

One-Pot Catalytic Asymmetric Cascade Synthesis of Cycloheptane Derivatives

Jan Vesely,^[a] Ramon Rios,^[a] Ismail Ibrahim,^[a] Gui-Ling Zhao,^[a] Lars Eriksson,^[b] and Armando Córdova^{*[a]}

The manuscript is dedicated to Prof. Jan-Erling Bäckvall on the occasion of his 60th birthday

Abstract: A regiospecific, highly chemo-, diastereo-, and enantioselective one-pot catalytic cascade synthesis of cycloheptane derivatives is presented. In this chiral-amine-catalyzed asymmetric process, six new bonds and five new stereocenters were formed with excellent stereocontrol (>25:1 d.r. and 98–>99 ee).

Keywords: asymmetric catalysis • cascade reaction • chiral amines • cycloaddition • cycloheptane derivatives

Introduction

Highly functionalized seven-membered carbocycles are a common structural motif in a multitude of natural and unnatural bioactive targets, such as the perhydroazulenes, the guanacastepene diterpenes, or the scabronines.^[1–4] Thus, the development of efficient methods for the asymmetric synthesis of complex cycloheptanes is an important ongoing research area.^[1–4] For example, asymmetric metal catalyzed [4+3]^[2b,c] and [5+2]^[3] cycloadditions or ring-expanding allylation reactions^[4] for the synthesis of functional seven-membered carbocycles have been reported. Moreover, Harmata and co-workers recently reported the first catalytic enantioselective [4+3] cycloaddition with a chiral amine catalyst.^[2a]

The asymmetric synthesis of functional carbocycles can also be accomplished by the use of domino reaction processes.^[5] One way to assemble complex molecules by domino reactions is to employ asymmetric organocatalysis.^[6] In particular, chiral amines have been used successfully in such processes based on the direct activation of carbonyl compounds by forming enamine and iminium intermediates.^[7] More-

over, the products derived from these reactions may have a functionality that allows for a subsequent cascade reaction to obtain further diversification or another valuable compound. For example, Enders and co-workers elegantly combined a chiral amine-catalyzed, three-component, domino reaction with a Lewis acid catalyzed intermolecular Diels–Alder reaction in one-pot for the syntheses of complex tricyclic compounds.^[7p] Hence, organocatalytic domino reactions may also be applicable for the challenge of developing a simple, one-pot, multicomponent, catalytic asymmetric synthesis of functional cycloheptanes.

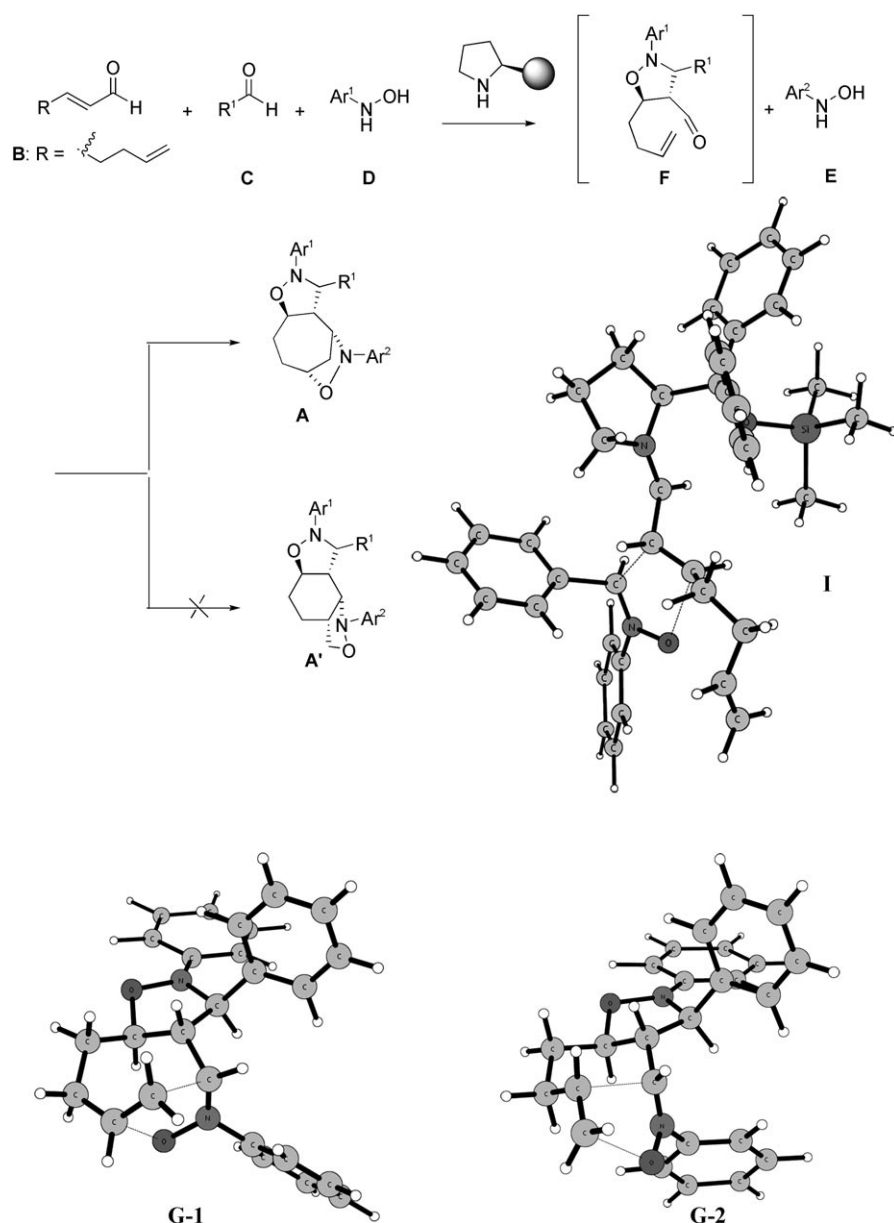
Based on our previous research, we envisaged a one-pot procedure to construct oxygen- and nitrogen-functionalized seven-membered carbocyclic frameworks (chiral tricyclic bis-isoxazolidines) **A**, which contain five stereogenic centers, with high stereocontrol [Eq. (1)]. The assembly of the functional cycloheptanes should be feasible by employing a chiral-amine-catalyzed, one-pot, three-component intermolecular [3+2] cycloaddition^[8] starting from simple aldehyde and hydroxylamine substrates **B–D** via transition state **I**,^[8f] followed directly by a two-component, intramolecular [3+2] cycloaddition of the nitrone intermediate formed between **F** and hydroxylamine **E**.^[9] We visualized that the polycyclic framework with a seven membered carbocycle **A** would predominate over the polycyclic framework with a six membered carbocycle **A'** due to a combination of steric and substitution effects of the [3+2] cycloaddition mode **G-1** as compared to mode **G-2** of the chiral dipole intermediate (Scheme 1).^[10]

This report presents the regiospecific; highly chemo-, diastereo-, and enantioselective, one-pot, organocatalytic cascade synthesis of functional cycloheptane derivatives.

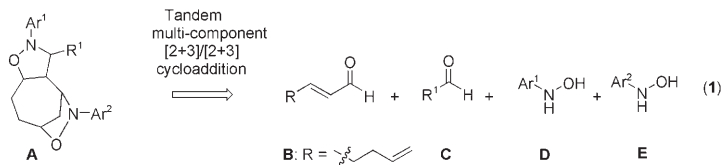
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Scheme 1. One-pot organocatalytic cascade synthesis of cycloheptane derivatives, plausible transition state **I**, [3+2] cycloaddition mode **G-1**, and [3+2] cycloaddition mode **G-2**. The figures were prepared with molecular mechanics by using frozen $-C$ and $-O$ distances.



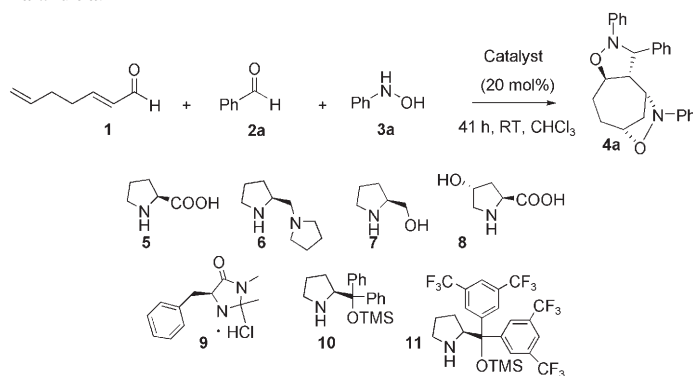
Results and Discussion

In an initial experiment, we reacted α,β -unsaturated aldehyde **1**, benzaldehyde **2a**, and hydroxylamine **3a** to give tricyclic bis-isoxazolidene **ent-4a** in the presence of a catalytic amount of (*S*)-proline (**5**) (Table 1, entry 1). The reaction

smoothly assembled **ent-4a** with a cycloheptane core as the only product with $>25:1$ d.r. and 55% *ee*. The other isolated materials were starting materials and nitron intermediates derived from the acceptor aldehyde and the aldehyde adduct from the first cycloaddition step. Thus, the reaction was regiospecific and no six-membered carbocycle was formed. Encouraged by this result, we performed a catalyst screen with chiral amines **6–11** (Table 1). To our delight, chiral-protected diarylprolinol **10**^[11] catalyzed the formation of the opposite enantiomer of functional cycloheptane derivative **4a** in 42% yield with excellent diastereo- and enantioselectivity ($>25:1$ d.r. and 99% *ee*; entry 6). Moreover, chiral amine **10** catalyzed the asymmetric formation of **4a** in toluene with excellent stereoselectivity (entry 8). Based on these results, we decided to investigate the enantioselective, one-pot, domino double [3+2] cycloaddition reactions between enal **1**, aldehydes **2** and hydroxylamines **3** catalyzed by amine **10** in more detail. (Table 2).

The organocatalytic cascade syntheses were regiospecific and highly chemo- and enantioselective. 1H NMR analysis of the crude reaction mixtures determined that only one predominant diastereoisomer was formed ($>25:1$ d.r.). The corresponding cycloheptane deriva-

tives **4** were isolated in good yields for a four-step procedure (nitron formation $\rightarrow$ cycloaddition $\rightarrow$ nitron formation $\rightarrow$ cycloaddition; 23–68% yield). In this process, six new bonds and five new stereocenters were formed with excellent stereocontrol. The one-pot reaction procedure also allowed for the variation of both enals **2** and hydroxylamines **3**. For example, the cascade reaction between enal **1**, cinnamic aldehyde (**2h**), 4-chlorophenyl hydroxylamine (**3b**), and phenyl hydroxylamine (**3a**) gave functional cycloheptane derivative **4j** as the only product in 51% yield with $>25:1$ d.r. and 99% *ee* (entry 10). Notably, changing the order of addition of the hydroxylamines **3b** and **3a** (first **3a** then **3b**) gave the functional carbocycle **4k** in 43% yield as a nearly enantio-

Table 1. Catalyst screen for the one-pot catalytic reaction between **1a**, **2a** and **3a**.^[a]

Entry	Catalyst	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1	5	24	> 25:1	–55 ^[e]
2	6	0	–	–
3	7	0	–	–
4	8	0	–	–
5	9	0	–	–
6	10	42	> 25:1	99
7	11	traces	n.d.	n.d.
8	10	29 ^[f]	> 25:1 ^[f]	99 ^[f]

[a] For a general procedure and the analytical data of **4a** see the Experimental Section. [b] Isolated yield of the pure product **4a** after silica-gel column chromatography. [c] Determined by NMR analyses of the crude reaction mixture. [d] Determined by chiral-phase HPLC analysis. [e] *ent*-**4a** was formed. [f] Toluene was used as the solvent.

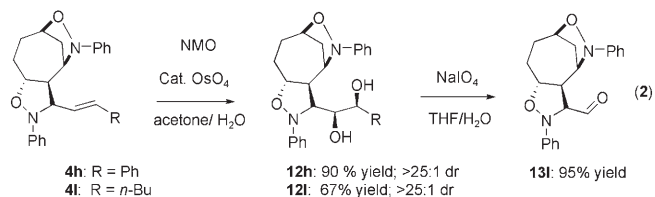
Table 2. Scope of the one-pot organocatalytic cascade synthesis of functional cycloheptane derivatives.^[a]

Entry	R ¹	R ²	R ³	Prod.	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1	Ph	Ph	Ph	4a	42	> 25:1	99
2	4-BrC ₆ H ₄	Ph	Ph	4b	42	> 25:1	98
3	4-CNC ₆ H ₄	Ph	Ph	4c	35	> 25:1	99
4	4-NO ₂ C ₆ H ₄	Ph	Ph	4d	23	> 25:1	99
5	Ph	4-ClC ₆ H ₄	4-ClC ₆ H ₄	4e	36	> 25:1	99
6	4-MeOC ₆ H ₄	4-ClC ₆ H ₄	4-ClC ₆ H ₄	4f	49	> 25:1	> 99
7	4-MeOC ₆ H ₄	Ph	Ph	4g	45	> 25:1	99
8	Ph-CH=CH-CH=CH-Ph	Ph	Ph	4h	48	> 25:1	98
9		4-ClC ₆ H ₄	Ph	4i	41	> 25:1	99
10		Ph	Ph	4j	51	> 25:1	99
11		Ph	4-ClC ₆ H ₄	4k	43	> 25:1	99
12		Ph	Ph	4l	44	> 25:1	99
13	Ph	PhCH ₂	Ph	4m	68	> 25:1	98

[a] For a general procedure and the analytical data of compounds **4** see the Experimental Section. [b] Isolated yield of the pure products **4** after silica-gel column chromatography. [c] Determined by NMR analyses of the crude reaction mixture. [d] Determined by chiral-phase HPLC analysis.

merically pure compound (> 25:1 d.r. and 99% ee; entry 11). Moreover, aldehydes such as 2-heptenal were excellent substrates and the corresponding cycloheptane derivative **4l** was obtained with > 25:1 d.r. and 99% ee

(entry 12). Nitrones derived from aliphatic aldehydes were also excellent substrates for the cascade reaction. For example, benzyl-protected **4m** was furnished in 68% yield with > 25:1 d.r. and 98% ee (entry 13). Notably, the one-pot reaction followed by highly diastereoselective dihydroxylation allowed for the formation of seven new stereocenters with excellent stereocontrol [Eq (2)]. Thus, compounds **12h** and **12l** were isolated in 90 and 67% yield with > 25:1 d.r., respectively. We also prepared the optically pure cycloheptane amino aldehyde derivative **13l** in 95% yield, which is an excellent precursor for further diversification and the synthesis of valuable amino acid derivatives or amino alcohols.



The relative and absolute configuration of the functional bis-isoxazolidine compounds **4** with a seven-membered carbocycle core was established by X-ray analysis of a single crystal of cycloheptane derivative **4j** (Figure 1).^[12]

Based on the relative and absolute configuration of **4j**, we propose the following reaction scheme for the stereochemical outcome of the domino reaction. Thus, efficient shielding of the *Si*-face of the chiral iminium intermediate **10** by the bulky aryl groups of **10** leads to stereoselective *Re*-facial *endo*-addition to the activated olefin via the initial plausible transition state **I** depicted in Scheme 1. This is in accordance with previous chiral-amine-catalyzed [3+2] cycloadditions.^[8] Next, the ring closure occurs through a regioselective intramolecular *endo*-addition via the [3+2] cycloaddition mode **G-1**. In the case of (*S*)-proline, the opposite facial attack occurs in the first [2+3] cycloaddition leading to formation of *ent*-**4**.

Conclusion

In summary, we report an unprecedented example of a regioselective and highly chemoselective one-pot organocatalytic cascade synthesis of bis-oxazolidines with a functionalized seven membered carbocycle

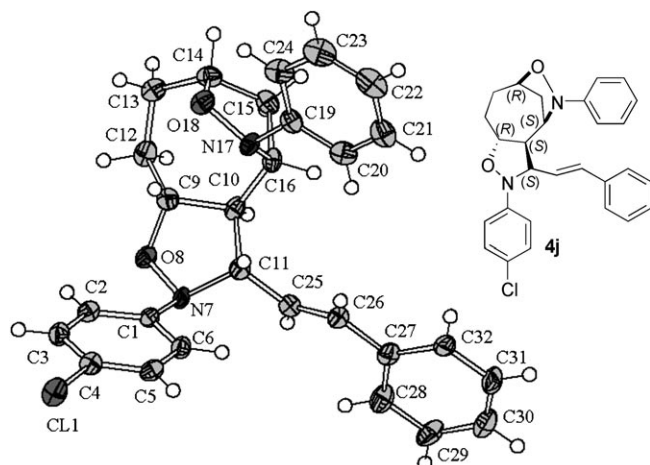


Figure 1. ORTEP picture of the crystalline cycloheptane compound **4j**.

core. The reaction is efficiently catalyzed by simple chiral pyrrolidine derivatives and provides a direct entry to nearly diastereo- and enantiomerically pure cycloheptane derivatives, wherein the formation of five new bonds and five stereocenters is controlled. Mechanistic studies, synthetic applications of this transformation, and the development of other enantioselective domino transformations based on this concept are ongoing in our laboratory.

Experimental Section

General. Chemicals and solvents were either purchased *puriss p. A.* from commercial suppliers or purified by standard techniques. Catalyst **10** was synthesized according to literature procedures.^[11] For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), $\text{Ce}(\text{SO}_4)_2 \cdot \text{H}_2\text{O}$ (10 g), and conc. H_2SO_4 (60 mL), in H_2O (940 mL) followed by heating or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), and acetic acid (10 mL), in ethanol (900 mL) followed by heating. Flash chromatography was performed over silica gel Merck 60 (particle size 0.040–0.063 mm), ^1H and ^{13}C NMR spectra were recorded on Varian AS 400. Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants J are given in Hz. The spectra were recorded in CDCl_3 as solvent at room temperature, TMS served as internal standard ($\delta = 0$ ppm) for ^1H NMR measurements, and CDCl_3 was used as internal standard ($\delta = 77.0$ ppm) for ^{13}C NMR measurements. HPLC was carried out using a Waters 2690 Millennium with photodiode array detector. Optical rotations were recorded on a Perkin Elmer 241 Polarimeter ($\lambda = 589$ nm, 1 dm cell at 25°C). High-resolution mass spectra were recorded on a Bruker MicrOTOF spectrometer.

Typical experimental procedure for the catalyst screen: *N*-Hydroxyarylamine **3a** (0.375 mmol, 1.5 equiv) was added to a stirred solution of aldehyde **2a** (0.375 mmol, 1.5 equiv) in CHCl_3 (1 mL). The reaction was stirred at room temperature for 1 h and then the catalyst (0.05 mmol, 20 mol %) and α,β -unsaturated aldehyde **1** (0.25 mmol, 1.0 equiv) were added. The reaction mixture was stirred at room temperature for 16 h followed by addition of *N*-hydroxyarylamine **3a** (0.25 mmol, 1.0 equiv) and the reaction was stirred for 24 h at room temperature. Next, the crude reaction mixture was purified directly by column chromatography to afford cycloheptane derivative **4a**.

Typical experimental procedure for the one-pot cascade synthesis of cycloheptane derivatives: *N*-Hydroxyarylamine **3** (0.375 mmol, 1.5 equiv)

was added to a stirred solution of aldehyde **2** (0.375 mmol, 1.5 equiv) in CHCl_3 (1 mL). The reaction was stirred at room temperature for 1 h and then catalyst **10** (0.05 mmol, 20 mol %) and α,β -unsaturated aldehyde **1** (0.25 mmol, 1.0 equiv) were added. The reaction mixture was stirred at room temperature for 16 h followed by addition of the same or another *N*-hydroxyarylamine (0.25 mmol, 1.0 equiv) and the reaction was stirred for 4 h at room temperature. Next, the crude reaction mixture was purified directly by column chromatography to afford the functional cycloheptane product **4**.

Data for 4a: Yellow oil; ^1H NMR (400 MHz, CDCl_3): $\delta = 7.72$ – 7.69 (m, 2H), 7.53 – 7.16 (m, 7H), 7.05 – 6.84 (m, 6H), 4.78 (br d, $J = 9.2$ Hz, 1H), 4.77 (d, $J = 10.0$ Hz, 1H), 4.52 (t, $J = 10.4$ Hz, 1H), 3.86 (dd, $J = 2.8$, 6.8 Hz, 1H), 2.33 – 2.01 (m, 4H), 1.86 – 1.77 ppm (m, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 153.7$, 152.3 , 141.7 , 129.4 , 129.1 , 128.9 , 128.2 , 127.5 , 122.7 , 121.2 , 115.4 , 113.9 , 79.3 , 77.0 , 74.3 , 66.0 , 62.0 , 33.3 , 29.1 , 25.3 ppm; $[\alpha]_D^{25} = +235.1$ ($c = 1.0$ in CHCl_3); HRMS (ESI): m/z calcd for $[\text{M}+\text{H}]^+$ ($\text{C}_{26}\text{H}_{26}\text{N}_2\text{O}_2$): 399.2067; found: 399.2079. The enantiomeric excess was determined by HPLC with an AD column (*n*-hexane: *i*PrOH = 93:7, $\lambda = 250$ nm), 0.5 mL min^{-1} ; t_R = major enantiomer 16.8 min, minor enantiomer 13.8 min.

Data for 4b: Yellow oil; ^1H NMR (400 MHz, CDCl_3): $\delta = 7.72$ – 7.58 (m, 4H), 7.36 – 7.20 (m, 5H), 7.05 – 6.82 (m, 5H), 4.77 (d, $J = 9.6$ Hz, 1H), 4.73 (d, $J = 9.6$ Hz, 1H), 4.51 (t, $J = 10$ Hz, 1H), 3.83 (dd, $J = 6.8$ Hz, $J' = 2.0$ Hz, 1H), 2.39 – 2.00 (m, 5H), 1.95 – 1.80 ppm (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 153.3$, 152.0 , 140.6 , 132.3 , 129.0 , 128.9 , 128.8 , 122.7 , 121.9 , 121.3 , 115.1 , 113.7 , 79.3 , 76.8 , 73.5 , 65.8 , 61.6 , 33.1 , 28.8 , 25.0 ppm; $[\alpha]_D^{25} = +180.7$ ($c = 0.5$ in CHCl_3); HRMS (ESI): m/z calcd for $[\text{M}+\text{Na}]^+$ ($\text{C}_{26}\text{H}_{25}\text{BrN}_2\text{O}_2$): 499.0992; found: 499.1002. The enantiomeric excess was determined by HPLC with an AD column (*n*-hexane: *i*PrOH = 90:10, $\lambda = 250$ nm), 1.0 mL min^{-1} ; t_R = major enantiomer 13.7 min, minor enantiomer 9.0 min.

Data for 4c: Yellow oil; ^1H NMR (400 MHz, CDCl_3): $\delta = 7.81$ (d, $J = 3.6$ Hz, 2H), 7.35 – 7.18 (m, 6H), 7.05 – 6.81 (m, 6H), 4.81 (d, $J = 10.4$ Hz, 1H), 4.77 (m, 1H), 4.55 (t, $J = 11.2$ Hz, 1H), 3.82 (m, 1H), 2.40 – 2.00 (m, 4H), 1.90 – 1.70 ppm (m, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 152.9$, 151.8 , 147.3 , 133.1 , 129.0 , 128.9 , 128.0 , 122.9 , 121.5 , 118.5 , 115.2 , 113.6 , 112.0 , 79.4 , 76.9 , 73.6 , 66.0 , 61.6 , 33.0 , 28.8 , 24.9 ppm; $[\alpha]_D^{25} = +73.5$ ($c = 0.5$ in CHCl_3). HRMS (ESI): m/z calcd, for $[\text{M}+\text{Na}]^+$ ($\text{C}_{27}\text{H}_{25}\text{N}_3\text{O}_2$): 446.1839; found: 446.1847. The enantiomeric excess was determined by HPLC with an OD-H column (*n*-hexane: *i*PrOH = 90:10, $\lambda = 250$ nm), 0.5 mL min^{-1} ; t_R = major enantiomer 19.6 min, minor enantiomer 32.5 min.

Data for 4d: Yellow oil; ^1H NMR (400 MHz, CDCl_3): $\delta = 8.37$ (d, $J = 8.8$ Hz, 2H), 7.88 (d, $J = 8.8$ Hz, 2H), 7.35 – 7.10 (m, 3H), 7.05 – 6.96 (m, 3H), 6.91 – 6.86 (m, 4H), 4.86 (d, $J = 9.2$ Hz, 1H), 4.79 (d, $J = 9.2$ Hz, 1H), 4.55 (t, $J = 10$ Hz, 1H), 3.82 (dd, $J = 6.8$ Hz, $J' = 2.0$ Hz, 1H), 2.40 – 2.00 (m, 4H), 1.90 – 1.70 ppm (m, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 152.4$, 151.8 , 149.3 , 129.7 , 129.2 , 129.0 , 128.9 , 128.1 , 124.5 , 122.9 , 121.6 , 115.1 , 113.6 , 79.5 , 76.9 , 73.3 , 66.0 , 61.6 , 33.0 , 28.7 , 24.9 ppm; $[\alpha]_D^{25} = +87.6$ ($c = 1.0$ in CHCl_3); HRMS (ESI): m/z calcd for $[\text{M}+\text{Na}]^+$ ($\text{C}_{26}\text{H}_{25}\text{N}_3\text{O}_2$): 466.1737; found 466.1722. The enantiomeric excess was determined by HPLC with an OD-H column (*n*-hexane: *i*PrOH = 90:10, $\lambda = 250$ nm), 0.5 mL min^{-1} ; t_R = major enantiomer 23.6 min, minor enantiomer 29.9 min.

Data for 4e: Yellow oil; ^1H NMR (400 MHz, CDCl_3): $\delta = 7.65$ – 7.63 (m, 2H), 7.52 – 7.48 (m, 3H), 7.24 – 7.09 (m, 4H), 6.97 – 6.85 (m, 4H), 4.77 (br d, $J = 9.6$ Hz, 1H), 4.66 (d, $J = 10.4$ Hz, 1H), 4.46 (t, $J = 10.0$ Hz, 1H), 3.79 (dd, $J = 1.6$ Hz, 6.4 Hz, 1H), 2.30 – 2.01 (m, 4H), 1.87 – 1.75 ppm (m, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 152.2$, 150.9 , 141.0 , 129.5 , 129.1 , 128.8 , 128.5 , 127.9 , 127.4 , 126.2 , 116.7 , 115.3 , 79.4 , 77.1 , 74.4 , 65.8 , 62.0 , 33.2 , 29.0 , 25.2 ppm; $[\alpha]_D^{25} = +57.3$ ($c = 0.5$ in CHCl_3); HRMS (ESI): m/z calcd for $[\text{M}+\text{H}]^+$ ($\text{C}_{26}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O}_2$): 466.1288; found: 467.1294. The enantiomeric excess was determined by HPLC with an AD column (*n*-hexane: *i*PrOH = 90:10, $\lambda = 250$ nm), 1.0 mL min^{-1} ; t_R = major enantiomer 17.1 min, minor enantiomer 11.1 min.

Data for 4f: White solid; ^1H NMR (400 MHz, CDCl_3): $\delta = 7.56$ – 7.53 (m, 2H), 7.23 – 6.86 (m, 10H), 4.76 (d, $J = 9.6$ Hz, 1H), 4.61 (d, $J = 10.0$ Hz, 1H), 4.45 (t, $J = 9.6$ Hz, 1H), 3.87 (s, 3H), 3.76 (dd, $J = 2.0$, 6.4 Hz, 1H), 2.29 – 2.01 (m, 4H), 1.87 – 1.75 ppm (m, 3H); ^{13}C NMR (100 MHz, CDCl_3):

δ = 159.8, 152.3, 150.9, 132.7, 129.2, 129.1, 128.8, 128.5, 127.8, 126.2, 116.7, 115.4, 114.9, 79.3, 77.0, 74.0, 65.5, 62.0, 55.5, 33.2, 29.0, 25.2 ppm; $[\alpha]_D = +143.1$ ($c = 1.0$ in CHCl_3); HRMS (ESI): m/z calcd for $[M+\text{Na}]^+$ ($\text{C}_{27}\text{H}_{26}\text{Cl}_2\text{N}_2\text{O}_3$): 519.1213; found: 519.1238. The enantiomeric excess was determined by HPLC with an OD-H column (n -hexane: i PrOH = 90:10, $\lambda = 250$ nm), 1.0 mL min $^{-1}$; t_R = major enantiomer 8.5 min, minor enantiomer 11.0 min.

Data for 4g: White solid; ^1H NMR (400 MHz, CDCl_3): δ = 7.63–7.59 (m, 2H), 7.28–7.15 (m, 5H), 7.05–6.83 (m, 7H), 4.77 (br d, $J = 9.2$ Hz, 1H), 4.72 (d, $J = 10.4$ Hz, 1H), 4.51 (t, $J = 6.4$ Hz, 1H), 3.87 (s, 3H), 3.83 (dd, $J = 2.0$, 6.8 Hz, 1H), 2.30–2.00 (m, 4H), 1.86–1.75 ppm (m, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 159.6, 153.8, 152.4, 133.4, 129.1, 128.9, 128.6, 122.7, 121.2, 115.4, 114.8, 114.1, 79.3, 77.1, 73.9, 65.8, 62.0, 55.5, 33.3, 29.1, 25.3 ppm; $[\alpha]_D = +143.1$ ($c = 1.0$ in CHCl_3); HRMS (ESI): m/z calcd for $[M+\text{Na}]^+$ ($\text{C}_{27}\text{H}_{28}\text{N}_2\text{O}_3$): 451.1992; found: 451.2002. The enantiomeric excess was determined by HPLC with an AD column. (n -hexane: i PrOH = 93:7, $\lambda = 250$ nm), 0.5 mL min $^{-1}$; t_R = major enantiomer 43.4 min, minor enantiomer 23.3 min.

Data for 4h: Yellow oil; ^1H NMR (400 MHz, CDCl_3): δ = 7.55–7.50 (m, 2H), 7.42–7.38 (m, 2H), 7.34–7.20 (m, 7H), 7.14–7.11 (m, 1H), 7.00–6.88 (m, 4H), 6.54 (dd, $J = 4.4$ Hz, $J' = 16.0$ Hz, 1H), 4.81 (d, $J = 7.2$ Hz, 1H), 4.45–4.37 (m, 2H), 4.02 (dd, $J = 6.8$ Hz, $J' = 2.0$ Hz, 1H), 2.30–2.13 (m, 3H), 2.06–1.70 ppm (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ = 153.8, 152.2, 136.3, 132.6, 130.1, 128.8, 128.8, 128.1, 126.6, 122.5, 121.4, 115.2, 114.3, 78.4, 77.2, 73.2, 62.1, 61.9, 33.1, 29.1, 25.2 ppm; $[\alpha]_D = +260.5$ ($c = 1.0$ in CHCl_3); HRMS (ESI): m/z calcd for $[M+\text{H}]^+$ ($\text{C}_{28}\text{H}_{28}\text{N}_2\text{O}_2$): 425.2224; found: 425.2228. The enantiomeric excess was determined by HPLC with an OD-H column. (n -hexane: i PrOH = 90:10, $\lambda = 250$ nm), 0.5 mL min $^{-1}$; t_R = major enantiomer 9.6 min, minor enantiomer 12.3 min.

Data for 4i: Yellow solid; ^1H NMR (400 MHz, CDCl_3): δ = 8.33–8.30 (m, 1H), 8.18–8.15 (m, 1H), 7.55–7.48 (m, 3H), 7.42–7.36 (m, 2H), 7.29–7.20 (m, 3H), 7.13–7.08 (m, 2H), 7.00–6.84 (m, 3H), 6.53 (dd, $J = 7.6$ Hz, 16.0 Hz, 1H), 4.81 (d, $J = 7.2$ Hz, 1H), 4.44–4.37 (m, 2H), 4.01 (dd, $J = 1.6$ Hz, 6.4 Hz, 1H), 2.28–2.15 (m, 3H), 2.10–1.68 ppm (m, 4H); ^{13}C NMR (100 MHz, CDCl_3): δ = 153.9, 152.3, 135.4, 132.1, 131.8, 131.4, 131.0, 129.8, 129.1, 129.0, 128.9, 128.2, 125.7, 122.8, 122.5, 122.1, 121.6, 115.4, 114.4, 78.5, 77.4, 73.1, 62.3, 62.1, 33.2, 29.2, 25.3 ppm; $[\alpha]_D = +129.4$ ($c = 1.0$ in CHCl_3); HRMS (ESI): m/z calcd for $[M+\text{Na}]^+$ ($\text{C}_{28}\text{H}_{27}\text{BrN}_2\text{O}_2$): 525.1148; found: 525.1157. The enantiomeric excess was determined by HPLC with an AD column (n -hexane: i PrOH = 93:7, $\lambda = 250$ nm), 1.0 mL min $^{-1}$; t_R = major enantiomer 51.6 min, minor enantiomer 44.8 min.

Data for 4j: Yellow oil; ^1H NMR (400 MHz, CDCl_3): δ = 7.55–7.15 (m, 10H), 6.95–6.83 (m, 5H), 6.52 (dd, $J = 8.4$ Hz, $J' = 16.0$ Hz, 1H), 4.81 (d, $J = 10$ Hz, 1H), 4.41–4.34 (m, 2H), 4.01 (dd, $J = 6.8$ Hz, $J' = 2.0$ Hz, 1H), 2.30–1.65 ppm (m, 7H); ^{13}C NMR (100 MHz, CDCl_3): δ = 152.4, 152.1, 136.1, 132.8, 129.7, 128.9, 128.8, 128.7, 128.2, 126.6, 126.3, 122.6, 115.6, 115.2, 78.5, 77.2, 73.6, 62.1, 61.9, 33.1, 29.0, 25.1 ppm; $[\alpha]_D = +125$ ($c = 1.0$ in CHCl_3); HRMS (ESI): m/z calcd for $[M+\text{Na}]^+$ ($\text{C}_{28}\text{H}_{27}\text{ClN}_2\text{O}_2$): 481.1653; found 481.1655. The enantiomeric excess was determined by HPLC with an OD-H column (n -hexane: i PrOH = 90:10, $\lambda = 250$ nm), 0.5 mL min $^{-1}$; t_R = major enantiomer 8.5 min, minor enantiomer 13.9 min.

Data for 4k: Yellow oil; ^1H NMR (400 MHz, CDCl_3): δ = 7.55–7.15 (m, 10H), 6.95–6.83 (m, 5H), 6.52 (dd, $J = 8.4$ Hz, $J' = 16.0$ Hz, 1H), 4.80 (d, $J = 9.6$ Hz, 1H), 4.41–4.35 (m, 2H), 3.97 (dd, $J = 6.8$ Hz, $J' = 2.0$ Hz, 1H), 2.30–1.65 ppm (m, 7H); ^{13}C NMR (100 MHz, CDCl_3): δ = 153.8, 150.9, 136.2, 132.7, 130.0, 128.9, 128.8, 128.2, 127.5, 126.6, 121.5, 116.5, 114.3, 78.3, 77.2, 73.3, 62.2, 61.8, 33.1, 29.0, 25.2 ppm; $[\alpha]_D = +147.5$ ($c = 1.0$ in CHCl_3); HRMS (ESI): m/z calcd for $[M+\text{H}]^+$ ($\text{C}_{28}\text{H}_{27}\text{ClN}_2\text{O}_2$): 459.1847; found 459.1834. The enantiomeric excess was determined by HPLC with an OD-H column. (n -hexane: i PrOH = 90:10, $\lambda = 250$ nm), 0.5 mL min $^{-1}$; t_R = major enantiomer 21.3 min, minor enantiomer 24.4 min.

Data for 4l: Yellow oil; ^1H NMR (400 MHz, CDCl_3): δ = 7.30–6.80 (m, 10H), 6.10–6.00 (m, 1H), 5.80–5.70 (m, 1H), 4.80 (d, $J = 9.6$ Hz, 1H), 4.34–4.19 (m, 2H) 3.94 (dd, $J = 6.4$ Hz, 1.6 Hz, 1H), 2.25–1.20 (m, 13H), 0.97 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 154.1, 152.4, 134.7, 130.7, 128.8, 128.6, 122.4, 121.1, 115.2, 114.3, 78.1, 73.1, 62.4, 61.6,

33.1, 32.1, 31.5, 30.9, 29.1, 25.2, 22.3, 14.0 ppm; $[\alpha]_D = +75.5$ ($c = 1.3$ in CHCl_3); HRMS (ESI): m/z calcd for $[M+\text{H}]^+$ ($\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_2$): 405.2537; found: 405.2548. The enantiomeric excess was determined by HPLC with an OD-H column (n -hexane: i PrOH = 90:10, $\lambda = 230$ nm), 0.5 mL min $^{-1}$; t_R = major enantiomer 12.6 min, minor enantiomer 15.6 min.

Synthesis of 4m: Catalyst **10** (0.05 mmol, 20 mol %) and $\alpha\beta$ unsaturated aldehyde **1** (0.25 mmol) were added to a small vial containing nitron derived from benzylamine and benzaldehyde (0.25 mmol, 1.0 equiv.) in CHCl_3 (1.0 mL). The reaction was stirred at room temperature for 3 days. Then hydroxylphenyl amine (0.25 mmol) was added and the reaction was stirred at room temperature for 4 h. The crude was purified by column chromatography to afford the desired product. Yellow oil; ^1H NMR (400 MHz, CDCl_3): δ = 7.60–7.00 (m, 15H), 4.79 (d, $J = 9.2$ Hz, 1H), 4.73 (t, $J = 9.2$ Hz, 1H), 4.32 (d, $J = 10.8$ Hz, 1H), 4.25 (d, $J = 13.6$ Hz, 1H), 4.02 (d, $J = 13.6$ Hz, 1H), 4.79 (dd, $J = 1.6$ Hz, 6.4 Hz, 1H), 2.20–1.40 ppm (m, 7H); ^{13}C NMR (100 MHz, CDCl_3): δ = 152.4, 139.5, 137.9, 128.9, 128.9, 128.6, 128.3, 128.1, 127.9, 126.9, 122.5, 115.3, 76.9, 75.5, 63.6, 62.6, 62.3, 33.1, 29.7, 29.1, 25.7 ppm; $[\alpha]_D = +45.5$ ($c = 0.5$ in CHCl_3); HRMS (ESI): m/z calcd for $[M+\text{H}]^+$ ($\text{C}_{27}\text{H}_{28}\text{N}_2\text{O}_2$): 413.2224; found: 413.2221. The enantiomeric excess was determined by HPLC with an OD-H column. (n -hexane: i PrOH = 93:7, $\lambda = 230$ nm), 0.5 mL min $^{-1}$; t_R = major enantiomer 13.6 min, minor enantiomer 23.2 min.

Typical dihydroxylation procedure: In a round-bottomed flask, compound **4h** or **4l** (0.25 mmol) was dissolved in an acetone/water (8:1) mixture (1.0 mL). Next, a catalytic amount of OsO_4 (2.5% mol %) and N -methyl morpholine N -oxide (0.75 mmol) were added. The reaction mixture was stirred at room temperature overnight. The crude product was purified by column chromatography (pentane/EtOAc mixtures) to afford the desired product **12**.

Data for 12h: Yellow oil; ^1H NMR (400 MHz, CDCl_3): δ = 7.50–7.10 (m, 11H), 7.00–6.90 (m, 4H), 5.12 (s, bs, 1H), 4.78 (d, $J = 10$ Hz, 1H), 4.32–4.18 (m, 3H), 4.04 (d, $J = 6.4$ Hz, 1H), 2.30–1.20 ppm (m, 7H); ^{13}C NMR (100 MHz, CDCl_3): δ = 152.5, 152.4, 141.4, 129.1, 128.7, 128.6, 127.8, 125.9, 122.4, 121.7, 115.3, 114.5, 78.9, 78.2, 72.1, 70.7, 64.2, 61.7, 33.4, 31.9, 25.1, 22.6 ppm; $[\alpha]_D = +64.5$ ($c = 1.0$ in CHCl_3); HRMS (ESI): m/z calcd for $[M+\text{Na}]^+$ ($\text{C}_{28}\text{H}_{30}\text{N}_2\text{O}_4$): 459.2278; found: 459.2259.

Data for 12l: Yellow oil; ^1H NMR (400 MHz, CDCl_3): δ = 7.30–6.90 (m, 10H), 4.79 (m, 1H), 4.40–4.00 (m, 5H), 2.20–1.10 (m, 15H), 0.87 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 152.4, 152.4, 130.8, 129.0, 128.8, 128.2, 115.4, 114.4, 78.7, 74.8, 72.2, 70.1, 68.1, 64.1, 60.4, 36.7, 31.9, 30.3, 29.3, 23.7, 22.7, 14.0 ppm; $[\alpha]_D = +21.5$ ($c = 0.2$ in CHCl_3); HRMS (ESI): m/z calcd for $[M+\text{Na}]^+$ ($\text{C}_{26}\text{H}_{34}\text{N}_2\text{O}_4$): 461.2411; found: 461.2410.

Typical experimental procedure for aldehyde formation: In a round-bottomed flask, diol **12** (0.2 mmol) was dissolved in a THF:water (1:1, 2 mL) mixture. Next, NaIO_4 (1.0 mmol) was added and the reaction was stirred at room temperature overnight. The crude product was purified by column chromatography (pentane:EtOAc mixtures) to afford the desired product **13**.

Data for 13l: Yellow oil; ^1H NMR (400 MHz, CDCl_3): δ = 9.96 (d, $J = 4.0$ Hz, 1H), 7.20–6.90 (m, 10H), 4.83 (d, $J = 9.2$ Hz, 1H), 4.34–4.20 (m, 2H), 4.1 (d, $J = 6.4$ Hz, 1H), 2.40–2.30 (m, 2H), 2.00–1.00 ppm (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ = 202.1, 152.5, 151.9, 129.1, 128.9, 122.7, 122.0, 115.3, 113.7, 78.4, 76.4, 62.3, 58.1, 32.8, 31.9, 24.7, 22.7 ppm; $[\alpha]_D = +33.1$ ($c = 1.0$ in CHCl_3); HRMS (ESI): m/z calcd for $[M+\text{Na}]^+$ ($\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_3$): 373.1523; found 373.1540.

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