CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200900696

An Organocatalytic Asymmetric Tandem Reaction for the Construction of Bicyclic Skeletons

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Abstract: Cyclic ketones react with (*E*)-2-nitroallylic acetates in the presence of catalytic pyrrolidine-thiourea, which affords bicyclic skeletons with four or five stereocenters in one single reaction with up to 98% *ee* in moderate to high yields. The cooperative effects of both enamine and the Brønsted acid are found to be crucial for the high reactivity and enantioselectivity of this cascade reaction, which is demonstrated by both theoretical calculation and experimental data.

Keywords: bifunctional catalysts · density functional calculations · ketones · organocatalysis · tandem reactions

Introduction

The efficient construction of carbon–carbon bonds with the control of multiple stereocenters in a single operation is of fundamental interest in synthetic chemistry. In this field, a modular combination of organocatalytic reactions into cascades has emerged as a powerful strategy.[1] Secondary amines and their salts have proven to be especially versatile in organizing a cascade reaction by means of enamine or iminium catalysis.[2,3] During the past several years, dozens of elegant aminocatalyst-triggered tandem reactions have been reported to furnish a product with more than one stereocenter.[3–6] However, only a few examples could afford complex molecules with four or more stereogenic centers[4–6] in one cascade reaction. Of the reactions developed, Enders et al. achieved a three-component cascade reaction that afforded cyclohexene derivatives with four stereocenters,[4a] which was applied to the diastereo- and enantioselective synthesis of pure polyfunctionalized tricyclic frameworks.[4b] Jørgensen et al. reported a domino Michael/aldol reaction of β-ketoesters and α,β-unsaturated ketones forming four contiguous stereogenic centers.[5a] Very recently, they developed an organocatalytic asymmetric one-pot reaction to create six stereocenters with excellent diastereo- and enantioselectivity.[5c] The groups of Córdova[6b] and Hayashi[6c] independently developed organocatalytic cascade reactions that generate four stereocenters in a simple operation. By an organocatalytic desymmetrization reaction, Miller and his co-worker reported a facile synthesis of D-myoinositol-1-phosphate with six stereocenters.[6a] In spite of the aforementioned achievements, the development of new organocatalytic cascade reactions that could install four or more stereocenters in one reaction remains very challenging and valuable in asymmetric catalysis.

(*E*)-2-Nitroallylic acetates **1** could serve as multiple-coupling reagents and install into the final product a nitro group, which can then be easily transformed into other functional groups. To the best of our knowledge, these particular compounds have never been used for organocatalytic asymmetric cascade reactions, although they have been combined with chiral enamines for a formal [3+3] carbocyclization.[7] We speculated that under the catalysis of suitable aminocatalysts, the combination of nitroallylic acetates **1** with cyclic ketone **2** might spontaneously undergo Michael/elimination/Michael reactions to give the bicycle [3.3.1] skeletons with four or five chiral centers. In this paper, we wish to report our efforts on this subject in detail.

Results and Discussion

(*E*)-2-Nitroallylic acetate **1a** is readily available through a Morita–Baylis–Hillman reaction (for details see the Sup-

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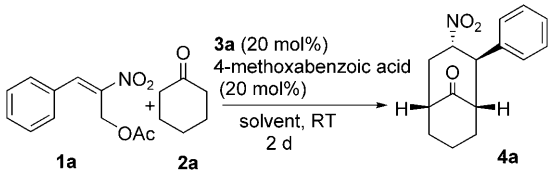
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200900696.

porting Information). We were pleased to find that when **1a** was treated with cyclohexanone in ethyl acetate, it afforded the desired product **4a** in 60% conversion with 95% *ee* in the presence of 20 mol% pyrrolidine-thiourea (**3a**) in combination with an equal amount of 4-methoxybenzoic acid as a cocatalyst.[8a] To improve the conversion, several solvents were screened. The results are summarized in Table 1. Toluene, THF, and CH_2Cl_2 were not as good as ethyl acetate, and only very low conversions were obtained (Table 1, entries 2–4). CH_3CN and isopropanol gave moderate to good conversions with excellent enantiomeric excess values (entries 5 and 6). The optimal reaction condition is solvent-free (entry 7). In this case, 99% conversion and 96% *ee* were achieved.

Table 1. Effects of solvents on the reaction of cyclohexanone **2a** and **1a**.[a]

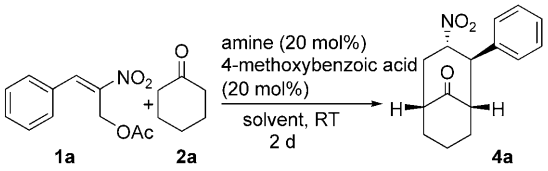


Entry[a]	Solvent	Conversion [%][b]	*ee* [%][c]
1	ethyl acetate	60	95
2	toluene	<5	–
3	THF	<5	–
4	CH_2Cl_2	<5	–
5	CH_3CN	57	95
6	*i*PrOH	77	95
7[d]	solvent-free	99	96

[a] Compounds **1a** (0.20 mmol) and **2a** (0.20 mL), solvent (1 mL), **3a** (20 mol%), and 4-methoxybenzoic acid (20% mol); reaction time: 48 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC analysis. [d] 1 mL of **2a**.

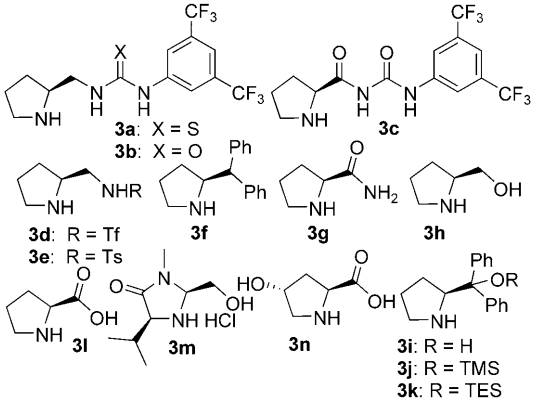
Using nitroolefin **1a** as a model substrate, a series of secondary amine catalysts were also investigated (Scheme 1). As shown in Table 2, pyrrolidine-urea (**3b**)[8] with an equal amount of 4-methoxybenzoic acid as a cocatalyst, which we recently identified as an excellent catalyst for a Michael addition of ketones to nitroolefins,[8c] promoted this reaction in moderate conversion with up to 95% *ee* (Table 2, entry 2). Pyrrolidine-thiourea (**3a**), which has a stronger hydrogen-bond donor than **3b**,[1f] afforded the product in 99% conversion and 75% yield with 96% *ee* (entry 1). This result also showed that the urea part of the catalyst plays an important role in activating the nitroolefin, thereby suggesting that hydrogen bonding speeds up the reaction. An attempt to further improve the reactivity by using catalyst **3c** with a more acidic hydrogen-bonding donor failed (entry 3), probably due to the effects of the amide on the formation of the enamine intermediate. Although it is known that catalyst **3d**[3d] gave better *ee* values in the reaction of ketones with alkylidene malonates than **3a**,[8b] compound **3d** afforded lower enantiomeric excess and conversion in the present reaction than **3a**. Both catalysts **3e** and **3f** also delivered high enantioselectivity, but the conversion is not satisfactory. Proline **3l** and (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylic acid (**3n**) gave very high conversion with low *ee* values (Table 2, entries 12 and 14). Other secondary amines **3g–k** and **3m**[2] were almost inactive (entries 7–11 and 13). These results demonstrated that the high reactivity of catalyst **3a** resulted from the cooperative effects of both the enamine and Brønsted acid catalysis. Under all conditions screened, only one diastereomer was observed through ^{1}H NMR spectroscopic analysis of the crude product. When the loading of **3a** was reduced from 20 to 10 mol%, although the enantiomeric excess was almost maintained, only 30% conversion was obtained, even when the reaction time was prolonged from 48 to 96 h (entry 15). One of the reasons for the cata-

Table 2. Catalyst screening for the asymmetric tandem reaction.[a]



Entry	Catalyst	Conversion [%][b]	*ee* [%][c]
1	**3a**	99 (75)[d]	96
2	**3b**	60	95
3	**3c**	<5	–
4	**3d**	67	86
5	**3e**	25	90
6	**3f**	39	92
7	**3g**	<5	–
8	**3h**	<5	–
9	**3i**	<5	–
10	**3j**	<5	–
11	**3k**	<5	–
12	**3l**	99	17
13[e]	**3m**	<5	–
14	**3n**	99	−8
15[f]	**3a**	30	95

[a] Catalyst (20 mol%) in neat 4-methoxybenzoic acid (20 mol%), **1a** (0.20 mmol), **2a** (1 mL); reaction time: 48 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC analysis. [d] Isolated yield. [e] No 4-methoxybenzoic acid was added. [f] 10 mol% of **3a** and 10 mol% of 4-methoxybenzoic acid; reaction time: 96 h.



Scheme 1. Catalysts screened.

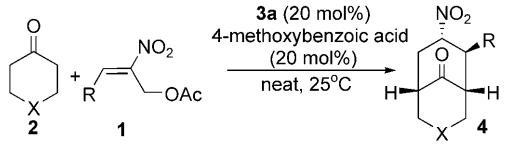
lyst deactivation is probably the addition of **3a** to nitroolefin **1a**, which led to the consumption of the catalyst.

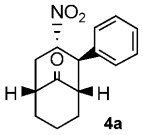
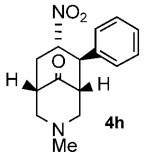
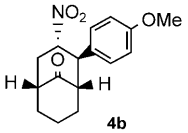
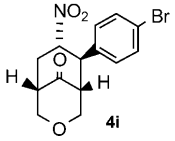
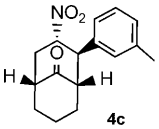
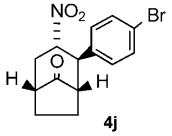
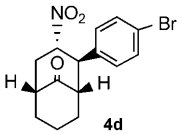
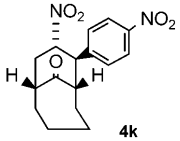
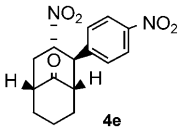
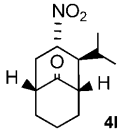
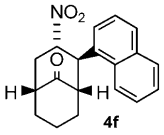
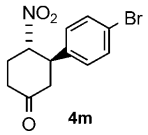
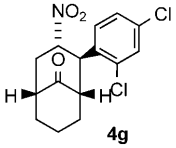
Under optimal conditions, the generality of this reaction was examined by investigating a variety of cyclic ketones (**2**) and nitroolefins (**1**). As shown in Table 3, aryl nitroolefins **1** reacted smoothly with cyclic ketones in good yields with excellent enantioselectivities and diastereoselectivities. Generally, substituents on aryl groups had little effect on both enantioselectivities and yields (entries 1–7). The enantiomeric excesses were all above 94%, with some reaching 98%. Heterocyclohexanone could also give the desired products with good to high enantioselectivities (entries 8 and 9), thereby providing easy access to optically active heterocyclic compounds with four stereocenters. In the case of cyclopentanone and tetrahydropyran-4-one, **3d** gave better yields than **3a**. By using **3d** as a catalyst, for example, cyclopentanone was also a suitable ketone and afforded the product with 93% *ee* in 94% yield (entry 10). Both cycloheptenone and acetone did not work in the current catalytic reaction (entries 11 and 12). Since Seebach et al. have reported that the enamine of either cycloheptenone or acetone can react with nitroolefin very well to afford the corresponding product,[7] these results suggested that the formation of the enamines from both cycloheptenone and acetone can be sluggish. Aliphatic nitroolefin was less active than aromatic nitroolefin in the current reaction. Thus, the reaction of aliphatic nitroolefin is quite slow. For example, only a trace amount of the desired product was observed when (*E*)-4-methyl-2-nitropent-2-enyl acetate was employed as a substrate (entry 12). Noticeably, the optically pure product **4d** (>99% *ee*) could be obtained by recrystallization from diethyl ether. Both the relative and absolute configurations of product **4d** were determined by X-ray diffraction analysis (Figure 1).[9] The nitro group and the aryl group are located in the *trans* position. The carbonyl group is oriented *trans* to the aryl group. The absolute configuration of compound **4d** is assigned as 1*S*,2*R*,3*S*,5*R* (Figure 1). This stereochemical outcome is consistent with the proposed mechanism (Scheme 2) as well as the DFT calculations (Scheme 3).

This tandem transformation could also be applied in making a bicyclic compound with five stereocenters. As shown in Scheme 4, for example, we found that the reaction took place smoothly to afford two isomers, **6a** (92% *ee*) and **6b** (77% *ee*), with a moderate selectivity (2.4:1) when compound **5** was employed. The relative configurations of products **6a** and **6b** were determined by X-ray diffraction analysis (Scheme 4).[9]

The reaction mechanism of enamine derived from cyclic ketones with nitroallylic carbonyl compounds has been well stud-

Table 3. Asymmetric tandem reaction.[a]



Entry	Product	Yield[b]/*ee*[c] [%]	Entry	Product	Yield[b]/*ee*[c] [%]
1	 **4a**	75/96	8	 **4h**	27/97
2	 **4b**	73/94	9[d]	 **4i**	77/77
3	 **4c**	75/96	10[d]	 **4j**	94/93
4	 **4d**	77/96 (>99)	11	 **4k**	trace
5	 **4e**	56/98	12	 **4l**	trace
6[e]	 **4f**	74/95	13	 **4m**	0
7[e]	 **4g**	78/98			

[a] Catalyst (20 mol%) in neat 4-methoxybenzoic acid (20 mol%), **1** (0.20 mmol), **2** (1 mL), reaction time: 48 h. [b] Isolated yield. [c] Estimated by chiral GC or HPLC analysis. [d] Compound **3d** as the catalyst (30 mol%). [e] Isolated as atropisomers. For details, see the Supporting Information.

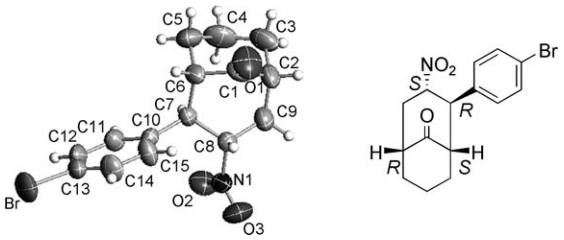
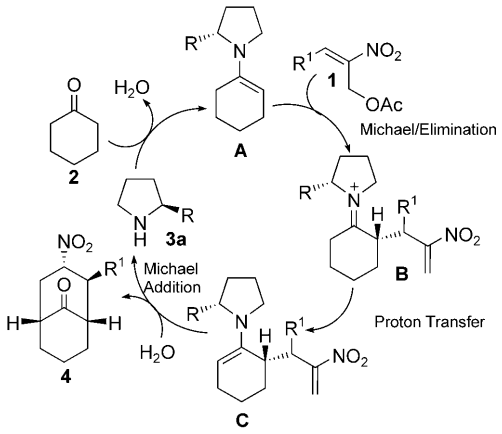
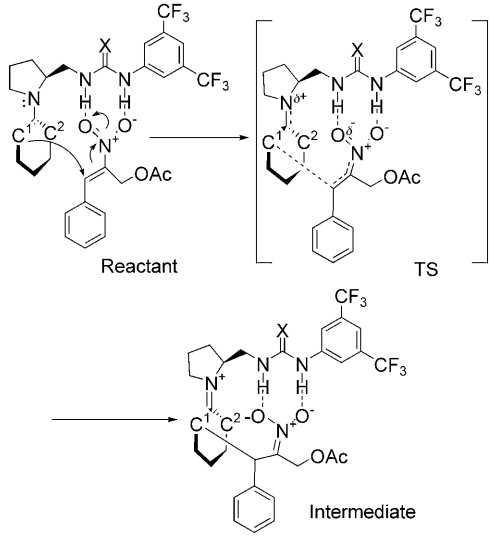


Figure 1. X-ray crystal structure of compound **4d**.

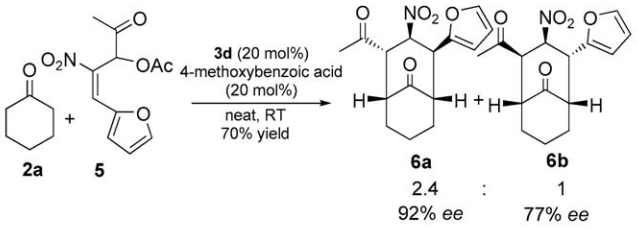


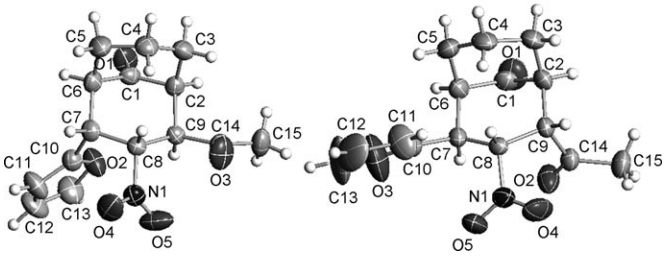
Scheme 2. A proposed mechanism for the formal [3+3] annulation reaction.



Scheme 3. The first C–C bond-forming step.

ied by Seebach et al.[7] On the basis of the mechanistic insight, the aforementioned asymmetric tandem reaction can be explained as outlined in Scheme 2. The formation of intermediate **A** by means of enamine catalysis facilitates the first Michael addition, followed by an elimination of acetate to afford **B**. Intermediate **B** is then isomerized to **C**, which





Scheme 4. The reaction of cyclohexanone **2a** with compound **5**.

undergoes an intramolecular Michael addition reaction, thus affording the desired product **4** and regenerating the catalyst to finish the catalytic cycle.

To find the origin of the high diastereoselectivity and enantioselectivity of this reaction, density functional theory[10] studies using the Gaussian 03 program[11] and the B3LYP[12] method were performed. In this tandem reaction, we concentrated on the transition states of the first C–C bond-forming step that involves the formation of the first two chiral centers (Scheme 3). The transition state (TS) is composed of the (*E*)-2-nitroallylic acetates and the enamine that formed from the ketones and catalyst **3a**.

There should be many possible conformational isomers for the transition state due to its flexibility. Based on a systematic conformational search (see the Supporting Information), four thiourea-based models were constructed and fully optimized at the B3LYP/6-31G** level (Figure 2). For each structure, harmonic vibration frequency calculations were carried out and thermal corrections were made, thereby demonstrating that all of the four structures are transition states. The solvent effect of the cyclohexanone itself was estimated using IEFPCM[13] with the gas-phase optimized structures.

Of the four transition states, double strong hydrogen bonds form between the two hydrogen atoms of the thiourea group and the two oxygen atoms of the nitro group in TS-*SR* or TS-*SS*, whereas only one oxygen atom of the nitro group form hydrogen bonds in TS-*RS* or TS-*RR*. Therefore, TS-*SR* and TS-*SS* are much more stable than TS-*RS* and TS-*RR*. In addition, the conformations of the enamines in TS-*SR*, TS-*RS*, and TS-*RR* are similar, in which the dihedral angles D_{1234} are −55.7°, −57.8°, and −32.1°, respectively (the definition of the dihedral angle D_{1234} is shown in Figure 2). In these transition-state structures, the thiourea group is far away from the cyclohexenyl group. In TS-*SS*, however, $D_{1234}=62.8°$; the thiourea group is to some extent eclipsed by the cyclohexenyl group, which will cause steric

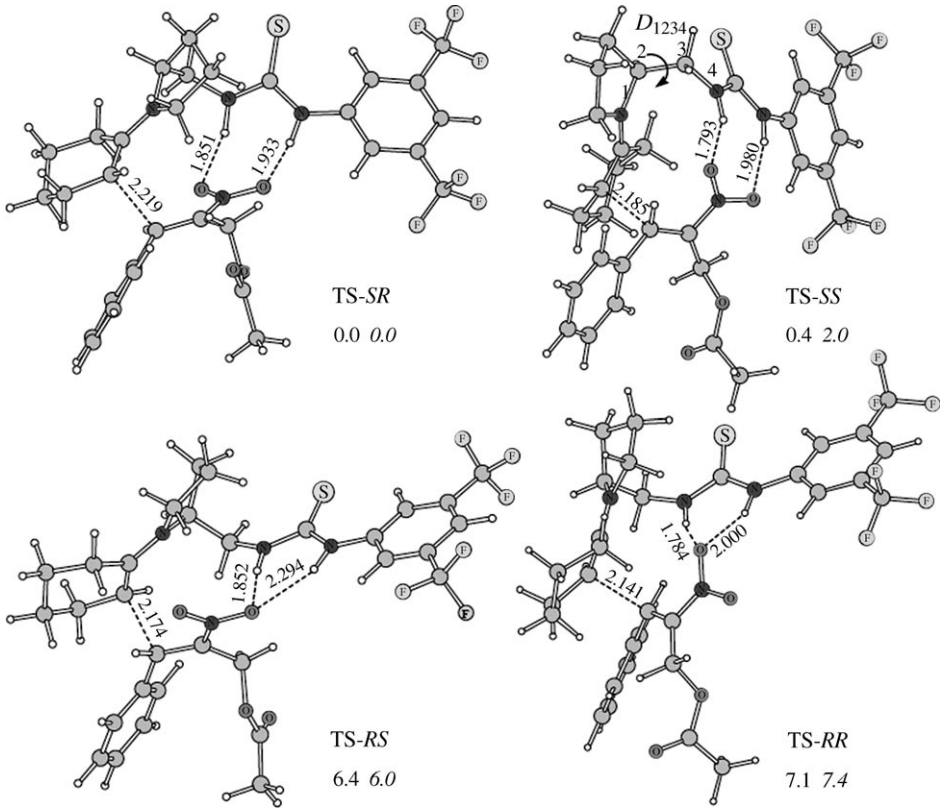


Figure 2. The optimized transition states with selected bond lengths [Å]. The relative free energies in the gas phase ΔG_{gas} (in bold text) and the relative free energies including the solvent effect ΔG_{sol} (in italic text) are in kcal mol^{-1} (298 K, calculated at B3LYP/6-31G** level).

strain. Furthermore, the larger dipole moment of TS-*SR* (13.95 debye) over that of TS-*SS* (12.88 debye) increase their energy difference to 2.0 kcal mol^{-1} by means of the solvent effect. Thus, the most stable transition structure is TS-*SR* and the enamine favors attacking the nitroolefin from the Re face. This result is consistent with the experimental observations.

Conclusion

In conclusion, we have developed a novel organocatalytic tandem reaction to construct bicyclic compounds with four or five stereocenters in a single reaction. This is also the first time that nitroallylic acetate has been applied in asymmetric organocatalytic cascade reactions. The combination of urea catalyst and enamine catalyst was essential for the high reactivity, diastereoselectivity, and enantioselectivity of this transformation, which was demonstrated by both experimental data and theoretical calculations. The extension of the application of nitroallylic acetate in other organocatalytic asymmetric transformations is now in progress in our laboratory.

Experimental Section

Typical procedure for the tandem reaction (using 4a as an example):[14] A mixture of **3a** (14.8 mg, 0.04 mmol, 20 mol %) and 4-methoxybenzoic acid (6.0 mg, 0.04 mmol, 20 mol %) in cyclohexanone (1 mL) was stirred for 10 min at 25 °C and then nitroolefin **1a** (44.2 mg, 0.2 mmol) was added. After the reaction was complete (monitored by TLC), the excess of cyclohexanone was removed under reduced pressure and the residue was purified by flash chromatography (petroleum/EtOAc = 1:7) to give product **6a** (75 %, 38.6 mg). Enantiomeric excess was determined by HPLC analysis (Chiralcel AD-H, *i*PrOH/hexane = 2:98, 0.6 mL min^{-1}, 214 nm; t_R(minor) = 37.97 min, t_R(major) = 40.35 min) and was found to be 96 % *ee*. $[\alpha]_D^{20} = +82.4$ ($c = 0.657$ in $CHCl_3$); ^{1}H NMR (300 MHz, [D]$CDCl_3$, TMS): $\delta = 7.34$–7.23 (m, 3H), 7.16 (d, $J = 7.8$ Hz, 2H), 4.59 (dt, $J = 5.1$, 12.6 Hz, 1H), 3.78 (dd, $J = 3.0$, 12.0 Hz, 1H), 2.80–2.67 (m, 3H), 2.58–2.50 (m, 1H), 2.38–1.86 (m, 5H), 1.76–1.68 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 215.8$, 140.7, 129.1, 127.9, 127.4, 86.2, 53.0, 51.2, 43.0, 35.5, 35.1, 32.6, 15.6 ppm; IR (film): 2941, 2859, 1724, 1553, 1455, 1371, 764, 701 cm^{-1}.

Compound 4j:[14] Procedure and scale are the same as those for the preparation of **4a** except **3d** (14.0 mg, 0.06 mmol, 30 mol %) was used as the catalyst. Yield: 61.5 mg (94 %). Enantiomeric excess was determined by HPLC analysis (Chiralcel AD-H, *i*PrOH/hexane = 5:95, 0.6 mL min^{-1}, 230 nm; t_R(minor) = 34.88 min, t_R(major) = 37.54 min) and was found to be 93 % *ee*. $[\alpha]_D^{20} = +83.2$ ($c = 0.653$ in $CHCl_3$); m.p. 134 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.41$ (d, $J = 8.7$ Hz, 2H), 7.00 (d, $J = 8.4$ Hz, 2H), 5.35–5.26 (m, 1H), 4.05–4.03 (m, 1H), 3.00 (t, $J = 12.3$ Hz, 1H), 2.57–2.41 (m, 3H), 2.29–2.08 (m, 2H), 2.06–1.98 (m, 1H), 1.93–1.84 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 214.6$, 135.1, 131.9, 129.9, 122.5, 79.8, 55.2, 47.8, 41.2, 34.3, 22.7, 21.4 ppm; IR (film): $\tilde{\nu} = 2964$, 2874, 1751, 1547, 1491, 1459, 1377, 1011 cm^{-1}; MS (EI): *m*/*z* (%): 44 (100), 55 (83), 116 (82), 115 (73), 169 (48), 41 (48), 128 (46), 171 (45); exact mass calcd for $C_{14}H_{15}BrNO_3$: 324.0325; found: 324.0229.

Acknowledgements

We are grateful for the financial support from the Natural Sciences Foundation of China (grant nos. 20821002 and 20672131), the Major State Basic Research Development Program (grant no. 2009CB825300), and the Chinese Academy of Sciences.

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[9] CCDC-714774 (**4d**), 714771 (**6a**) and 714772 (**6b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[14] For more examples, please see the Supporting Information.

Received: March 18, 2009
Published online: September 16, 2009

