 3 H), 3.78 (s, 3 H), 2.77–2.84 (m, 1 H), 2.57 (dd, *J* = 8.0, 17.2 Hz, 1 H), 2.42 (s, 3 H), 2.39 (dd, *J* = 4.4, 17.2 Hz, 1 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 149.2, 149.0, 144.5, 135.9, 135.6, 132.1, 131.4, 129.8, 128.7 (two signals overlapping), 127.3, 127.2, 125.2, 118.6, 111.3, 109.2, 94.5, 62.5, 61.0, 56.0, 55.8, 36.5, 32.6, 21.6, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{30}N_2NaO_8S$: 577.1621; found: 577.1617.

HPLC: Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ = 220 nm); minor isomer: t_R = 16.2 min; major isomer: t_R = 39.8 min; 99% ee.

Ethyl [(2*R*,3*S*,4*R*)-3-Nitro-2-(4-tolyl)-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl]acetate (3af)
White solid; yield: 60 mg (78%); mp 154–156 °C; $[\alpha]_D^{27}$ –8.4 (*c* 0.90, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (dd, *J* = 0.8, 8.0 Hz, 1 H), 7.56 (d, *J* = 8.4 Hz, 2 H), 7.42 (t, *J* = 7.6 Hz, 1 H), 7.26–7.33 (m, 3 H), 7.09–7.16 (m, 4 H), 7.44 (d, *J* = 8.0 Hz, 1 H), 5.98 (d, *J* = 7.2 Hz, 1 H), 4.81 (dd, *J* = 7.2, 9.2 Hz, 1 H), 4.11 (dq, *J* = 2.0, 7.2 Hz, 2 H), 2.70–2.79 (m, 1 H), 2.56 (dd, *J* = 7.6, 17.2 Hz, 1 H), 2.43 (s, 3 H), 2.37 (dd, *J* = 4.0, 17.2 Hz, 1 H), 2.33 (s, 3 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 144.4, 138.3, 136.7, 135.9, 135.6, 131.5, 129.8, 129.7, 128.7, 127.7, 127.3, 127.2, 126.2, 124.9, 94.8, 62.7, 61.0, 36.5, 32.6, 21.6, 21.1, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{28}N_2NaO_6S$: 531.1566; found: 531.1565.

HPLC: Chiralpak AD-H column and AD-H guard column (10% EtOH–hexanes, 1.0 mL/min flow, λ = 254 nm); minor isomer: t_R = 11.0 min; major isomer: t_R = 12.5 min; 97% ee.

Ethyl [(2*R*,3*S*,4*R*)-2-(4-Chlorophenyl)-3-nitro-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl]acetate (3ag)
White solid; yield: 57 mg (72%); mp 181–183 °C; $[\alpha]_D^{27}$ –15.1 (*c* 0.95, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (dd, *J* = 0.8, 8.0 Hz, 1 H), 7.55 (d, *J* = 8.4 Hz, 2 H), 7.44 (t, *J* = 8.0 Hz, 1 H), 7.26–7.34 (m, 5 H), 7.16 (d, *J* = 8.4 Hz, 2 H), 7.04 (d, *J* = 8.0 Hz, 1 H), 5.96 (d, *J* = 7.2 Hz, 1 H), 4.78 (dd, *J* = 4.8, 6.8 Hz, 1 H), 4.11 (dq, *J* = 1.6, 7.2 Hz, 2 H), 2.69 (ddd, *J* = 3.6, 8.0, 11.2 Hz, 1 H), 2.56 (dd, *J* = 8.0, 17.2 Hz, 1 H), 2.38–2.48 (m, 4 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 144.7, 138.2, 135.6, 135.2, 134.5, 131.4, 129.9, 129.3, 128.9, 127.8, 127.7, 127.6, 127.2, 124.9, 94.5, 62.3, 61.1, 36.5, 32.3, 21.6, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{25}ClN_2NaO_6S$: 551.1020; found: 551.1020.

HPLC: Chiralpak AD-H column and AD-H guard column (10% EtOH–hexanes, 1.0 mL/min flow, λ = 254 nm); minor isomer: t_R = 11.7 min; major isomer: t_R = 13.0 min; 96% ee.

Ethyl [(2*R*,3*S*,4*R*)-2-(2-Chlorophenyl)-3-nitro-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl]acetate (3ah)
White solid; yield: 73 mg (92%); mp 143–144 °C; $[\alpha]_D^{22}$ –63.5 (*c* 1.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 7.6 Hz, 1 H), 7.59 (d, *J* = 8.4 Hz, 2 H), 7.45 (t, *J* = 7.6 Hz, 1 H), 7.39 (dd, *J* = 1.2, 8.0 Hz, 1 H), 7.13–7.33 (m, 6 H), 7.07 (d, *J* = 7.6 Hz, 1 H), 6.39 (d, *J* = 7.6 Hz, 1 H), 4.94 (dd, *J* = 7.6, 10.4 Hz, 1 H), 4.10 (dq, *J* = 4.0, 7.2 Hz, 2 H), 2.70–2.77 (m, 1 H), 2.52 (dd, *J* = 8.0, 17.2 Hz, 1 H), 2.44 (s, 3 H), 2.33 (dd, *J* = 4.4, 17.2 Hz, 1 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 144.7, 137.3, 136.3, 135.0, 132.4, 130.3, 130.2, 129.9, 129.8, 128.9, 128.7, 127.6, 127.4, 127.0, 126.9, 125.4, 92.1, 61.1, 59.6, 36.3, 33.0, 21.7, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{25}ClN_2NaO_6S$: 551.1020; found: 551.1018.

HPLC: Chiralpak AD-H column and AD-H guard column (10% *i*-PrOH–hexanes, 1.0 mL/min flow, λ = 254 nm); minor isomer: t_R = 13.8 min; major isomer: t_R = 18.1 min; 97% ee.

Ethyl [(2*R*,3*S*,4*R*)-2-(2-Bromophenyl)-3-nitro-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl]acetate (3ai)

White solid; yield: 64 mg (74%); mp 133–135 °C; $[\alpha]_D^{23}$ –76.3 (*c* 0.20, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.0 Hz, 1 H), 7.55–7.64 (m, 3 H), 7.44 (t, *J* = 7.6 Hz, 1 H), 7.06–7.34 (m, 7 H), 6.40 (d, *J* = 7.6 Hz, 1 H), 4.95 (dd, *J* = 7.6, 10.0 Hz, 1 H), 4.10 (dq, *J* = 3.6, 7.2 Hz, 2 H), 2.86–3.03 (m, 1 H), 2.52 (dd, *J* = 8.0, 17.2 Hz, 1 H), 2.44 (s, 3 H), 2.33 (dd, *J* = 4.4, 17.2 Hz, 1 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 144.7, 139.1, 136.3, 135.0, 133.5, 130.1, 129.9, 128.9, 128.7, 128.3, 127.4, 127.0, 126.8, 125.6, 122.3, 92.2, 61.2, 61.1, 36.2, 33.1, 21.7, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{25}BrN_2NaO_6S$: 595.0514; found: 595.0518.

HPLC: Chiralpak AD-H column and AD-H guard column (10% *i*-PrOH–hexanes, 1.0 mL/min flow, λ = 254 nm); minor isomer: t_R = 17.4 min; major isomer: t_R = 20.6 min; 97% ee.

Ethyl [(2*R*,3*S*,4*R*)-2-(4-Fluorophenyl)-3-nitro-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl]acetate (3aj)

White solid; yield: 62 mg (80%); mp 163–165 °C; $[\alpha]_D^{27}$ –20.4 (*c* 0.96, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (dd, *J* = 0.8, 8.0 Hz, 1 H), 7.55 (d, *J* = 8.4 Hz, 2 H), 7.44 (t, *J* = 7.6 Hz, 1 H), 7.19–7.35 (m, 5 H), 6.99–7.06 (m, 3 H), 5.97 (d, *J* = 7.2 Hz, 1 H), 4.79 (dd, *J* = 7.2, 10.8 Hz, 1 H), 4.11 (dq, *J* = 1.6, 7.2 Hz, 2 H), 2.69 (ddd, *J* = 3.6, 8.0, 10.8 Hz, 1 H), 2.56 (dd, *J* = 8.0, 17.2 Hz, 1 H), 2.38–2.46 (m, 4 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 144.6, 135.6, 135.3, 131.6, 129.9, 128.8, 128.2, 128.1, 127.8, 127.6, 127.2, 124.9, 116.2, 116.0, 94.7, 61.3, 61.1, 36.5, 32.3, 21.6, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{25}FN_2NaO_6S$: 535.1315; found: 535.1311.

HPLC: Chiralpak AD-H column and AD-H guard column (10% EtOH–hexanes, 1.0 mL/min flow, λ = 254 nm); minor isomer: t_R = 9.2 min; major isomer: t_R = 10.5 min; 96% ee.

Ethyl [(2*R*,3*S*,4*R*)-3-Nitro-2-(4-nitrophenyl)-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl]acetate (3ak)

White solid; yield: 62 mg (76%); mp 167–169 °C; $[\alpha]_D^{24}$ +29.0 (*c* 0.51, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 8.8 Hz, 2 H), 7.89 (d, *J* = 7.6 Hz, 1 H), 7.41–7.59 (m, 5 H), 7.26–7.38 (m, 3 H), 7.05 (d, *J* = 8.0 Hz, 1 H), 6.05 (d, *J* = 7.2 Hz, 1 H), 4.83 (dd, *J* = 7.2, 11.2 Hz, 1 H), 4.10 (dq, *J* = 1.6, 7.2 Hz, 2 H), 2.54–2.71 (m, 2 H), 2.39–2.49 (m, 4 H), 1.23 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6, 147.9, 146.6, 145.0, 135.3, 134.8, 131.3, 130.0, 129.1, 127.9, 127.8, 127.4, 127.2, 125.0, 124.4, 94.1, 62.3, 61.2, 36.6, 31.9, 21.6, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{25}N_3NaO_8S$: 562.1260; found: 562.1257.

HPLC: Chiralpak AD-H column and AD-H guard column (10% EtOH–hexanes, 1.0 mL/min flow, λ = 254 nm); minor isomer: t_R = 27.0 min; major isomer: t_R = 32.8 min; 94% ee.

Ethyl [(2*S*,3*S*,4*R*)-3-Nitro-2-(2-thienyl)-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl]acetate (3al)

White solid; yield: 62 mg (83%); mp 144–145 °C; $[\alpha]_D^{24}$ +10.5 (*c* 0.70, $CHCl_3$).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 7.7 Hz, 1 H), 7.58 (d, *J* = 7.7 Hz, 2 H), 7.41 (t, *J* = 7.7 Hz, 1 H), 7.28–7.33 (m, 3 H), 7.24 (d, *J* = 4.9 Hz, 1 H), 7.04 (d, *J* = 7.7 Hz, 1 H), 6.92–6.98 (m, 2 H), 6.34 (d, *J* = 6.3 Hz, 1 H), 4.93 (dd, *J* = 6.3, 11.2 Hz, 1 H), 4.09–4.17 (m, 2 H), 2.71–2.76 (m, 1 H), 2.61 (dd, *J* = 8.4, 17.5 Hz, 1 H), 2.41–2.47 (m, 4 H), 1.23 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 169.8, 144.6, 143.4, 135.4, 135.0, 131.5, 129.9, 128.7, 128.4, 127.8, 127.3, 127.2, 125.9, 125.3, 124.9, 95.0, 61.1, 59.2, 36.4, 32.5, 21.6, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{24}N_2NaO_6S_2$: 523.0973; found: 523.0973.

HPLC: Chiralpak AD-H column and AD-H guard column (20% *i*-PrOH–hexanes, 1.0 mL/min flow, λ = 254 nm); minor isomer: t_R = 8.4 min; major isomer: t_R = 20.3 min; 98% ee.

Ethyl {(2*R*,3*S*,4*R*)-2-Isopropyl-3-nitro-1-tosyl-1,2,3,4-tetrahydroquinolin-4-yl}acetate (3am)

White solid; yield: 65 mg (94%); mp 99–101 °C; $[\alpha]_D^{25}$ –5.4 (*c* 1.0, $CHCl_3$).

^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 7.7 Hz, 1 H), 7.52 (d, *J* = 8.4 Hz, 2 H), 7.39 (t, *J* = 7.7 Hz, 1 H), 7.27 (t, *J* = 7.7 Hz, 1 H), 7.21 (d, *J* = 8.4 Hz, 2 H), 6.99 (d, *J* = 7.7 Hz, 1 H), 4.74 (dd, *J* = 4.9, 7.7 Hz, 1 H), 4.69 (dd, *J* = 4.9, 11.2 Hz, 1 H), 4.08 (dq, *J* = 3.5, 7.0 Hz, 2 H), 2.56 (dd, *J* = 7.7, 16.8 Hz, 1 H), 2.47–2.53 (m, 2 H), 2.39 (s, 3 H), 1.73 (septet, *J* = 7.0 Hz, 1 H), 1.21 (t, *J* = 7.0 Hz, 3 H), 1.00 (dd, *J* = 6.3, 7.0 Hz, 6 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 170.0, 144.1, 136.1, 136.0, 131.9, 129.6, 128.5, 128.4, 127.6, 127.2, 124.6, 92.6, 65.4, 60.9, 36.6, 34.5, 32.1, 21.6, 19.0, 18.6, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{28}N_2NaO_6S$: 483.1566; found: 483.1568.

HPLC: Chiralpak AD-H column and AD-H guard column (5% EtOH–hexanes, 1.0 mL/min flow, λ = 254 nm); minor isomer: t_R = 7.0 min; major isomer: t_R = 8.5 min; 70% ee.

Acknowledgment

This research was supported by Nano-Material Development Program and Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Education, Science, and Technology (NRF-2012M3A7B4049648 and NRF-2013R1A1A2009850)

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000084.

References

(1) For reviews on tetrahydroquinolines, see: (a) Sridharan, V.; Suryavanshi, P. A.; Menéndez, J. C. *Chem. Rev.* **2011**, *111*, 7157. (b) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357. (c) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, *17*, 2862. (d) Kouznetsov, V.; Palma, A.; Ewert, C.;

Varlamov, A. *J. Heterocycl. Chem.* **1998**, *35*, 761. (e) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031.

(2) (a) Skerlj, R. T.; Bridger, G. J.; Kaller, A.; McEachern, E. J.; Crawford, J. B.; Zhou, Y.; Atsma, B.; Langille, J.; Nan, S.; Veale, D.; Wilson, T.; Harwig, C.; Hatse, S.; Princen, K.; De Clercq, E.; Schols, D. *J. Med. Chem.* **2010**, *53*, 3376. (b) Ramesh, E.; Manian, R. D. R. S.; Raghunathan, R.; Sainath, S.; Raghunathan, M. *Bioorg. Med. Chem.* **2009**, *17*, 660. (c) Liou, J.-P.; Wu, Z.-Y.; Kuo, C.-C.; Chang, C.-Y.; Lu, P.-Y.; Chen, C.-M.; Hsieh, H.-P.; Chang, J.-Y. *J. Med. Chem.* **2008**, *51*, 4351. (d) Urbina, J. M.; Cortés, J. C. G.; Palma, A.; López, S. N.; Zacchino, S. A.; Enriz, R. D.; Ribas, J. C.; Kouznetzov, V. V. *Bioorg. Med. Chem.* **2000**, *8*, 691.

(3) For examples of syntheses of chiral tetrahydroquinolines, see: (a) Wang, T.; Zhuo, L.-G.; Li, Z.; Chen, F.; Ding, Z.; He, Y.; Fan, Q.-H.; Xiang, J.; Yu, Z.-X.; Chan, A. S. C. *J. Am. Chem. Soc.* **2011**, *133*, 9878. (b) Mori, K.; Ehara, K.; Kurihara, K.; Akiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 6166. (c) Kang, Y. K.; Kim, S. M.; Kim, D. Y. *J. Am. Chem. Soc.* **2010**, *132*, 11847. (d) Xie, M.; Chen, X.; Zhu, Y.; Gao, B.; Lin, L.; Liu, X.; Feng, X. *Angew. Chem. Int. Ed.* **2010**, *49*, 3799. (e) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986. (f) Han, Z.-Y.; Xiao, H.; Chen, X.-H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 9182. (g) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. *J. Am. Chem. Soc.* **2009**, *131*, 4598. (h) Fustero, S.; Moscardó, J.; Jiménez, D.; Pérez-Carrión, M. D.; Sánche-Roselló, M.; del Pozo, C. *Chem. Eur. J.* **2008**, *14*, 9868. (i) Guo, Q.-S.; Du, D.-M.; Xu, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 759.

(4) (a) Jia, Z.-X.; Luo, Y.-C.; Wang, Y.; Chen, L.; Xu, P.-F.; Wang, B. *Chem. Eur. J.* **2012**, *18*, 12958. (b) Tan, H. R.; Ng, H. F.; Chang, J.; Wang, J. *Chem. Eur. J.* **2012**, *18*, 3865. (c) Dagousset, G.; Zhu, J.-P.; Masson, G. *J. Am. Chem. Soc.* **2011**, *133*, 14804. (d) Jensen, K. L.; Dickmeiss, G.; Donslund, B. S.; Poulsen, P. H.; Jørgensen, K. A. *Org. Lett.* **2011**, *13*, 3678. (e) Dickmeiss, G.; Jensen, K. L.; Worgull, D.; Franke, P. T.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 1580. (f) Jia, Z.-X.; Luo, Y.-C.; Xu, P.-F. *Org. Lett.* **2011**, *13*, 832.

(5) For selected reviews on organocatalysis, see: (a) Pellissier, H. *Recent Developments in Asymmetric Organocatalysis*; Royal Society of Chemistry: Cambridge, **2010**. (b) *Special issue on Asymmetric Organocatalysis* **2010**, *291*, 1. (c) *Enantioselective Organocatalysis: Reactions and Experimental Procedures*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, **2007**. (d) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (e) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138. (f) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638. (g) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267. (h) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (i) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416.

(6) For selected reviews on domino reactions, see: (a) Pellissier, H. *Asymmetric Domino Reactions*; Royal Society of Chemistry: Cambridge, **2013**. (b) Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 8492. (c) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (d) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037. (e) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570. (f) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477. (g) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1. (h) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134. (i) Guo, H.-C.; Ma, J.-A. *Angew. Chem. Int. Ed.* **2006**, *45*, 354. (j) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, **2006**.

(7) For selected reviews on catalysis by bifunctional cinchona thioureas, see: (a) Marqués-López, E.; Herrera, R. P. In *New Strategies in Chemical Synthesis and Catalysis*; Pignataro, B., Ed.; Wiley-VCH: Weinheim, **2010**, Chap. 8, 175. (b) Han, B.; Li, J.-L.; Xiao, Y.-C.; Zhou, S.-L.; Chen, Y.-C. *Curr. Org. Chem.* **2011**, *15*, 4128. (c) Takemoto, Y. *Chem. Pharm. Bull.* **2010**, *58*, 593. (d) *Cinchona Alkaloids in Synthesis and Catalysis: Ligands, Immobilization and Organocatalysis*; Song, C. E., Ed.; Wiley-VCH: Weinheim, **2009**. (e) Connon, S. J. *Chem. Commun.* **2008**, 2499. (f) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 7496.

(8) Du and co-workers used a bifunctional cinchona squaramide derivative as the catalyst: (a) Yang, W.; He, H.-X.; Gao, Y.; Du, D.-M. *Adv. Synth. Catal.* **2013**, *355*, 3670. We used a bifunctional cinchona thiourea derivative as the catalyst: (b) Kim, S.; Kang, K.-T.; Kim, S.-G. *Tetrahedron* **2014**, *70*, 5114.

(9) Du and co-workers reported one example of this reaction between **1a** and **2a** in which a squaramide derivative was used as the catalyst. See ref. 8a.

(10) (a) Sakamoto, S.; Inokuma, T.; Takemoto, Y. *Org. Lett.* **2011**, *13*, 6374. (b) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

(11) Crystallographic data for compound **3ae** have been deposited with the accession number CCDC 990345, and can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk; Web site: www.ccdc.cam.ac.uk/conts/retrieving.html.

(12) (a) Li, X.; Yang, C.; Jin, J.-L.; Xue, X.-S.; Cheng, J.-P. *Chem. Asian J.* **2013**, *8*, 997. (b) Zhu, J. L.; Zhang, Y.; Liu, C.; Zheng, A.-M.; Wang, W. *J. Org. Chem.* **2012**, *77*, 9813. (c) Wang, X.-F.; Hua, Q.-L.; Cheng, Y.; An, X.-L.; Yang, Q. Q.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem. Int. Ed.* **2010**, *49*, 8379. (d) Baslé, O.; Raimondi, W.; Sanchez Duque, M. de M.; Bonne, D.; Constantieux, T.; Rodriguez, J. *Org. Lett.* **2010**, *12*, 5246. (e) Tan, B.; Lu, Y.; Zeng, X.; Chua, P. J.; Zhong, G. *Org. Lett.* **2010**, *12*, 2682. (f) Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151. (g) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.