Dynamic Article Links 🕟

# Organic & Biomolecular Chemistry

Cite this: Org. Biomol. Chem., 2011, 9, 1809

# A one-pot asymmetric organocatalytic tandem reaction for the synthesis of oxazine derivatives<sup>†</sup>

Zhichao Jin, Feng Yu, Xiao Wang, Huicai Huang, Xiaoyan Luo, Xinmiao Liang and Jinxing Ye\*

*Received 4th September 2010, Accepted 7th December 2010* DOI: 10.1039/c0ob00669f

An easy one-pot tandem reaction catalyzed by a chiral secondary amine for the synthesis of optically active oxazine derivatives has been performed and the corresponding substituted benzo[*d*]pyrido[2,1-*b*][1,3]oxazine derivatives were afforded in generally high yields (up to 99%) and excellent enantioselectivities (up to >99%).

# Introduction

Heterocyclic compounds have always been one of the most popular structures in almost every discipline in chemistry.<sup>1</sup> Most of them have diverse biological or medical activities and are very common in natural and non-natural compounds.<sup>2</sup> The synthesis of them has drawn the attention of many organic chemists for over a century and it is still a challenging subject today both in the total synthesis of natural products and organic synthetic methodologies.<sup>3</sup>

Among the large numbers of heterocyclic compounds, fused heterocycles are a family of the most important ones, which are considered as "privileged structures" and contribute greatly to both the pharmaceutical and agrochemical industries.<sup>4</sup> Therefore, great efforts have been made in order to develop efficient approaches for the preparations of various fused heterocyclic compounds.<sup>5</sup> Of these well established strategies, asymmetric organocatalytic tandem reaction has been one of the most attractive methods mainly due to its high stereoselectivities, easy operation and "environmental friendliness".<sup>6</sup>

Substituted oxazine derivatives have emerged as a challenging synthetic structure recently and have appealed to the interests of several scientists.<sup>7</sup> For example, Liu<sup>8</sup> and coworkers reported an efficient one-pot gold-catalyzed tandem coupling/cyclization reaction for the synthesis of pyrrolo/pyrido[2,1-*a*][1,3]benzoxazinones and pyrrolo/pyrido [2,1-*a*]quinazolinones recently, and Eycken<sup>9</sup> *et al.* previously described a solvent-free procedure for the synthesis of different pyridopyridazines and quinolines under both MW and conventional heating conditions. However, to the best of our knowledge, no reports have presented efficient protocols for the enantioselective synthesis of this kind of fused benzopyrido-oxazine derivatives. Asymmetric organocatalytic tandem reactions, especially those catalyzed by proline and its derivatives,

have resulted in the success of the synthesis of many complicated heterocyclic compounds in a highly enantioselective manner.<sup>10</sup> For example, an enantioselective secondary-amine-catalyzed conjugate addition for the synthesis of optically active quinolizidine derivatives has been performed by Franzén *et al.*<sup>11</sup> recently, and a similar structure which has been accomplished by Zhao<sup>12</sup> and coworkers also represents an elegant example of this methodology. Herein, we wish to describe an enantioselective tandem reaction catalyzed by a simple secondary amine to afford a series of substituted benzo[*d*]pyrido[2,1-*b*][1,3] oxazine derivatives.

# **Results and discussion**

Initially, the rationally designed aryl amide **1a** was applied in the tandem reaction with cinnamyl aldehyde **2a** in order to prepare the pyrido[1,2-*a*]quinazoline derivative **3** as shown in Scheme 1 (Route a). The model reaction was firstly carried out using Jørgensen–Hayashi catalyst **A** for the Michael addition under reported conditions.<sup>13</sup> As we expected, the process went smoothly and the aryl amide **1a** vanished within 1 h. Then excess aqueous HBr solution was added into the reaction mixture to promote the annulation step of the tandem reaction. To our great surprise,



Scheme 1 Two possible processes for the tandem reaction of aryl amide 1a and cinnamyl aldehyde 2a.

Engineering Research Centre of Pharmaceutical Process Chemistry, Ministry of Education, School of Pharmacy, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China. E-mail: yejx@ ecust.edu.cn

<sup>†</sup> Electronic supplementary information (ESI) available. CCDC reference number 793001. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00669f





N H OTMS			∧ Н В		N N H OH C	
Α						
Entry <sup>a</sup>	1	Cat.	Equiv. <sup><i>b</i></sup>	Solvent	Conv. (%) <sup>e</sup>	ee(%) <sup>d</sup>
1	1a	Α	0.1	$CH_2Cl_2$	Full	96
2	1b	Α	0.1	$CH_2Cl_2$	Full <sup>e</sup>	92
3	1a	В	0.1	$CH_2Cl_2$	13	f
4	1a	С	0.1	$CH_2Cl_2$	38	72
5	1a	Α	0.1	DMF	Full	96
6	1a	Α	0.1	THF	63	92
7	1a	Α	0.1	Toluene	64	92
8	1a	Α	0.1	CH <sub>3</sub> CN	Full	95
9	1a	Α	0.1	1,4-Dioxane	79	91
10	1a	Α	0.1	EtOAc	64	90
11	1a	Α	0.1	2-Propanol	92	f
12	1a	Α	0.1	CH <sub>3</sub> Cl	Full	94
13	1a	Α	0.05	$CH_2Cl_2$	Full	97
14	1a	Α	0.02	CH <sub>2</sub> Cl <sub>2</sub>	50	97

<sup>*a*</sup> Unless otherwise indicated, all reactions were carried out using 1.0 equiv of 1 (0.20 mmol), 1.5 equiv of 2a, 0.5 mL solvent, and 2.0 equiv of HBr aq. <sup>*b*</sup> The amount of catalyst used in each reaction. <sup>*c*</sup> Determined by <sup>1</sup>H NMR on the crude reaction mixture before the addition of HBr in water. <sup>*d*</sup> Enantiomeric excess of the major diastereoisomer, which was determined by chiral HPLC. <sup>*c*</sup> 4 days was needed for the Michael addition step of the tandem reaction. <sup>*f*</sup> No annulation product was isolated in 24 h after aqueous HBr had been added.

the product we got upon isolation by column chromatography was the oxazine derivative **4a** instead of the predicted quinazoline derivative **3**! Obviously, a hydrolyzation process had occurred on the addition of the aqueous acid solution before the annulation step took place (Scheme 1, Route b). This unexpected result prompted us to examine the direct synthesis of **4a** from the carboxylic acid **1b**. Results showed that neither the reactivity nor the enantioselectivity of the reaction could be as good as that of the reaction in which **1a** was applied as the nucleophilic reagent (Table 1, entries 1 and 2), which was most probably because of the serious hindrance against the Michael addition step by the interactions between the carboxylic group in **1b** and the aminocatalyst **A**.

The reaction conditions for the Michael addition of the tandem sequence were then firstly optimized using the aryl amide **1a** as the nucleophilic reagent based on both the conversion of **1a** and the ee value of the final product **4a**. After screening of a number of different catalysts and solvents, it was found that the tandem reaction proceeded very well in a wide scope of solvents with both high enantioselectivities and reactivities when **A** was applied as the catalyst at room temperature. It appeared that the reaction failed to complete in protonic solvents such as 2-propanol while in non-protonic solvents, regardless of the polarities of them, the product

 Table 2
 Screening of the acid additives for the hydrolyzation/annulation

 step of the tandem reaction
 \$\$\$



<sup>*a*</sup> Unless otherwise indicated, all reactions were carried out using 1.0 equiv of **1a** (0.20 mmol), 1.5 equiv of **2a**, 0.5 mL CH<sub>2</sub>Cl<sub>2</sub>, and 2.0 equiv of the certain acid additive. <sup>*b*</sup> The temperature under which the hydrolyzation/annulation step of the tandem reaction was carried out. <sup>*c*</sup> The reaction time taken for the hydrolyzation/annulation step. <sup>*d*</sup> Isolated yield. <sup>*e*</sup> Determined by <sup>1</sup>H NMR on the crude reaction mixture.

could be obtained with excellent ee values ranging from 90% to 96%. A slight increase of enantioselectivity was observed when the reaction was carried out using 5.0 mol% of catalyst A in  $CH_2Cl_2$ . When the loading of catalyst A was decreased to 2.0 mol%, the same level of ee value could also be obtained while the reaction rate was found to be subject to an obvious decrease.

Having established the best reaction conditions for the Michael addition, the hydrolyzation/annulation step catalyzed by acid additives was subsequently investigated, mainly based on the total yield and the diastereomeric ratio of the final product **4a** (Table 2). Experimental data showed that the type of the acid used had a significant influence on both the d.r. value and the total yield of **4a**, while the temperature under which the hydrolyzation/annulation step was carried out contributed little to the diastereoselectivity of the final product. After a series of investigations, the oxazine derivative **4a** could be obtained as two separable diastereoisomers with a 4:1 ratio in 74% yield.

With the optimized conditions for both the Michael addition and the hydrolyzation/annulation steps at hand, the scope of this approach was next examined by synthesizing a series of substituted benzo[*d*]pyrido[2,1-*b*][1,3]oxazine derivatives (Table 3). To our delight, all the main products were obtained with excellent enantioselectivities in moderate to good yields, regardless of the properties of the substituents on the cinnamyl aldehydes, albeit with generally moderate diastereoselectivities for the two separable diastereoisomers. It could be inferred that the reaction time for the hydrolyzation/annulation step affected the total yields of the final products greatly. For example, the product **4a** could be afforded in a yield of 58% after stirring for 1 day after the acid TsOH·H<sub>2</sub>O was added, but when the reaction time of the second step was prolonged to 3 days, the yield of the final product **4a** could be raised to 74%.

Having successfully extended the scope of the tandem reaction of **1a** and a variety of cinnamyl aldehydes **2** in an enantioselective manner, we next tried to apply this approach further to include

#### Table 3 Expanding of the scope of the tandem reaction



<sup>*a*</sup> Unless otherwise indicated, all reactions were carried out using 1.0 equiv of **1a** (0.40 mmol), 1.5 equiv of **2**, 0.05 equiv of catalyst **A**, 1.0 mL CH<sub>2</sub>Cl<sub>2</sub>, and 2.0 equiv of. TsOH·H<sub>2</sub>O. <sup>*b*</sup> The time needed for the first step of Michael addition, which was determined by TLC evidence of the disappearance of the nucleophilic reagent. <sup>*c*</sup> The time needed for the cyclization step of the tandem reaction. <sup>*d*</sup> Isolated yield of both diastereoisomers. <sup>*c*</sup> Enantiomeric excess of the major diastereoisomer, which was determined by chiral HPLC. The value within parentheses represents the ee value of the minuture. <sup>*d*</sup> Without full conversion of **1a**. <sup>*k*</sup> 10 mmol% catalyst was used. <sup>*i*</sup> 0.5 mL CH<sub>2</sub>Cl<sub>2</sub> was added.

Fable 4	Further expanding	g of the scope	e of the tandem	reaction
---------	-------------------	----------------	-----------------	----------



<sup>*a*</sup> Unless otherwise indicated, all reactions were carried out using 1.0 equiv of **1c** (0.40 mmol), 1.5 equiv of **2**, 0.05 equiv of catalyst **A**, 1.0 mL CH<sub>2</sub>Cl<sub>2</sub>, and 2.0 equiv of. TsOH·H<sub>2</sub>O. <sup>*b*</sup> The time needed for the first step of Michael addition, which was determined by TLC evidence of the disappearance of the nucleophilic reagent. <sup>*c*</sup> Isolated yield of the product mixture **4** of both diastereoisomers. <sup>*d*</sup> Enantiomeric excess of both diastereoisomers, which was determined by chiral HPLC. <sup>*c*</sup> Determined by <sup>1</sup>H NMR on the product mixture. <sup>*f*</sup> Without full conversion of **1c**. <sup>*g*</sup> 0.7 mL CH<sub>2</sub>Cl<sub>2</sub> was added.

reaction of the newly designed aryl amide **1c** under similar conditions (Table 4). These reactions proceeded well with high enantioselectivities in good to excellent yields even with 5.0 mol%

of catalyst **A** at room temperature for the Michael addition. Unfortunately, the diastereomeric ratios failed to increase conspicuously after a number of attempts at the annulation step of the sequences, probably due to the flexibility of the methylene group in the aryl amide.

The absolute configuration of the isolated major diastereoisomer **4k** was determined by an X-ray analysis on the single crystal (Scheme 2),<sup>14</sup> which was identical to that produced by our assumed process summarized in Scheme 3, based on previous work by Jørgensen *et al.*,<sup>15</sup> Franzén *et al.*<sup>11</sup> and Rios *et al.*,<sup>16</sup> as well as other related reports.<sup>17</sup>



Scheme 2 X-ray crystal structure of 4k.



Scheme 3 Assumed process of the tandem reaction.

# Conclusions

In conclusion, an easy one-pot tandem reaction catalyzed by a chiral secondary amine which afforded a series of oxazine derivatives has been developed. This approach could prepare the required substituted benzo[*d*]pyrido[2,1-*b*][1,3]oxazine derivatives in generally high yields and excellent enantioselectivities. Further investigations towards this methodology are currently being studied well and will be presented in the near future.

# Experimental

## **General methods**

Proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectra and carbon nuclear magnetic resonance (<sup>13</sup>C NMR) spectra were recorded on a Bruker AV-400 spectrometer (400 MHz and 100 MHz). Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (CDCl<sub>3</sub>:  $\delta$  7.26). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl<sub>3</sub>:  $\delta$ 77.16). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz). Mass spectra (ESI) were measured on a Waters Micromass LCT spectrometer. High performance liquid chromatography (HPLC) was performed on an Agilent 1100 Series chromatographs using a Daicel Chiralpak IA and IC column (0.46 cm × 25 cm) as noted.

#### General procedure for the asymmetric tandem reaction of 1a and 2

To a solution of aryl amide **1a** (0.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.6 mL) was added the solution of the catalyst **A** (0.02 mmol) and cinnamyl aldehyde (0.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.4 mL) and the reaction mixture was stirred at room temperature for 1.5 h (determined by TLC evidence of the disappearance of **1a**). Then TsOH·H<sub>2</sub>O (0.8 mmol) was added into the mixture in one portion and the solution was stirred for 1 day. Lastly the reaction mixture was separated by column chromatography with petrol ether : ethyl acetate = 9:1 to 4:1 as eluant to give the product of both diastereoisomers as a white solid with a yield of 53%.

#### General procedure for the asymmetric tandem reaction of 1c and 2

To a solution of methyl 3-(2-(hydroxymethyl)phenylamino)-3oxopropanoate **1c** (0.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.6 mL) was added the solution of the catalyst **A** (0.02 mmol) and cinnamyl aldehyde (0.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.4 mL) and the reaction mixture was stirred at room temperature for 1.5 h (determined by TLC evidence of the disappearance of **1c**). Then the reaction mixture was cooled down to -20 °C and stirred for about an hour. After that TsOH·H<sub>2</sub>O (0.8 mmol) was added into the mixture in one portion and the solution was stirred at -20 °C for 4 days. Lastly the reaction mixture was separated by column chromatography with petrol ether : ethyl acetate = 9 : 1 as eluant to give the product mixture of both diastereoisomers as a white solid with a yield of 86%.

Methyl 3-(2-carbamoylphenylamino)-3-oxopropanoate (1a). Mp 120–121 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 11.79 (br s, 1H), 8.42–8.40 (d, J = 8.4 Hz, 1H), 8.28 (br s, 1H), 7.82–7.80 (d, J = 7.2 Hz, 1H), 7.75 (br s, 1H), 7.52–7.48 (t, J = 14.8 Hz, 1H), 7.17–7.13 (t, J = 14.8 Hz, 1H), 3.68 (s, 3H), 3.57 (s, 2H). <sup>13</sup>C-NMR (100 MHz, (CD<sub>3</sub>)<sub>2</sub>SO): δ (ppm) 171.0, 168.3, 164.4, 139.4, 132.5, 129.0, 123.4, 121.0, 52.5, 44.9. HRMS (EI): exact mass calculated for [M]<sup>+</sup> (C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>) requires m/z 236.0797, found m/z 236.0799.

**2-(3-Methoxy-3-oxopropanamido)benzoic acid (1b).** Mp 112– 114 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 11.39 (br s, 1H), 8.75 (br s, 1H), 8.72–8.70 (d, J = 8.4 Hz, 1H), 8.16–8.13 (dd, J =7.6 Hz, 0.8 Hz, 1H), 7.64–7.60 (td, J = 15.6 Hz, 0.8 Hz, 1H), 7.19–7.16 (t, J = 15.2 Hz, 1H), 3.83 (s, 3H), 3.61 (s, 2H). <sup>13</sup>C-NMR (100 MHz, (CD<sub>3</sub>)<sub>2</sub>SO):  $\delta$  (ppm) 171.7, 168.2, 164.6, 140.9, 135.3, 131.7, 123.5, 121.0, 115.2, 52.7, 44.3. HRMS (EI): exact mass calculated for [M]<sup>+</sup> (C<sub>11</sub>H<sub>11</sub>NO<sub>5</sub>) requires *m*/*z* 237.0637, found *m*/*z* 237.0633.

Methyl 3-(2-(hydroxymethyl)phenylamino)-3-oxopropanoate (1c). Mp 75–76 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 9.61

(br s, 1H), 7.54–7.52 (d, J = 8.0 Hz, 1H), 7.48–7.47 (d, J = 7.2 Hz, 1H), 7.28–7.18 (m, 2H), 5.29 (br s, 1H), 4.55 (s, 2H), 3.69 (s, 3H), 3.55 (s, 2H). <sup>13</sup>C-NMR (100 MHz, (CD<sub>3</sub>)<sub>2</sub>SO):  $\delta$  (ppm) 168.8, 164.6, 135.7, 135.2, 127.8, 127.4, 125.6, 124.6, 60.3, 52.4, 43.4. HRMS (EI): exact mass calculated for [M]<sup>+</sup> (C<sub>11</sub>H<sub>13</sub>NO<sub>4</sub>) requires m/z 223.0845, found m/z 223.0846.

(2*R*,3*S*,4*aS*)-Methyl 1,6-dioxo-3-phenyl-1,2,3,4,4a,6-hexahydrobenzo[d]pvrido[2,1-b][1,3]oxazine-2-carboxylate (4a). The product was obtained in 58% yield, white solid. Mp 72-74 °C;  $[\alpha]_{D}^{22} = +46.3^{\circ} (c = 1.00 \text{ in } CH_2Cl_2); ^{1}H \text{ NMR} (400 \text{ MHz}, CDCl_3):$  $\delta$  (ppm) 8.17–8.14 (dd, J = 8.0, 1.2 Hz, 1H), 7.87–7.85 (d, J =8.4 Hz, 1H), 7.71–7.67 (td, J = 15.6, 1.6 Hz, 1H), 7.46–7.37 (m, 3H), 7.34–7.28 (m, 3H), 5.75–5.74 (d, J = 2.4 Hz, 1H), 4.05–3.98 (td, J = 25.2, 2.8 Hz, 1H), 3.90–3.87 (d, J = 12.4 Hz, 1H), 3.61 (s, 3H), 2.63–2.58 (m, 1H), 2.53–2.45 (m, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 167.9, 165.7, 163.3, 140.7, 139.2, 134.4, 130.4, 129.2, 128.0, 127.0, 126.9, 124.4, 119.8, 84.6, 57.0, 52.5, 37.7, 34.1. HRMS (EI): exact mass calculated for  $[M]^+$  ( $C_{20}H_{17}NO_5$ ) requires m/z 351.1107, found m/z 351.1105. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM,  $1.0 \text{ mL min}^{-1}$ ]: 9.0 min (major), 16.0 min (minor), ee = 97%.

(2R,3S,4aS)-Methyl 1,6-dioxo-3-*m*-tolyl-1,2,3,4,4a,6-hexahydrobenzo[d]pyrido[2,1-b][1,3]oxazine-2-carboxylate (4b). The product was obtained in 57% yield, white solid. Mp 97-101 °C;  $[\alpha]_{D}^{22} = +70.6^{\circ} (c = 1.00 \text{ in } CH_2Cl_2); {}^{1}H \text{ NMR} (400 \text{ MHz}, CDCl_3):$  $\delta$  (ppm) 8.16–8.14 (dd, J = 8.0, 0.8 Hz, 1H), 7.87–7.85 (d, J =8.4 Hz, 1H), 7.71–7.66 (td, J = 15.6, 1.2 Hz, 1H), 7.45–7.41 (t, J = 15.2 Hz, 1H), 7.28–7.25 (t, J = 14.0 Hz, 1H), 7.13–7.00 (m, 3H), 5.74–5.73 (d, J = 2.4 Hz, 1H), 4.01–3.94 (td, J = 25.2, 3.2 Hz, 1H), 3.89-3.86 (d, J = 12.4 Hz, 1H), 3.61 (s, 3H), 2.60-2.56 (m, 1H), 2.51–2.44 (m, 1H), 2.37 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$ (ppm) 168.0, 165.8, 163.3, 140.7, 139.1, 138.8, 134.4, 130.4, 129.0, 128.7, 127.7, 127.0, 124.4, 123.8, 119.8, 84.7, 56.9, 52.5, 37.6, 34.1, 21.5. HRMS (EI): exact mass calculated for [M]<sup>+</sup> (C<sub>21</sub>H<sub>19</sub>NO<sub>5</sub>) requires m/z 365.1263, found m/z 365.1259. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM,  $1.0 \text{ mL min}^{-1}$ ]: 8.3 min (major), 14.4 min (minor), ee = 97%.

(2R,3S,4aS)-Methyl 3-(2-methoxyphenyl)-1,6-dioxo-1,2,3,4,4a, 6-hexahydrobenzo[d]pyrido[2,1-b][1,3]oxazine-2-carboxylate (4c). The product was obtained in 63% yield, white solid. Mp 99-101 °C;  $[\alpha]_{D}^{22} = +69.7^{\circ}$  (c = 1.00 in CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 8.17–8.15 (dd, J = 8.0, 1.2 Hz, 1H), 7.89–7.87 (d, J =8.0 Hz, 1H), 7.71–7.66 (td, J = 15.6, 1.6 Hz, 1H), 7.45–7.41 (t, J = 15.2 Hz, 1H), 7.31–7.28 (m, 1H), 7.22–7.19 (dd, J = 7.6, 1.2 Hz, 1H), 6.98–6.93 (m, 1H), 5.71–5.70 (d, J = 2.8 Hz, 1H), 4.39–4.35 (d, J = 12.4 Hz, 1H), 4.20-4.12 (td, J = 25.2, 3.2 Hz, 1H), 3.91(s, 3H), 3.59 (s, 3H), 2.88–2.80 (m, 1H), 2.54–2.50 (m, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 168.4, 166.4, 163.6, 157.7, 140.9, 134.3, 130.4, 129.4, 129.1, 126.8, 126.5, 124.3, 121.0, 119.8, 111.3, 85.1, 55.4, 54.4, 52.4, 35.6, 31.6. HRMS (EI): exact mass calculated for  $[M]^+$  (C<sub>21</sub>H<sub>19</sub>NO<sub>6</sub>) requires m/z 381.1212, found m/z381.1213. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL min-1]: 8.9 min (major), 30.9 min (minor), ee = 93%.

(2R,3S,4aS)-Methyl 1,6-dioxo-3-*p*-tolyl-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4d). The product was obtained in 52% yield, white solid. Mp 174–175 °C; [ $\alpha$ ]<sup>22</sup><sub>D</sub> = +149.4° (*c* = 1.00 in CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 8.15–8.13 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.86–7.84 (d, *J* = 8.4 Hz, 1H), 7.70–7.66 (td, *J* = 15.6, 1.2 Hz, 1H), 7.44–7.41 (t, *J* = 15.2 Hz, 1H), 7.18 (s, 4H), 5.73–5.73 (d, *J* = 2.4 Hz, 1H), 4.00–3.93 (td, *J* = 25.2, 3.2 Hz, 1H), 3.87–3.84 (d, *J* = 12.4 Hz, 1H), 3.60 (s, 3H), 2.59–2.54 (m, 1H), 2.51–2.43 (m, 1H), 2.35 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ (ppm) 168.0, 165.8, 163.3, 140.7, 137.7, 136.2, 134.4, 130.4, 129.8, 126.9, 126.7, 124.4, 119.8, 84.7, 57.1, 52.5, 37.3, 34.1, 21.1. HRMS (EI): exact mass calculated for [M]<sup>+</sup> (C<sub>21</sub>H<sub>19</sub>NO<sub>5</sub>) requires *m*/*z* 365.1263, found *m*/*z* 365.1260. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL min<sup>-1</sup>]: 8.9 min (major), 12.6 min (minor), ee = 95%.

(2R,3S,4aS)-Methyl 3-(4-methoxyphenyl)-1,6-dioxo-1,2,3,4,4a, 6-hexahydrobenzo[d]pyrido[2,1-b][1,3]oxazine-2-carboxylate (4e). The product was obtained in 48% yield, white solid. Mp 194-196 °C;  $[\alpha]_{D}^{22} = +89.2^{\circ}$  (c = 1.00 in CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 8.15–8.13 (dd, J = 7.6, 0.8 Hz, 1H), 7.85–7.83 (d, *J* = 8.0 Hz, 1H), 7.70–7.65 (td, *J* = 15.6, 1.2 Hz, 1H), 7.44–7.40 (t, J = 15.2 Hz, 1H), 7.22–7.20 (m, 2H), 6.91–6.89 (m, 2H), 5.73–5.72 (d, J = 2.4 Hz, 1H), 3.98–3.91 (td, J = 25.2, 3.2 Hz, 1H), 3.83– 3.80 (m, 4H), 3.60 (s, 3H), 2.58–2.53 (m, 1H), 2.49–2.41 (m, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ (ppm) 168.0, 165.8, 163.3, 159.1, 140.7, 134.4, 131.2, 130.4, 128.0, 126.9, 124.4, 119.8, 114.5, 84.7, 57.3, 52.3, 52.5, 36.9, 34.2. HRMS (EI): exact mass calculated for  $[M]^+$  (C<sub>21</sub>H<sub>19</sub>NO<sub>6</sub>) requires m/z 381.1212, found m/z 381.1213. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL min<sup>-1</sup>]: 15.4 min (major), 25.1 min (minor), ee = 95%.

(2*R*,3*S*,4*aS*)-Methyl 3-(2-chlorophenyl)-1,6-dioxo-1,2,3,4,4a, 6-hexahydrobenzo[d]pyrido[2,1-b][1,3]oxazine-2-carboxylate (4f). The product was obtained in 69% yield, white solid. Mp 186- $188 \,^{\circ}\text{C}; \ [\alpha]_{D}^{22} = +115.2^{\circ} \ (c = 1.00 \text{ in } \text{CH}_2\text{Cl}_2); \,^{1}\text{H NMR} \ (400 \text{ MHz}, 100 \text{ MHz})$ CDCl<sub>3</sub>):  $\delta$  (ppm) 8.13–8.11 (d, J = 7.6 Hz, 1H), 7.85–7.83 (d, J =8.0 Hz, 1H), 7.68–7.64 (t, J = 16.0 Hz, 1H), 7.46–7.39 (m, 2H), 7.32-7.23 (m, 3H), 5.72-5.71 (d, J = 2.8 Hz, 1H), 4.55-4.48 (td, J = 25.6, 2.4 Hz, 1H), 4.15–4.12 (d, J = 12.4 Hz, 1H), 3.60 (s, 3H), 2.62–2.59 (m, 1H), 2.48–2.38 (m, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 167.7, 165.6, 163.2, 140.6, 136.3, 134.4, 133.9, 130.6, 130.4, 129.1, 127.6, 127.0, 124.3, 119.8, 84.6, 55.0, 52.6, 34.7, 33.0, 26.9. HRMS (EI): exact mass calculated for [M]+  $(C_{20}H_{16}NO_5Cl)$  requires m/z 385.0717, found m/z 385.0709. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, DCM, 0.7 mL min-1]: 5.6 min (minor), 6.6 min (major), ee = 97%.

(2*R*,3*S*,4*aS*)-Methyl 3-(3-chlorophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4g). The product was obtained in 35% yield, white solid. Mp 190–192 °C;  $[\alpha]_{D}^{22} = +81.2^{\circ}$  (*c* = 1.00 in CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 8.16–8.14 (d, *J* = 7.6 Hz, 1H), 7.86–7.84 (d, *J* = 8.4 Hz, 1H), 7.71–7.67 (t, *J* = 15.6 Hz, 1H), 7.46–7.42 (t, *J* = 15.2 Hz, 1H), 7.35–7.28 (m, 3H), 7.22–7.18 (m, 1H), 5.75–5.74 (d, *J* = 2.4 Hz, 1H), 4.03–3.96 (td, *J* = 25.6, 2.8 Hz, 1H), 3.86–3.83 (d, *J* = 12.4 Hz, 1H), 3.63 (s, 3H), 2.60–2.57 (m, 1H), 2.51–2.44 (m, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 167.7, 165.3, 163.1, 141.2, 140.6, 135.0, 134.5, 130.5, 128.3, 127.1, 127.1, 125.3, 124.4, 119.7, 84.4, 56.8, 52.7, 37.4, 33.8. HRMS (EI): exact

mass calculated for  $[M]^+$  (C<sub>20</sub>H<sub>16</sub>NO<sub>5</sub>Cl) requires *m/z* 385.0717, found *m/z* 385.0721. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL min<sup>-1</sup>]: 7.7 min (major), 8.9 min (minor), ee = 95%.

(2R,3S,4aS)-Methyl 3-(4-chlorophenyl)-1,6-dioxo-1,2,3,4,4a,6hexahydrobenzo[d]pyrido[2,1-b][1,3]oxazine-2-carboxylate (4h). The product was obtained in 84% yield, white solid. Mp 188-190 °C;  $[\alpha]_{D}^{22} = +89.5^{\circ}$  (c = 1.00 in CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 8.11–8.10 (d, J = 6.8 Hz, 1H), 7.82–7.80 (d, J =8.0 Hz, 1H), 7.68–7.63 (td, J = 15.6, 1.2 Hz, 1H), 7.43–7.39 (t, J = 15.2 Hz, 1H), 7.35–7.33 (d, J = 8.4 Hz, 2H), 7.24–7.22 (d, J = 8.4 Hz, 2H), 5.73–5.73 (d, J = 2.0 Hz, 1H), 4.00–3.93 (td, J = 24.8, 3.2 Hz, 1H), 3.85–3.82 (d, J = 12.4 Hz, 1H), 3.59 (s, 3H), 2.55–2.42 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 167.8, 165.4, 163.2, 140.6, 137.7, 134.5, 133.8, 130.4, 129.4, 128.4, 127.0, 124.3, 119.7, 84.5, 56.9, 52.6, 37.2, 33.8. HRMS (EI): exact mass calculated for  $[M]^+$  (C<sub>20</sub>H<sub>16</sub>NO<sub>5</sub>Cl) requires m/z 385.0717, found m/z 385.0719. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, DCM, 0.7 mL min<sup>-1</sup>]: 5.9 min (minor), 7.1 min (major), ee = 93%.

(2R,3S,4aS)-Methyl 3-(2-fluorophenyl)-1,6-dioxo-1,2,3,4,4a,6hexahydrobenzo[d]pyrido[2,1-b][1,3]oxazine-2-carboxylate (4i). The product was obtained in 84% yield, white solid. Mp 180- $182 \,^{\circ}\text{C}; \, [\alpha]_{D}^{22} = +70.9^{\circ} \, (c = 1.00 \text{ in } \text{CH}_2\text{Cl}_2); \,^1\text{H NMR} \, (400 \text{ MHz}, 100 \text{ MHz})$ CDCl<sub>3</sub>):  $\delta$  (ppm) 8.12–8.10 (d, J = 7.6 Hz, 1H), 7.84–7.82 (d, J = 8.4 Hz, 1H), 7.68–7.64 (td, J = 15.6, 1.2 Hz, 1H), 7.42–7.38 (t, J = 15.2 Hz, 1H), 7.32-7.26 (m, 2H), 7.15-7.06 (m, 2H),5.73-5.72 (d, J = 2.4 Hz, 1H), 4.18-4.03 (m, 2H), 3.57 (s, 3H), 2.75-2.68 (td, J = 26.8, 4.0 Hz, 1H), 2.57-2.53 (m, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ (ppm) 167.9, 165.5, 163.3, 140.7, 134.4, 130.3, 129.8, 129.6, 127.0, 125.7, 124.8, 124.4, 119.8, 116.5, 116.3, 84.7, 55.1, 52.5, 34.2, 32.1. HRMS (EI): exact mass calculated for  $[M]^+$  (C<sub>20</sub>H<sub>16</sub>NO<sub>5</sub>F) requires m/z 369.1013, found m/z 369.1010. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL min<sup>-1</sup>]: 7.8 min (major), 14.9 min (minor), ee = 95%.

(2R,3S,4aS)-Methyl 3-(4-fluorophenyl)-1,6-dioxo-1,2,3,4,4a,6hexahydrobenzo[d]pyrido[2,1-b][1,3]oxazine-2-carboxylate (4j). The product was obtained in 76% yield, colorless oil.  $\left[\alpha\right]_{\rm D}^{22}$  = +72.5° (c = 1.00 in CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ (ppm) 8.13–8.11 (dd, J = 8.0, 1.2 Hz, 1H), 7.84–7.82 (d, J =8.0 Hz, 1H), 7.69–7.64 (td, J = 15.6, 1.2 Hz, 1H), 7.44–7.40 (t, J = 15.2 Hz, 1H), 7.29-7.25 (m, 2H), 7.09-7.04 (m, 2H), 5.74-5.73 (d, J = 2.4 Hz, 1H), 4.02–3.95 (td, J = 24.8, 3.2 Hz, 1H), 3.84–3.81 (d, J = 12.4 Hz, 1H), 3.59 (s, 3H), 2.57–2.53 (m, 1H), 2.51–2.43 (m, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 167.9, 165.5, 163.5, 163.2, 161.0, 140.6, 135.0, 134.4, 130.4, 128.6, 128.6, 127.0, 124.3, 119.7, 116.2, 116.0, 84.5, 57.1, 52.6, 37.0, 34.0. HRMS (EI): exact mass calculated for  $[M]^+$  (C<sub>20</sub>H<sub>16</sub>NO<sub>5</sub>F) requires m/z 369.1013, found m/z 369.1014. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL min<sup>-1</sup>]: 7.7 min (major), 9.7 min (minor), ee = 94%.

(2*R*,3*S*,4*aS*)-Methyl 3-(2-bromophenyl)-1,6-dioxo-1,2,3,4,4a,6hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4k). The product was obtained in 85% yield, white solid. Mp 190– 192 °C;  $[\alpha]_{D}^{22} = +82.6^{\circ}$  (*c* = 1.00 in CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 8.12–8.10 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.84–7.82 (d,  $J = 8.0 \text{ Hz}, 1\text{H}, 7.70-7.60 \text{ (m, 2H)}, 7.43-7.11 \text{ (m, 4H)}, 5.70-5.70 \text{ (d, } J = 2.4 \text{ Hz}, 1\text{H}), 4.56-4.49 \text{ (td, } J = 25.2, 2.4 \text{ Hz}, 1\text{H}), 4.12-4.09 \text{ (d, } J = 12.8 \text{ Hz}, 1\text{H}), 3.60 \text{ (s, 3H)}, 2.63-2.59 \text{ (m, 1H)}, 2.41-2.32 \text{ (m, 1H)}. {}^{13}\text{C} \text{ NMR} (100 \text{ MHz}, \text{CDCl}_3): \delta \text{ (ppm)} 167.7, 165.6, 163.2, 140.6, 138.0, 134.4, 134.0, 130.4, 129.3, 128.2, 127.2, 126.9, 124.4, 124.3, 119.8, 84.6, 55.2, 52.6, 36.9, 33.4. HRMS (EI): exact mass calculated for [M]<sup>+</sup> (C<sub>20</sub>H<sub>16</sub>NO<sub>5</sub>Br) requires$ *m/z*429.0212, found*m/z*429.0213. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, DCM, 0.7 mL min<sup>-1</sup>]: 5.6 min (minor), 6.8 min (major), ee = 94%.

(2R,3S,4aS)-Methyl 3-(4-bromophenyl)-1,6-dioxo-1,2,3,4,4a,6hexahydrobenzo[d]pyrido[2,1-b][1,3]oxazine-2-carboxylate (4l). The product was obtained in 78% yield, white solid. Mp 120- $122 \,^{\circ}\text{C}; \, [\alpha]_{\text{D}}^{22} = +95.7^{\circ} \, (c = 1.00 \text{ in } \text{CH}_2\text{Cl}_2); \,^{1}\text{H NMR} \, (400 \text{ MHz}, 100 \text{ MHz})$ CDCl<sub>3</sub>):  $\delta$  (ppm) 8.12–8.10 (d, J = 6.8 Hz, 1H), 7.83–7.81 (d, J = 8.0 Hz, 1H), 7.68–7.64 (td, J = 15.6, 1.2 Hz, 1H), 7.51–7.49 (t, J = 8.4 Hz, 2H), 7.43-7.39 (t, J = 15.2 Hz, 1H), 7.19-7.16 (d, J = 15.2 Hz, 1H)J = 8.4 Hz, 2H), 5.73–5.72 (d, J = 2.4 Hz, 1H), 4.00–3.93 (td, J = 24.8, 3.2 Hz, 1H), 3.85–3.82 (d, J = 12.4 Hz, 1H), 3.59 (s, 3H), 2.55–2.52 (m, 1H), 2.50–2.42 (m, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 167.8, 165.4, 163.2, 140.6, 138.2, 134.5, 132.3, 130.4, 128.7, 127.1, 124.3, 121.9, 119.7, 84.5, 56.8, 52.6, 37.2, 33.8. HRMS (EI): exact mass calculated for  $[M]^+$  (C<sub>20</sub>H<sub>16</sub>NO<sub>5</sub>Br) requires m/z 429.0212, found m/z 429.0214. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 0.6 mL min<sup>-1</sup>]: 13.4 min (major), 15.2 min (minor), ee >99%.

(2R,3S,4aS)-Methyl 3-(4-nitrophenyl)-1,6-dioxo-1,2,3,4,4a,6hexahydrobenzo[d]pyrido[2,1-b][1,3]oxazine-2-carboxylate (4m). The product was obtained in 89% yield, yellow solid. Mp 84-86 °C;  $[\alpha]_{D}^{22} = +59.3^{\circ}$  (c = 1.00 in CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 8.23–8.21 (d, J = 8.4 Hz, 2H), 8.11–8.09 (d, J = 6.8 Hz, 1H), 7.82–7.80 (d, J = 8.0 Hz, 1H), 7.68–7.64 (td, J = 15.6, 1.2 Hz, 1H), 7.52–7.49 (d, J = 8.4 Hz, 2H), 7.44–7.40 (t, J = 15.0 Hz, 1H), 5.77 (m, 1H), 4.16–4.07 (m, 1H), 3.95–3.92 (d, J = 12.4 Hz, 1H), 3.58 (s, 3H), 2.58–2.56 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 167.5, 164.9, 163.0, 147.6, 146.5, 140.5, 134.6, 130.4, 128.2, 127.2, 124.4, 124.4, 119.7, 84.3, 56.4, 52.7, 37.6, 33.4. HRMS (EI): exact mass calculated for [M]<sup>+</sup>  $(C_{20}H_{16}N_2O_7)$  requires m/z 396.0958, found m/z 396.0961. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, *n*-hexane/DCM = 1/1, 1.0 mL min<sup>-1</sup>]: 19.8 min (minor),  $31.3 \min$  (major), ee = 94%.

(2*R*,3*S*)-Methyl 1-oxo-3-phenyl-1,2,3,4,4a,6-hexahydrobenzo-[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4n). The product was obtained as a mixture of both diastereoisomers in 86% yield, colorless oil.  $[\alpha]_{D}^{22} = +11.0^{\circ}$  (*c* = 1.00 in CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 8.16–7.80 (m, 1H), 7.36–7.34 (m, 2H), 7.32–7.24 (m, 4H), 7.21–7.15 (m, 1H), 7.07–7.03 (m, 1H), 5.21–4.93 (m, 3H), 3.97–3.42 (m, 5H), 2.59–2.39 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 169.8, 169.0, 166.0, 165.5, 140.5, 139.9, 137.1, 135.3, 129.0, 129.0, 127.7, 127.6, 127.2, 127.0, 126.9, 126.8, 126.4, 126.1, 125.7, 125.3, 125.2, 124.5, 124.4, 123.7, 84.0, 82.8, 67.8, 67.2, 58.4, 57.5, 52.4, 52.2, 38.4, 37.6, 35.2, 35.1. HRMS (EI): exact mass calculated for [M]<sup>+</sup> (C<sub>20</sub>H<sub>19</sub>NO<sub>4</sub>) requires *m/z* 337.1314, found *m/z* 337.1313. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL min<sup>-1</sup>]: 13.9 min (major), 18.3 min (minor), ee = 94%; 15.9 min (major), 51.4 min (minor), ee = 97%.

(2*R*,3*S*)-Methyl 1-oxo-3-*m*-tolyl-1,2,3,4,4a,6-hexahydrobenzo-[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4o). The product was obtained as a mixture of both diastereoisomers in 97% yield, colorless oil.  $[\alpha]_D^{22} = -5.4^\circ$  (*c* = 1.00 in CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 8.16–7.81 (m, 1H), 7.28–7.04 (m, 7H), 5.21– 4.93 (m, 3H), 3.94–3.42 (m, 5H), 2.58–2.10 (m, 5H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 169.9, 169.0, 166.1, 165.5, 140.5, 139.9, 138.6, 138.5, 137.2, 135.3, 128.9, 128.8, 128.5, 128.3, 127.8, 127.7, 127.2, 126.8, 126.4, 126.1, 125.7, 125.3, 125.2, 124.5, 124.4, 123.9, 123.8, 123.7, 84.0, 82.8, 67.8, 67.2, 58.4, 57.5, 52.4, 52.2, 38.2, 37.5, 35.3, 35.2. HRMS (EI): exact mass calculated for [M]<sup>+</sup> (C<sub>21</sub>H<sub>21</sub>NO<sub>4</sub>) requires *m*/*z* 351.1471, found *m*/*z* 351.1468. [IC column, 254 nm, DCM, 1.0 mL min<sup>-1</sup>]: 11.6 min (major), 25.0 min (minor), ee = 97%; 14.6 min (major), 48.3 min (minor), ee = 97%.

(2*R*,3*S*)-Methyl 1-oxo-3-*p*-tolyl-1,2,3,4,4a,6-hexahydrobenzo-[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4p). The product was obtained as a mixture of both diastereoisomers in 89% yield, white solid. Mp 124–126 °C;  $[\alpha]_D^{22} = +9.1^{\circ}$  (*c* = 1.00 in CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 8.16–7.81 (m, 1H), 7.28–7.03 (m, 7H), 5.20–4.93 (m, 3H), 3.93–3.42 (m, 5H), 2.57–2.06 (m, 5H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 169.9, 169.0, 166.1, 165.5, 137.5, 137.3, 137.2, 137.1, 137.0, 135.3, 129.7, 129.6, 127.2, 126.8, 126.8, 126.4, 126.1, 125.7, 125.3, 125.2, 124.5, 124.4, 123.7, 84.0, 82.8, 67.8, 67.2, 58.5, 57.6, 52.4, 52.2, 37.9, 37.2, 35.4, 35.2, 21.1. HRMS (EI): exact mass calculated for [M]<sup>+</sup> (C<sub>21</sub>H<sub>21</sub>NO<sub>4</sub>) requires *m*/*z* 351.1471, found *m*/*z* 351.1469. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL min<sup>-1</sup>]: 11.3 min (minor), 12.9 min (major), ee = 99%; 16.1 min (major), 31.6 min (minor), ee = 94%.

(2*R*,3*S*)-Methyl 3-(4-methoxyphenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[d]pyrido[2,1-b][1,3]oxazine-2-carboxylate (4q). The product was obtained as a mixture of both diastereoisomers in 98% yield, yellow solid. Mp 75–77 °C;  $[\alpha]_{D}^{22} = +11.4^{\circ}$  (c = 1.00 in CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ(ppm) 8.14–7.78 (m, 1H), 7.28-7.13 (m, 4H), 7.05-7.02 (m, 1H), 6.89-6.86 (m, 2H), 5.19-4.92 (m, 3H), 3.90-3.39 (m, 8H), 2.55-2.05 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ (ppm) 169.9, 169.1, 166.0, 165.5, 159.0, 158.8, 137.2, 135.3, 132.6, 132.0, 128.0, 127.9, 127.2, 126.8, 126.4, 126.1, 125.6, 125.3, 125.2, 124.5, 124.4, 123.7, 114.3, 114.3, 84.0, 82.8, 67.8, 67.2, 58.7, 57.9, 55.2, 52.4, 52.2, 37.6, 36.8, 35.5, 35.2. HRMS (EI): exact mass calculated for [M]<sup>+</sup> (C<sub>21</sub>H<sub>21</sub>NO<sub>5</sub>) requires m/z 367.1420, found m/z 367.1423. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL min<sup>-1</sup>]: 15.0 min (major), 24.2 min (minor), ee = 92%; 17.0 min (major),  $39.9 \min(\text{minor}), ee = 93\%$ .

(2*R*,3*S*)-Methyl 3-(3-chlorophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4r). The product was obtained as a mixture of both diastereoisomers in 76% yield, yellow solid. Mp 78–80 °C;  $[\alpha]_D^{22} = +4.5^\circ$  (*c* = 1.00 in CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 8.13–7.78 (m, 1H), 7.43–7.04 (m, 7H), 5.30–4.94 (m, 3H), 3.95–3.44 (m, 5H), 2.59–2.06 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 169.6, 168.7, 165.6, 165.0, 142.5, 142.0, 137.0, 135.1, 134.8, 134.7, 130.3, 130.3, 130.2, 128.0, 127.8, 127.3, 127.1, 126.9, 126.5, 126.1, 125.8, 125.3, 125.2, 125.1, 124.5, 124.4, 123.7, 83.8, 82.6, 67.8, 67.2, 58.1, 57.3, 52.6, 52.4, 38.0, 37.3, 35.0, 34.9. HRMS (EI): exact mass calculated for  $[M]^+$  (C<sub>20</sub>H<sub>18</sub>NO<sub>4</sub>Cl) requires m/z 371.0924, found m/z 371.0921. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, *n*-hexane/DCM = 2/1, 1.0 mL min<sup>-1</sup>]: 12.9 min (minor), 28.3 min (major), ee = 97%; 15.0 min (minor), 17.7 min (major), ee = 97%.

(2R,3S)-Methyl 3-(4-chlorophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[d]pyrido[2,1-b][1,3]oxazine-2-carboxylate (4s). The product was obtained as a mixture of both diastereoisomers in 99% yield, white solid. Mp 129–132 °C;  $[\alpha]_{D}^{22} = +4.3^{\circ}$  (c = 1.00 in CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 8.12–7.77 (m, 1H), 7.33-7.30 (m, 2H), 7.26-7.14 (m, 4H), 7.06-7.02 (m, 1H), 5.20-4.92 (m, 3H), 3.93-3.41 (m, 5H), 2.55-2.06 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 169.6, 168.8, 165.7, 165.1, 139.0, 138.5, 137.0, 135.2, 133.5, 133.3, 129.2, 129.1, 128.4, 128.4, 127.1, 126.8, 126.4, 126.1, 125.8, 125.3, 124.5, 124.4, 123.7, 83.8, 82.6, 67.8, 67.2, 58.2, 57.4, 52.5, 52.3, 37.8, 37.0, 35.1, 34.9. HRMS (EI): exact mass calculated for [M]<sup>+</sup>  $(C_{20}H_{18}NO_4Cl)$  requires m/z 371.0924, found m/z 371.0916. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, *n*-hexane/DCM = 2/1, 1.0 mL min<sup>-1</sup>]: 13.5 min (minor), 41.1 min (major), ee = 93%; 14.1 min (minor), 24.1 min (major), ee = 93%.

(2R,3S)-Methyl 3-(2-fluorophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[d]pyrido[2,1-b][1,3]oxazine-2-carboxylate (4t). The product was obtained as a mixture of both diastereoisomers in 99% yield, yellow solid. Mp 106–111 °C;  $[\alpha]_{D}^{22} = -3.4^{\circ}$  (c = 1.00 in CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 8.13–7.79 (m, 1H), 7.28-7.04 (m, 7H), 5.21-4.91 (m, 3H), 4.19-3.40 (m, 5H), 2.58–2.16 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 169.6, 168.9, 165.8, 165.3, 137.1, 135.3, 129.3, 129.3, 129.2, 129.0, 129.0, 128.4, 128.3, 127.2, 127.1, 127.0, 126.8, 126.7, 126.6, 126.4, 126.1, 125.7, 125.3, 125.3, 124.7, 124.7, 124.6, 124.6, 124.5, 124.4, 123.7, 116.3, 116.1, 116.1, 116.0, 83.9, 82.8, 67.8, 67.2, 56.4, 55.6, 52.5, 52.3, 34.2, 33.5, 33.2, 32.9. HRMS (EI): exact mass calculated for  $[M]^+$  (C<sub>20</sub>H<sub>18</sub>NO<sub>4</sub>F) requires m/z 355.1220, found m/z 355.1219. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, *n*-hexane/DCM = 1/1, 1.0 mL min<sup>-1</sup>]: 6.3 min (minor), 9.5 min (major), ee = 95%; 7.3 min (minor), 8.0 min (major), ee = 95%; 7.3 min (minor), ee = 95%94%.

(2R,3S)-Methyl 3-(4-fluorophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[d]pyrido[2,1-b][1,3]oxazine-2-carboxylate (4u). The product was obtained as a mixture of both diastereoisomers in 63% yield, yellow solid. Mp 144–149 °C;  $[\alpha]_{D}^{22} = +16.2^{\circ}$  (c = 1.00 in CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 8.13–7.78 (m, 1H), 7.28-7.02 (m, 7H), 5.30-4.94 (m, 3H), 3.95-3.45 (m, 5H), 2.58–2.08 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 169.7, 168.9, 165.8, 165.2, 163.3, 160.8, 137.1, 136.3, 136.2, 128.6, 128.5, 127.1, 126.8, 126.4, 125.8, 125.3, 124.5, 124.4, 123.7, 116.0, 115.9, 115.8, 115.7, 83.8, 82.7, 67.8, 67.2, 58.5, 57.7, 52.5, 52.3, 37.7, 36.9, 35.3, 35.1. HRMS (EI): exact mass calculated for  $[M]^+$  (C<sub>20</sub>H<sub>18</sub>NO<sub>4</sub>F) requires m/z 355.1220, found m/z 355.1215. The enantiomeric excess was determined by HPLC. [IA column,  $254 \text{ nm}, n\text{-hexane/DCM} = 3/1, 1.0 \text{ mL min}^{-1}$ : 23.1 min (minor), 78.5 min (major), ee = 99%; 25.8 min (minor), 50.2 min (major), ee = 94%.

(2R,3S)-Methyl 3-(4-bromophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[d]pyrido[2,1-b][1,3]oxazine-2-carboxylate (4v). The product was obtained in 86% yield, white solid. Mp 146-148 °C;  $[\alpha]_{D}^{22} = +15.9^{\circ} (c = 1.00 \text{ in } CH_2Cl_2); ^{1}H \text{ NMR} (400 \text{ MHz}, CDCl_3):$  $\delta$  (ppm) 8.12–7.77 (m, 1H), 7.48–7.46 (m, 2H), 7.27–7.23 (m, 1H), 7.20–7.11 (m, 3H), 7.06–7.02 (m, 1H), 5.20–4.92 (m, 3H), 3.92-3.42 (m, 5H), 2.55-2.06 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 169.6, 168.8, 165.6, 165.1, 139.5, 139.0, 137.0, 135.2, 132.1, 132.1, 128.8, 128.7, 127.1, 126.8, 126.4, 126.1, 125.8, 125.3, 124.5, 124.4, 123.7, 121.6, 121.4, 83.8, 82.6, 67.8, 67.2, 58.1, 57.3, 52.5, 52.4, 37.8, 37.1, 35.0, 34.9. HRMS (EI): exact mass calculated for  $[M]^+$  (C<sub>20</sub>H<sub>18</sub>NO<sub>4</sub>Br) requires m/z 415.0419, found m/z 415.0416. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, *n*-hexane/DCM = 3/1, 1.0 mL min<sup>-1</sup>]: 27.4 min (minor), 102.3 min (major), ee = 99%; 30.4 min (minor), 54.5 min (major), ee = 96%.

(2*R*,3*S*,4*aR*)-Methyl 1,6-dioxo-3-phenyl-1,2,3,4,4a,6-hexahydrobenzo[d]pyrido[2,1-b][1,3]oxazine-2-carboxylate (4a1). White solid. Mp 181–183 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ (ppm) 8.15-8.13 (dd, J = 8.0, 1.2 Hz, 1H), 8.07-8.05 (d, J = 8.4 Hz, 1H), 7.70–7.67 (td, J = 15.6, 1.2 Hz, 1H), 7.42–7.38 (m, 3H), 7.35–7.32 (m, 1H), 7.27-7.26 (m, 2H), 5.89-5.85 (dd, J = 8.4, 6.8 Hz, 1H), 3.82-3.79 (d, J = 12.0 Hz, 1H), 3.65 (s, 3H), 3.59-3.52 (td, J = 26.0, 2.8 Hz, 1H), 2.79–2.73 (m, 1H), 2.53–2.44 (m, 1H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 169.0, 165.3, 162.2, 139.8, 138.8, 134.8, 130.3, 129.2, 128.1, 126.9, 126.5, 123.0, 118.5, 84.4, 57.8, 52.7, 38.1, 34.2. HRMS (EI): exact mass calculated for  $[M]^+$  (C<sub>20</sub>H<sub>17</sub>NO<sub>5</sub>) requires m/z 351.1107, found m/z 351.1106. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL min<sup>-1</sup>]: 12.6 min (major), 18.1 min (minor), ee = 98%.

(3*R*,4*S*,6*S*)-Methyl 1-(2-carbamoylphenyl)-6-hydroxy-2-oxo-4phenyl piperidine-3-carboxylate (4a2). The intermediate product was isolated as a mixture of two diastereomers by column chromatography after full conversion of 1a using ethyl acetate and then 1,4-dioxane as the eluent. White solid. Mp 198–199 °C; <sup>1</sup>H-NMR (400 MHz, (CD<sub>3</sub>)<sub>2</sub>SO):  $\delta$  (ppm) 8.15–6.89 (m, 9H), 6.46– 5.18 (m, 1H), 3.95–3.81 (m, 1H), 3.57–3.24 (m, 4H), 2.58–2.37 (m, 1H), 2.03–1.37 (m, 1H). <sup>13</sup>C-NMR (100 MHz, (CD<sub>3</sub>)<sub>2</sub>SO):  $\delta$ (ppm) 174.9, 174.4, 174.0, 173.9, 170.9, 170.6, 146.9, 144.2, 143.7, 140.8, 139.7, 136.9, 136.0, 135.4, 134.2, 134.0, 133.6, 133.2, 132.9, 132.8, 132.5, 132.4, 132.3, 132.1, 87.0, 86.0, 62.5, 61.8, 56.9, 42.9, 42.2, 41.8, 41.7, 35.7. HRMS (EI): exact mass calculated for [M]<sup>+</sup> (C<sub>20</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub>) requires *m*/*z* 368.1372, found *m*/*z* 368.1378.

#### Acknowledgements

We acknowledge National Natural Science Foundation of China (20902018), the Fundamental Research Funds for the Central Universities, Shanghai Pujiang Program (08PJ1403300) and Innovation Program of Shanghai Municipal Education Commission (11ZZ56) for financial support.

## Notes and references

For some selected examples and reviews, see: (a) Y. Yoshida and G. Saito, *Phys. Chem. Chem. Phys.*, 2010, **12**, 1675–1684; (b) C. Pettinari, N. Masciocchi, L. Pandolfo and D. Pucci, *Chem.-Eur. J.*, 2010, **16**, 1106–1123; (c) K. M. Dawood, N. M. Elwan, A. A. Farahat and

B. F. Abdel-Wahab, J. Heterocyclic. Chem., 2010, 47, 243–267; (d) Y. Matsuya and H. Nemoto, Heterocycles, 2010, 81, 57–66.

- 2 For some related introductions, see: (a) M. N. Rahman, J. Z. Vlahakis, G. Roman, D. Vukomanovic, W. A. Szarek, K. Nakatsu and Z. Jia, J. Inorg. Biochem., 2010, **104**, 324–330; (b) Z. Jakopin and M. S. Dolenc, *Curr. Med. Chem.*, 2010, **17**, 651–671.
- 3 For related reviews, see: (a) M. D. McReynolds, J. M. Dougherty and P. R. Hanson, Chem. Rev., 2004, 104, 2239–2258; (b) F. Alonso, I. P. Beletskaya and M. Yus, Chem. Rev., 2004, 104, 3079–3160; (c) A. Deiters and S. F. Martin, Chem. Rev., 2004, 104, 2199–2238; (d) G. Zeni and R. C. Larock, Chem. Rev., 2004, 104, 2285–2310; (e) L. Yet, Chem. Rev., 2000, 100, 2963–3008; (f) J. Tsuji, Transition Metal Reagents and Catalysts, John Wiley & Sons Ltd.: New York, 2000; (g) M. Beller, C. Bolm, Transition Metals for Organic Synthesis, Wiley-VCH Verlag GmbH: Weinheim, Germany, 1998; (h) S. Murahashi, S. G. Davies, Transition Metal Catalyzed Reactions, Blackwell Science: Oxford, 1999.
- 4 For selected reviews, see: (a) N. D. Clement and K. J. Cavell, Angew. Chem., Int. Ed., 2004, 43, 3845–3847; (b) I. Nakamura and Y. Yamamoto, Chem. Rev., 2004, 104, 2127–2198; (c) N. T. Patil and Y. Yamamoto, Chem. Rev., 2008, 108, 3395–3442; (d) G. Evano, N. Blanchard and M. Toumi, Chem. Rev., 2008, 108, 3054–3131.
- 5 For selected examples, see: (a) Y. Murata, D. Yamashita, K. Kitahara, Y. Minasako, A. Nakazaki and S. Kobayashi, Angew. Chem., Int. Ed., 2009, 48, 1400–1403; (b) J. Barluenga, A. Mendoza, F. Rodriguez and F. J. Fananas, Angew. Chem., Int. Ed., 2009, 48, 1644–1647; (c) Y. B. Zhao, B. Mariampillai, D. A. Candito, B. Laleu, M. Z. Li and M. Lautens, Angew. Chem., Int. Ed., 2009, 48, 1849–1852; (d) C. F. Bender, F. K. Yoshimoto, C. L. Paradise and J. K. De Brabander, J. Am. Chem. Soc., 2009, 131, 11350–11352; (e) X. X. Wu, J. Y. Zhou and B. B. Snider, Angew. Chem., Int. Ed., 2009, 48, 1283–1286.
- 6 For recent reviews of organocatalysis, see: (a) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, Chem. Rev., 2007, 107, 5471-5569; (b) S. Bertelsen, M. Nielsen and K. A. Jørgensen, Angew. Chem., Int. Ed., 2007, 46, 7356-7359; (c) B. Westermann, M. Ayaz and S. Berkel,, Angew. Chem. Int. Ed., 2010, 40, 846-849; (d) B. List, Chem. Commun., 2006, 819-824; (e) P. Melchiorre, M. Marigo, A. Carlone and G. Bartoli, Angew. Chem., Int. Ed., 2008, 47, 6138-6171; (f) J. Seayad and B. List, Org. Biomol. Chem., 2005, 3, 719-724; (g) M. J. Gaunt, C. C. C. Johansson, A. McNally and N. T. Vo, Drug Discovery Today, 2007, 2, 8-27; for a recent review of organocatalytic tandem reactions, see: (h) D. Enders, C. Grondal and M. R. M. Hüttl, Angew. Chem., Int. Ed., 2007, 46, 1570-1581; (i) C. J. Chapman and C. G. Frost, Synthesis, 2007, 1, 1-21; (j) C. Grondal, M. Jeanty and D. Enders, Nat. Chem., 2010, 2, 167-178; for some selected recent examples of organocatalytic tandem reactions, see: (k) J. Zhou and B. List, J. Am. Chem. Soc., 2007, 129, 7498-7499; (1) H. Xie, L. Zu, H. Li, J. Wang and W. Wang, J. Am. Chem. Soc., 2007, 129, 10886-10894; (m) Y. Hayashi, H. Gotoh, R. Masui and H. Ishikawa, Angew. Chem., Int. Ed., 2008, 47, 4012-4015; (n) M. Lu, D. Zhu, Y. Lu, Y. Hou, B. Tan and G. Zhong, Angew. Chem., Int. Ed., 2008, 47, 10187-10191; (o) D. Zhu, M. Lu, L. Dai and G. Zhong, Angew. Chem., Int. Ed., 2009, 48, 6089-6092; (p) B. Tan, Z. Shi, P. J. Chua, Y. Li and G. Zhong, Angew. Chem., Int. Ed., 2009, 48, 758-761; (q) H. Jiang, P. Elsner, K. L. Jensen, A. Falcicchio, V. Marcos and K. A. Jøgensen, Angew. Chem., Int. Ed., 2009, 48, 6844-6848; (r) L. Wu, G. Bencivenni, M. Mancinelli, A. Mazzanti, G. Bartoli and P. Melchiorre, Angew. Chem., Int. Ed., 2009, 48, 7196-7199; (s) G. Bencivenni, L. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M. Song, G. Bartoli and P. Melchiorre, Angew. Chem., Int. Ed., 2009, 48, 7200-7203; (t) Q. Cai, Z. Zhao and S.-L. You, Angew. Chem., Int. Ed., 2009, 48, 7428-7431; (u) B. Tan, D. Zhu, L. Zhang, P. J. Chua, X. Zeng and G. Zhong, Chem.-Eur. J., 2010, 16, 3842-3848; (v) J. Li, S. Zhou, B. Han, L. Wu and Y. Chen, Chem. Commun., 2010, 46, 2665-2667; (w) S. Rendler and

D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2010, **132**, 5027–5029; (x) D. Enders, C. Wang, M. Mukanova and A. Greb, *Chem. Commun.*, 2010, **46**, 2447–2449; (y) Y. Wang, D. Yu, Y. Liu, H. Wei, Y. Luo, D. J. Dixon and P. Xu, *Chem. Eur. J.*, 2010, **16**, 3922–3926; (z) K. Jiang, Z. Jia, X. Yin, L. Wu and Y. Chen, *Org. Lett.*, 2010, **12**, 2766–2769.

- 7 For some selected examples of the synthesis for oxazine derivatives, see: (a) Q. Meng, Q. Liu, J. Li, R. Xing, X. Shen and B. Zhou, Synlett., 2009, 20, 3283–3286; (b) D. Zhao, M. Jonhansson and J. Bäckvall, Eur. J. Org. Chem., 2007, (26), 4431–4436; (c) M. A. Mitchell and B. C. Benicewicz, Synthesis, 1994, (7), 675–677; (d) H. Vorbrueggen and K. Krolikiewicz, Tetrahedron, 1993, 49, 9353–9372; (e) M. A. Mitchell, B. C. Benicewicz, D. A. Langlois and P. Thiessen, Polym. Mater. Sci. Eng., 1993, 68, 22–23; (f) A. Doemling and I. K. Ugi, Tetrahedron, 1993, 49, 9495–9500.
- 8 E. Feng, Y. Zhou, D. Zhang, L. Zhang, H. Sun, H. Jiang and H. Liu, J. Org. Chem., 2010, 75, 3274–3282.
- 9 N. Kaval, B. Halasz-Dajka, G. Vo-Thanh, W. Dehaen, J. Van Der Eycken, P. Mátyus, A. Loupy and E. Van Der Eycken, *Tetrahedron*, 2005, 61, 9052–9057.
- 10 For selected examples of the preparation of heterocyclic compounds by organocatalytic tandem reactions in the past couple of years, see: (a) P. Goswami and B. Das, Synth. Commun., 2010, 40, 1685-1693; (b) J. Li, L. Lu and W. Su, Tetrahedron Lett., 2010, 51, 2434-2437; (c) P. Tiseni and R. Peters, Chem.-Eur. J., 2010, 16, 2503-2517; (d) S. Indumathi, S. Perumal, D. Banerjee, P. Yogeeswari and D. Sriram, Eur. J. Med. Chem., 2009, 44, 4978-4984; (e) C. Joannesse, C. P. Johnston, C. Concellón, C. Simal, D. Philp and A. D. Smith, Angew. Chem., Int. Ed., 2009, 48, 8914-8918; (f) S. Samai, G. Chandra Nandi, P. Singh and M. S. Singh, Tetrahedron, 2009, 65, 10155–10161; (g) Y. C. Teo, F. F. Yong, C. Y. Poh, Y. K. Yan and G. L. Chua, Chem. Commun., 2009, 6258-6260; (h) D. B. Ramachary and R. Sakthidevi, Chem.-Eur. J., 2009, 15, 4516-4522; (i) X. Zhang, S. Zhang and W. Wang, Angew. Chem. Int. Ed., 2010, 49, 1481-1484; (j) Z. Xue, T. Liu, Z. Lu, H. Huang, H. Tao and C. Wang, Chem. Commun., 2010, 46, 1727-1729; (k) Z. He, B. Han, R. Li, L. Wu and Y. Chen, Org. Biomol. Chem., 2010, 8, 755-757; (1) D. Zhu, M. Lu, L. Dai and G. Zhong, Angew. Chem., Int. Ed., 2009, 48, 6089–6092; (*m*) B. Jiang, C. Li, F. Shi, S. Tu, P. Kaur, W. Wever and G. Li, *J. Org. Chem.*, 2010, **75**, 2962–2965; (*n*) H. Jiang, P. Elsner, K. L. Jensen, A. Falcicchio, V. Marcos and K. A. Jørgensen, Angew. Chem., Int. Ed., 2009, 48, 6844-6848; (o) H. Gotoh, D. Okamura, H. Ishikawa and Y. Hayashi, Org. Lett., 2009, 11, 4056-4059; (p) L. Hong, L. Wang, W. Sun, K. Wong and R. Wang, J. Org. Chem., 2009, 74, 6881-6884.
- (a) J. Franzén and A. Fisher, Angew. Chem., Int. Ed., 2009, 48, 787–791;
   (b) W. Zhang and J. Franzén, Adv. Synth. Catal., 2010, 352, 499–518.
- 12 X. Wu, X. Dai, L. Nie, H. Fang, J. Chen, Z. Ren, W. Cao and G. Zhao, *Chem. Commun.*, 2010, 46, 2733–2735.
- 13 (a) D. Enders, M. R. M. Hüttl, C. Grondal and G. Raabe, *Nature*, 2006, 441, 861–863; (b) Y. Hayashi, T. Okano, S. Aratake and D. Hazelard, *Angew. Chem., Int. Ed.*, 2007, 46, 4922–4925; (c) D. Enders, C. Wang and J. W. Bats, *Angew. Chem., Int. Ed.*, 2008, 47, 7539–7542.
- 14 The crystallographic data of **4k** for this paper† has been deposited in the Cambridge Structural Database, Cambridge Crystallographic Data Centre, Cambridge CB2 1EZ, United Kingdom (CCDC reference no. 793001).
- (a) S. Brandau, A. Landa, J. Franzén, M. Marigo and K. A. Jøgensen, *Angew. Chem., Int. Ed.*, 2006, **45**, 4305–4309; (b) M. Marigo, S. Bertelsen, A. Landa and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2006, **128**, 5475–5479; (c) A. Carlone, M. Marigo, C. North, A. Landa and K. A. Jørgensen, *Chem. Commun.*, 2006, 4928–4930.
- 16 G. Valero, J. Schimer, I. Cisarova, J. Vesely, A. Moyano and R. Rios, *Tetrahedron Lett.*, 2009, 50, 1943–1946.
- 17 J. M. Kremsner and C. O. Kappe, Eur. J. Org. Chem., 2005, 3672-3679.