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SYNTHESIS OF ENANTIOENRICHED INDOLOPIPERAZINONES *VIA* IRIDIUM(I) *N*-HETEROCYCLIC CARBENE COMPLEX CATALYZED ASYMMETRIC INTRAMOLECULAR ALLYLIC AMINATION REACTION

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Abstract – Systematic study on employing the D-camphor derived carbenes as the chiral ligands in iridium-catalyzed intramolecular allylic amination reaction was carried out. Under mild reaction conditions, enantioenriched indolopiperazinones were obtained in good yields (75-95%) and high enantioselectivity (88-94% ee).

INTRODUCTION

Heterocycles bearing an indolopiperazinone scaffold are present in a large number of biologically active molecules.[1] However, the synthesis of these compounds *via* a catalytic asymmetric manner is rare yet highly desirable.[2] Iridium-catalyzed allylic substitution reactions, which feature high regio- and enantioselective control for broad substrates, have gained significant progress during the last decade.[3,4] The asymmetric intramolecular allylic amination reactions catalyzed by an iridium complex can provide facile access to versatile enantioenriched *N*-containing heterocycles.[5] Recently, we found the highly enantioenriched indolopiperazinones can be conveniently obtained *via* an iridium-catalyzed asymmetric intramolecular allylic amination reaction using *N*-heterocyclic carbene[6-9] as the chiral ligand.[10] Moreover, we were able to prove that the active catalytic species might contain a five-membered cyclometalated structure generated through a C-H activation process at the *ortho*-position of *N*-aryl group of the ligand.[11,12] Among several chiral *N*-heterocyclic carbenes tested, Enders' carbene[13] turned out to be the optimal one (Figure 1). Preliminary investigation also showed D-camphor derived triazolium salt **L1**,[14] developed by our group, can be a suitable ligand precursor in this transformation. Herein, we report our systematic study on the D-camphor derived triazolium carbenes as the chiral ligands in the iridium-catalyzed intramolecular allylic amination reaction.

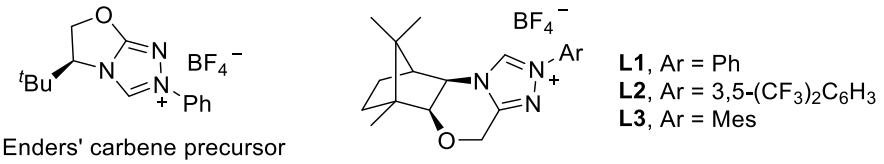
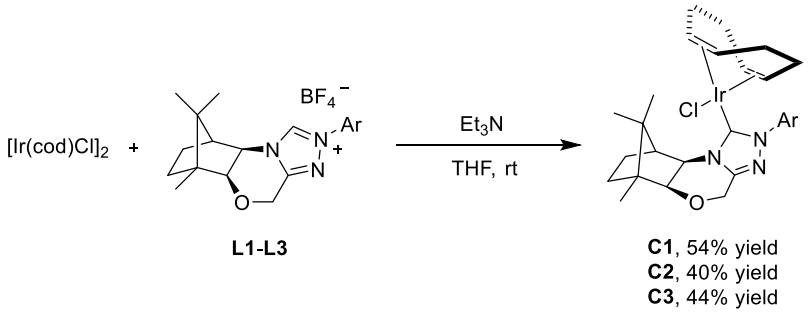


Figure 1. Enders' carbene precursor and D-camphor derived triazolium salts

RESULTS AND DISCUSSION

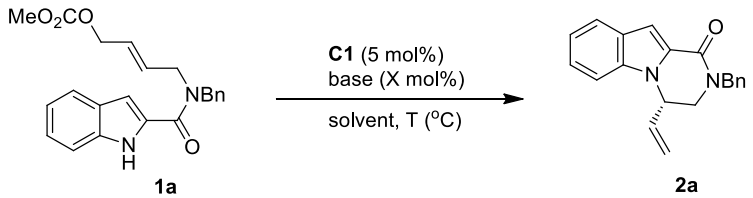
We first synthesized the iridium carbene complexes from the D-camphor derived triazolium salts. Treatment of $[Ir(cod)Cl]_2$ with triazolium salts (**L1**-**L3**) in the presence of excess Et_3N yielded the desired iridium(I) *N*-heterocyclic carbene complexes **C1-C3** (40-54% yields, Scheme 1) after the purification by alumina column chromatography, which also demonstrated their good stability against oxygen and moisture. Single crystals suitable for the X-ray crystal structure analysis were obtained from their corresponding saturated solutions of CH_2Cl_2 and *n*-hexane. The structures of complexes **C1-C3** were all confirmed by X-ray diffraction analysis (see the Supporting Information for details).



Scheme 1. Synthesis of iridium *N*-heterocyclic carbene complexes

With the chiral iridium(I) carbene complexes in hand, we next examined their catalytic performance in iridium-catalyzed intramolecular allylic amination reaction of **1a**. The results are summarized in Table 1. It was found that the base has a great influence on this reaction. No reaction took place when Et_3N was used as the base in the presence of 5 mol% of catalyst **C1** in THF at 50 ^oC (entry 1, Table 1). To our delight, the reaction with K_3PO_4 afforded the desired allylic indolopiperazinone **2a** with excellent enantioselectivity (89% ee) albeit in low yield (27%, entry 2, Table 1). Further screening of bases revealed that DBU is the optimal one (entries 3 and 4, Table 1). The ee of **2a** was increased to 92% under an ambient temperature (entry 5, Table 1). Notably, catalytic amount of DBU (10 mol%) proved to be beneficial to this reaction in terms of yield (entry 6, Table 1). Various solvents (such as dioxane, Et_2O, CH_2Cl_2, $CHCl_3$ and DCE) were well tolerated (entries 7-11, Table 1) and CH_2Cl_2 led to the best results (81% yield, 92% ee, entry 9, Table 1).

Table 1. Reaction condition optimization[a]

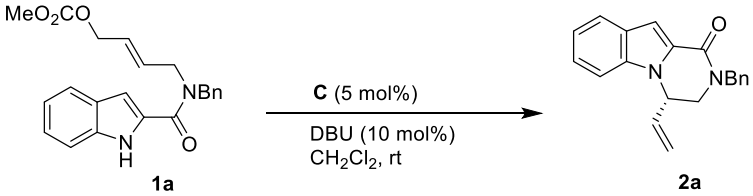


entry	base	solvent	T (°C)	t (h)	**2a**, yield (%)[b]	ee (%)[c]
1	Et_3N	THF	50	48	n.r.	-
2	K_3PO_4	THF	50	48	27	89
3	DBN	THF	50	5	60	84
4	DBU	THF	50	4	73	88
5	DBU	THF	rt	24	62	92
6[d]	DBU	THF	rt	24	73	93
7[d]	DBU	dioxane	rt	24	41	83
8[d]	DBU	Et_2O	rt	24	65	90
9[d]	DBU	CH_2Cl_2	rt	6	81	92
10[d]	DBU	$CHCl_3$	rt	24	71	87
11[d]	DBU	DCE	rt	24	42	90

[a] *Reaction conditions*: **C1**/**1a**/base = 0.05/1.0/1.0, 0.1 M of **1a**. [b] Isolated yield. [c] Ee was determined by HPLC analysis. [d] 10 mol% of DBU used.

We also tested the other iridium carbene complexes as the catalysts for this reaction. However, complexes **C2** and **C3** were found ineffective in this reaction (entries 2,3, Table 2). These results suggest the formation of the catalytically active iridium complex (Figure 2), probably *via* a C-H insertion of the Ir center into the specific C-H bond of the ligand, is dominated by the steric hinderance and/or the electronic properties of the *N*-heterocyclic carbene ligand.

Table 2. Screening of iridium *N*-heterocyclic carbene complexes[a]



entry	**C**	t (h)	**2a**, yield (%)[b]	ee (%)[c]
1	**C1**	6	81	92
2	**C2**	24	n.r.	-
3	**C3**	24	n.r.	-

[a] *Reaction conditions*: **C**/**1a**/DBU = 0.05/1.0/0.1, 0.1 M of **1a** in CH_2Cl_2 at room temperature. [b] Isolated yield. [c] Ee was determined by HPLC analysis.

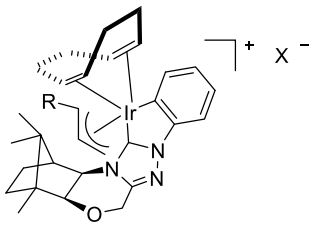
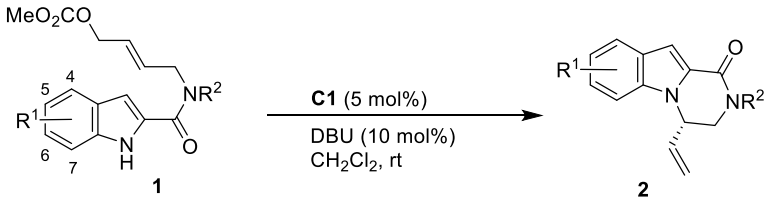


Figure 2. Possible catalytically active iridacycle derived from **C1**

The substrate scope was examined under the optimal conditions (5 mol% of **C1**, 0.2 mmol of **1**, 10 mol% of DBU in 2 mL of CH_2Cl_2 at room temperature, entry 1, Table 2). The results are summarized in Table 3. Substrates bearing either an electron-donating group (5-Me, 5-MeO, 6-MeO, **1b-1d**, Table 3) or an electron-withdrawing group (5-F, 5-Cl, 5-Br, 6-Cl, 6-Br, **1e-1i**, Table 3) on the phenyl ring of the indoles were well tolerated and afforded the corresponding allylic amination products in excellent yields (75-89%) and enantioselectivity (88-94% ee). In addition, substrates with various *N*-substituents of the amide reacted smoothly to afford the indolopiperazinones in good yields (77-95%) with excellent enantioselectivity (90-93% ee, Bn, PMB, allyl and Me, **2a**, **2j-2l**, Table 3).

Table 3. Substrate scope of Ir-catalyzed allylic amination reaction of indoles[a]



entry	R^1	R^2	yield (%)[b]	ee (%)[c]
1	H	Bn	**2a**, 81	92
2	5-Me	Bn	**2b**, 86	93
3	5-MeO	Bn	**2c**, 87	94
4	6-MeO	Bn	**2d**, 89	89
5	5-F	Bn	**2e**, 84	88
6	5-Cl	Bn	**2f**, 78	91
7	5-Br	Bn	**2g**, 77	91
8	6-Cl	Bn	**2h**, 75	91
9	6-Br	Bn	**2i**, 75	92
10	H	PMB	**2j**, 95	93
11	H	allyl	**2k**, 82	93
12	H	Me	**2l**, 77	90

[a] *Reaction conditions*: **C1**/**1**/DBU = 0.05/1.0/0.1, 0.1 M of **1** in CH_2Cl_2 at room temperature. [b] Isolated yield. [c] Ee was determined by HPLC analysis.

In summary, our study showed that D-camphor derived triazolium carbene was an efficient chiral ligand in iridium-catalyzed asymmetric intramolecular allylic amination reaction. Various enantioenriched

indolopiperazinones could be obtained in good yields (75-95%) and excellent enantioselectivity (88-94% ee).

EXPERIMENTAL

General Methods. Unless stated otherwise, all reactions were carried out in flame-dried glassware under argon atmosphere. All solvents were purified and dried according to standard methods prior to use.

^{1}H NMR spectra were obtained at 300 MHz or 400 MHz and recorded relative to tetramethylsilane signal (0 ppm) or residual protio-solvent. ^{13}C NMR spectra were obtained at 75 MHz or 100 MHz, and chemical shifts were recorded relative to the solvent resonance ($CDCl_3$, 77.0 ppm). ^{19}F NMR spectra were obtained at 282 MHz and recorded relative to $CFCl_3$ (0 ppm). Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad singlet, coupling constant(s) in Hz, integration). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm).

General procedure for synthesis of iridium carbene complexes: Et_3N (1.0 mL, 7.0 mmol) was added in one portion to a mixture of $[Ir(cod)Cl]_2$ (335 mg, 0.50 mmol) and chiral triazolium salt **L** (1.00 mmol) in THF (100 mL). The reaction mixture was stirred at room temperature for 16 h, concentrated *in vacuo*. Then the residue was purified by alumina (activated, neutral, Brockmann I) column chromatography (eluent: petroleum ether/EtOAc: 4/1) to afford the product.

C1 Yellow solid, 54% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, J = 7.2 Hz, 2H), 7.49-7.46 (m, 3H), 4.94 (AB, J_{AB} = 15.0 Hz, 1H), 4.80-4.71 (m, 3H), 4.44-4.38 (m, 2H), 3.89 (d, J = 6.9 Hz, 1H), 2.85-2.78 (m, 1H), 2.36-1.67 (m, 8H), 1.51-1.22 (m, 5H), 1.06 (s, 3H), 0.95 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.5, 149.3, 140.2, 128.44, 128.38, 128.2, 124.4, 123.9, 85.1, 84.6, 61.4, 59.4, 54.5, 52.0, 50.1, 47.6, 33.2, 32.51, 32.49, 29.9, 28.5, 25.4, 22.0, 21.2, 11.4; Anal. Calcd for $C_{27}H_{35}N_3ClOIr$: C, 50.26; H, 5.47; N, 6.51. Found: C, 50.26; H, 5.43; N, 6.38.

C2 Yellow solid, 40% yield. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 9.43 (s, 2H), 7.94 (s, 1H), 5.01 (AB, J_{AB} = 14.4 Hz, 1H), 4.95-4.91 (m, 1H), 4.76-4.71 (m, 1H), 4.57 (d, J = 4.4 Hz, 1H), 4.43 (BA, J_{BA} = 15.2 Hz, 1H), 4.03-3.98 (m, 2H), 2.85-2.80 (m, 1H), 2.54 (t, J = 7.2 Hz, 1H), 2.35-2.27 (m, 1H), 2.13-1.99 (m, 4H), 1.87-1.81 (m, 1H), 1.71 (dt, J = 2.8, 12.0 Hz, 1H), 1.58-1.55 (m, 2H), 1.51-1.47 (m, 1H), 1.39-1.33 (m, 1H), 1.30-1.26 (m, 1H), 1.04 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 186.3, 149.9, 141.5, 131.8 (q, J = 33.4 Hz), 124.9 (m), 123.9, 121.4 (m), 87.6, 87.1, 85.4, 62.7, 59.6, 55.0, 52.3, 51.2, 50.2, 48.7, 34.5, 33.0, 32.4, 31.0, 28.1, 26.9, 21.6, 20.6, 11.3; ^{19}F NMR (376MHz, CD_2Cl_2) δ -63.1 (s); Anal. Calcd for $C_{29}H_{33}N_3F_6ClOIr$: C, 44.58; H, 4.26; N, 5.38. Found: C, 44.45; H, 4.34; N, 5.12.

C3 Yellow solid, 44% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (s, 1H), 6.90 (s, 1H), 4.90 (AB, J_{AB} = 14.7 Hz, 1H), 4.62-4.53 (m, 4H), 4.41 (BA, J_{BA} = 14.7 Hz, 1H), 3.95 (d, J = 6.9 Hz, 1H), 3.05 (d, J = 8.4

Hz, 1H), 2.67-2.63 (m, 1H), 2.37 (s, 3H), 2.36 (s, 3H), 2.10-1.89 (m, 4H), 1.84 (s, 3H), 1.71-1.26 (m, 7H), 1.09 (d, *J* = 6.0 Hz, 1H), 1.05 (s, 3H), 0.95 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.5, 148.6, 139.3, 136.5, 136.2, 135.4, 129.2, 128.1, 84.8, 84.1, 84.0, 61.0, 59.2, 53.2, 51.5, 51.1, 50.2, 47.7, 33.6, 33.1, 32.7, 29.1, 29.0, 25.1, 21.9, 21.2, 20.6, 19.5, 17.5, 11.4; Anal. Calcd for $C_{30}H_{41}N_3ClOIr$: C, 52.42; H, 6.01; N, 6.11. Found: C, 52.62; H, 6.03; N, 6.04.

General procedure for the Ir-catalyzed intramolecular allylic amination reaction of indoles: A flame-dried Schlenk tube was cooled to room temperature and filled with argon. To this flask were added C**1** (6.5 mg, 0.01 mmol, 5 mol%), **1** (0.20 mmol), DBU (3.1 mg, 0.02 mmol), and CH_2Cl_2 (2 mL). The reaction mixture was stirred at rt. After the reaction was complete (monitored by TLC), the solvents were evaporated *in vacuo*. The crude reaction mixture was filtrated through celite and washed with EtOAc. The solvents were removed under reduced pressure. Then the residue was purified by silica gel column chromatography to afford the products (eluent: petroleum ether/EtOAc = 4/1).

2a[10] Pale yellow oil, 81% yield, 92% ee [Daicel Chiralcel OD-H, hexane/2-propanol = 90/10, *v* = 1.0 ml·min^{-1}, λ = 254 nm, t (minor) = 20.38 min, t (major) = 31.75 min]; $[\alpha]_D^{20}$ +6.4 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.43 (dd, *J* = 12.6, 2.1 Hz, 1H), 3.91 (dd, *J* = 12.9, 4.5 Hz, 1H), 4.54-4.68 (m, 2H), 4.87-5.00 (m, 2H), 5.07 (d, *J* = 10.5 Hz, 1H), 5.72 (ddd, *J* = 15.6, 10.5, 5.4 Hz, 1H), 7.14 (t, *J* = 6.9 Hz, 1H), 7.21-7.38 (m, 8H), 7.72 (d, *J* = 8.1 Hz, 1H).

2b[10] Yellow solid, 86% yield, 93% ee [Daicel Chiralpak AD-H, hexane/2-propanol = 80/20, *v* = 1.0 ml·min^{-1}, λ = 230 nm, t (major) = 24.02 min, t (minor) = 29.46 min]; $[\alpha]_D^{21}$ +7.0 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.42 (dd, *J* = 12.8, 2.4 Hz, 1H), 3.92 (dd, *J* = 12.8, 4.8 Hz, 1H), 4.57-4.64 (m, 2H), 4.89-4.97 (m, 2H), 5.07 (d, *J* = 10.0 Hz, 1H), 5.72 (ddd, *J* = 15.6, 10.0, 5.2 Hz, 1H), 7.09-7.16 (m, 2H), 7.24-7.36 (m, 6H), 7.50 (s, 1H).

2c[10] White solid, 87% yield, 94% ee [Daicel Chiralpak AD-H, hexane/2-propanol = 80/20, *v* = 1.0 ml·min^{-1}, λ = 230 nm, t (major) = 28.39 min, t (minor) = 45.66 min]; $[\alpha]_D^{20}$ +3.8 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.41 (dd, *J* = 12.4, 2.0 Hz, 1H), 3.84 (s, 3H), 3.91 (dd, *J* = 12.8, 4.8 Hz, 1H), 4.60 (d, *J* = 14.8 Hz, 1H), 4.62 (d, *J* = 16.8 Hz, 1H), 4.87-4.96 (m, 2H), 5.09 (d, *J* = 10.4 Hz, 1H), 5.72 (ddd, *J* = 15.6, 10.4, 5.2 Hz, 1H), 6.96 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.10-7.16 (m, 2H), 7.24-7.34 (m, 6H).

2d[10] Yellow oil, 89% yield, 89% ee [Daicel Chiralpak AD-H, hexane/2-propanol = 80/20, *v* = 1.0 ml·min^{-1}, λ = 230 nm, t (major) = 14.51 min, t (minor) = 19.40 min]; $[\alpha]_D^{25}$ +21.9 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.42 (dd, *J* = 12.6, 1.8 Hz, 1H), 3.83 (s, 3H), 3.92 (dd, *J* = 12.6, 4.2 Hz, 1H), 4.59 (d, *J* = 15.0 Hz, 1H), 4.61 (d, *J* = 16.8 Hz, 1H), 4.87-5.05 (m, 2H), 5.10 (d, *J* = 10.2 Hz, 1H), 5.72 (ddd, *J* = 15.6, 10.5, 5.1 Hz, 1H), 6.63 (s, 1H), 6.82 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.24-7.37 (m, 6H), 7.59 (d, *J* = 8.7 Hz, 1H).

2e[10] Yellow solid, 84% yield, 88% ee [Daicel Chiralpak AD-H, hexane/2-propanol = 80/20, *v* = 1.0 ml·min^{-1}, λ = 254 nm, t (major) = 20.09 min, t (minor) = 25.97 min]; $[\alpha]_D^{17}$ +3.1 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (dd, *J* = 11.2, 1.2 Hz, 1H), 3.92 (dd, *J* = 12.8, 4.4 Hz, 1H), 4.57-4.64 (m, 2H), 4.89-4.96 (m, 2H), 5.09 (d, *J* = 10.4 Hz, 1H), 5.72 (ddd, *J* = 16.8, 10.4, 5.2 Hz, 1H), 7.03 (dt, *J* = 15.2, 2.8 Hz, 1H), 7.17 (dd, *J* = 9.2, 4.4 Hz, 1H), 7.24-7.36 (m, 7H).

2f[10] Pale yellow oil, 78% yield, 91% ee [Daicel Chiralpak AD-H, hexane/2-propanol = 80/20, *v* = 1.0 ml·min^{-1}, λ = 254 nm, t (major) = 17.92 min, t (minor) = 24.91 min]; $[\alpha]_D^{17}$ +12.3 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.45 (dd, *J* = 12.9, 2.1 Hz, 1H), 3.94 (dd, *J* = 12.6, 4.8 Hz, 1H), 4.53-4.64 (m, 2H), 4.89-4.98 (m, 2H), 5.10 (d, *J* = 9.9 Hz, 1H), 5.71 (ddd, *J* = 15.6, 10.5, 5.4 Hz, 1H), 7.13-7.19 (m, 1H), 7.20-7.38 (m, 7H), 7.68 (d, *J* = 1.2 Hz, 1H).

2g[10] Yellow solid, 77% yield, 91% ee [Daicel Chiralpak AD-H, hexane/2-propanol = 80/20, *v* = 1.0 ml·min^{-1}, λ = 254 nm, t (major) = 26.51 min, t (minor) = 33.90 min]; $[\alpha]_D^{16}$ +8.7 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.45 (d, *J* = 12.9 Hz, 1H), 3.94 (dd, *J* = 12.6, 4.8 Hz, 1H), 4.57 (d, *J* = 17.1 Hz, 1H), 4.59 (d, *J* = 14.7 Hz, 1H), 4.91-4.99 (m, 2H), 5.10 (d, *J* = 10.2 Hz, 1H), 5.70 (ddd, *J* = 16.8, 10.5, 5.4 Hz, 1H), 7.12 (d, *J* = 9.0 Hz, 1H), 7.24-7.40 (m, 7H), 7.85 (s, 1H).

2h[10] Yellow solid, 75% yield, 91% ee [Daicel Chiralpak AD-H, hexane/2-propanol = 80/20, *v* = 1.0 ml·min^{-1}, λ = 230 nm, t (major) = 23.53 min, t (minor) = 29.22 min]; $[\alpha]_D^{26}$ +10.2 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.45 (dd, *J* = 12.9, 2.1 Hz, 1H), 3.94 (dd, *J* = 12.6, 4.8 Hz, 1H), 4.53-4.64 (m, 2H), 4.89-4.98 (m, 2H), 5.10 (d, *J* = 9.9 Hz, 1H), 5.71 (ddd, *J* = 15.6, 10.5, 5.4 Hz, 1H), 7.13-7.19 (m, 1H), 7.20-7.38 (m, 7H), 7.68 (d, *J* = 1.2 Hz, 1H).

2i[10] Colorless oil, 75% yield, 92% ee [Daicel Chiralpak AD-H, hexane/2-propanol = 80/20, *v* = 1.0 ml·min^{-1}, λ = 230 nm, t (major) = 18.96 min, t (minor) = 24.65 min]; $[\alpha]_D^{16}$ +16.2 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.45 (d, *J* = 11.4 Hz, 1H), 3.92 (dd, *J* = 12.6, 4.2 Hz, 1H), 4.59 (d, *J* = 14.4 Hz, 1H), 4.61 (d, *J* = 16.8 Hz, 1H), 4.85-4.98 (m, 2H), 5.12 (d, *J* = 10.5 Hz, 1H), 5.71 (ddd, *J* = 16.2, 10.2, 5.1 Hz, 1H), 7.20-7.38 (m, 7H), 7.44 (s, 1H), 7.57 (d, *J* = 8.7 Hz, 1H).

2j[10] Pale yellow oil, 95% yield, 93% ee [Daicel Chiralpak AD-H, hexane/2-propanol = 80/20, *v* = 1.0 ml·min^{-1}, λ = 230 nm, t (major) = 24.83 min, t (minor) = 34.87 min]; $[\alpha]_D^{17}$ -4.4 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (dd, *J* = 12.8, 2.0 Hz, 1H), 3.79 (s, 3H), 3.90 (dd, *J* = 12.8, 4.4 Hz, 1H), 4.53 (d, *J* = 14.8 Hz, 1H), 4.60 (d, *J* = 17.2 Hz, 1H), 4.89 (d, *J* = 14.8 Hz, 1H), 4.94-4.96 (m, 1H), 5.08 (d, *J* = 10.4 Hz, 1H), 5.71 (ddd, *J* = 16.8, 10.4, 5.2 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.23-7.31 (m, 4H), 7.34 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 1H).

2k[10] White solid, 82% yield, 93% ee [Daicel Chiralcel OD-H, hexane/2-propanol = 85/15, *v* = 1.0 ml·min^{-1}, λ = 230 nm, t (minor) = 16.68 min, t (major) = 34.39 min]; $[\alpha]_D^{27}$ -22.1 (*c* 1.00, CH_2Cl_2). ^{1}H

NMR (300 MHz, $CDCl_3$) δ 3.52 (dd, *J* = 12.6, 1.8 Hz, 1H), 3.91-4.04 (m, 2H), 4.40 (d, *J* = 15.0 Hz, 1H), 4.41 (d, *J* = 15.3 Hz, 1H), 4.69 (d, *J* = 17.1 Hz, 1H), 4.98-5.08 (m, 1H), 5.16 (d, *J* = 9.9 Hz, 1H), 5.25 (d, *J* = 4.5 Hz, 1H), 5.28 (d, *J* = 16.2 Hz, 1H), 5.71-5.98 (m, 2H), 7.11-7.20 (m, 1H), 7.23-7.35 (m, 3H), 7.71 (d, *J* = 8.1 Hz, 1H).

2l[10] White solid, 77% yield, 90% ee [Daicel Chiralcel OD-H, hexane/2-propanol = 80/20, *v* = 1.0 ml·min^{-1}, λ = 230 nm, t (minor) = 13.30 min, t (major) = 27.78 min]; $[\alpha]_D^{18}$ -13.9 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.15 (s, 3H), 3.50 (dd, *J* = 12.4, 2.0 Hz, 1H), 4.08 (dd, *J* = 12.4, 4.4 Hz, 1H), 4.76 (dd, *J* = 16.8, 8.0 Hz, 1H), 4.99-5.05 (m, 1H), 5.17 (d, *J* = 10.0 Hz, 1H), 5.95 (ddd, *J* = 16.0, 10.0, 5.6 Hz, 1H), 7.12-7.18 (m, 1H), 7.24-7.32 (m, 3H), 7.71 (d, *J* = 8.4 Hz, 1H).

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