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PAPER

Enantioselective synthesis of 2,5-dihydrobenzo[*b*]azepine derivatives *via* iridium-catalyzed asymmetric allylic amination with 2-allylanilines and ring-closing-metathesis reaction†‡

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Iridium-catalyzed asymmetric allylic amination of allylic carbonates with 2-allylanilines was realized. With a catalyst generated from 2 mol% of $[Ir(dbcot)Cl]_2$ (dbcot = dibenzo[*a*,*e*]cyclooctatetraene) and 4 mol% of phosphoramidite ligand (**L3**), the amination products were obtained in up to 99% yield and 99% ee. Subjecting amination products to trifluoroacetyl protection and ring-closing-metathesis reaction provided an efficient synthesis of enantioenriched 2,5-dihydrobenzo[*b*]azepine derivatives.

Introduction

Benzannulated nitrogen heterocycles constitute the core structure of numerous biologically active compounds that display a wide range of pharmacological activities.[1] Among them, benzazepines represent an interesting class of these heterocycles.[2] In particular, compounds bearing the 1-benzazepine moiety have exhibited biological activity toward various targets. For example, OPC-31260[3] (**A1**) and OPC-41061[4] (**A2**) (potent orally effective non-peptide vasopressin V_2 receptor antagonists), **B**[5] (against *Trypanosoma cruzi* and *Leishmania chagasi* parasites), all have 1-benzazepine as a key structural element (Fig. 1). Due to their widespread occurrence and extensive utilization as building blocks in pharmaceuticals, efficient diversity-oriented syntheses[6] of 1-benzazepine derivatives, especially *via* a catalytic asymmetric approach,[7] are highly desirable.

Ir-catalyzed asymmetric allylic substitution reactions have gained rapid development in recent years.[8] With respect to nucleophiles, a wide range of carbon[9] and heteroatom[10] (*e.g.*, *O*, *N*, *S*) nucleophiles have been employed. The utilization of substituted anilines as suitable nucleophiles in Ir-catalyzed asymmetric allylic substitution reactions has also been documented in the literature.[11] As part of our ongoing program towards Ir-catalyzed allylic substitution reaction,[12] we developed an Ir-catalyzed domino allylic vinylation/asymmetric allylic amination reaction for the construction of enantioenriched 1-benzazepine (a, Scheme 1).[13] However, substitution on the 1-benzazepine moiety was limited to only a 2-vinyl group despite the high efficiency of this method. Therefore, a novel approach to 1-benzazepine which would allow the diverse variation of substituents is required.

Recently, enantioenriched 1,2-dihydroquinolines were successfully obtained *via* the combination of Ir-catalyzed enantioselective allylic amination with *o*-aminostyrenes and a subsequent RCM reaction, reported by our group.[14] Pioneered by Evans *et al.*,[15] transition-metal-catalyzed allylic amination and RCM reaction strategy led to various optically active nitrogen-containing heterocycles including natural products and pharmaceutically interesting compounds.[16,17] We envisaged that this

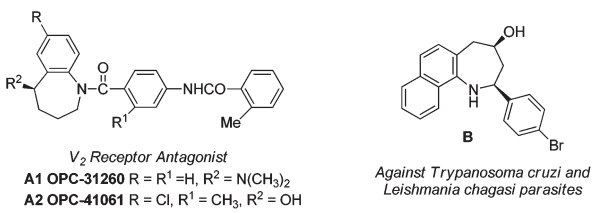
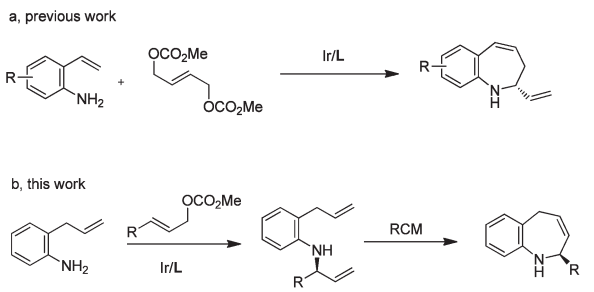


Fig. 1 Biologically active compounds with 1-benzazepine moiety.



Scheme 1 Methods for the preparation of enantioenriched 1-benzazepines.

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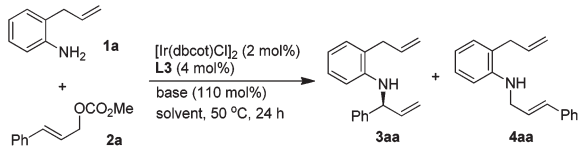
Table 1 Optimization of reaction conditions for Ir-catalyzed allylic amination with 2-allylaniline[a]



Entry	Solvent	Base	Yield[b] (**3aa** + **4aa**, %)	**3aa**/**4aa**[c]	ee[d] (%)
1	THF	K_3PO_4	91	94 : 6	94
2	THF	Cs_2CO_3	56	98 : 2	97
3	THF	KOAc	54	97 : 3	98
4	THF	DABCO	15	95 : 5	15
5	THF	DBU	48	98 : 2	48
6	THF	Et_3N	94	97 : 3	99
7	THF	—	87	95 : 5	97
8	Dioxane	Et_3N	83	96 : 4	99
9	CH_2Cl_2	Et_3N	97	97 : 3	98
10	CH_3CN	Et_3N	96	97 : 3	92
11	Toluene	Et_3N	78	93 : 7	96
12	Et_2O	Et_3N	86	94 : 6	98

[a] Reaction conditions: $[Ir(dbcot)Cl]_2$/**L3**/**1a**/**2a**/base = 0.02/0.04/1.0/1.1/1.1, 0.1 M of **1a**. [b] Isolated yield. [c] Determined by ^1H NMR of the crude reaction mixture. [d] Determined by HPLC analysis.

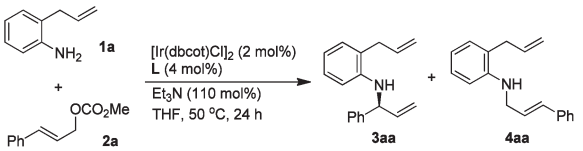
strategy could be applicable to the synthesis of enantioenriched 1-benzazepine derivatives using 2-allylanilines as nucleophiles (b, Scheme 1). In this paper, we report such an efficient synthesis of enantioenriched 2,5-dihydrobenzo[*b*]azepine derivatives *via* Ir-catalyzed allylic asymmetric amination with 2-allylanilines and a subsequent RCM reaction.

Results and discussion

We began our studies by utilizing 2-allylaniline (**1a**) and cinnamyl methyl carbonate (**2a**) as the model substrates. $[Ir(dbcot)Cl]_2$, introduced by Helmchen and coworkers in an Ir-catalyzed allylic substitution reaction,[18] was chosen as the iridium precursor based on our previous work on asymmetric allylic amination with *o*-aminostyrenes.[14] The results are summarized in Table 1.

With the Ir-catalyst generated *in situ* from 2 mol% of $[Ir(dbcot)Cl]_2$ and 4 mol% of **L3**, the reaction of **1a** and **2a** in the presence of 110 mol% of K_3PO_4 in THF gave the desired branched amination product with excellent results (91% yield, 94% ee and b (branched) : l (linear) = 94 : 6, entry 1, Table 1). Examination of bases disclosed that various bases tested all afforded good regioselectivities. However, yields dramatically decreased in the reactions with bases such as Cs_2CO_3 and KOAc although slightly better enantioselectivities were obtained (entries 2, 3, Table 1). Both DABCO and DBU had a deleterious effect on yields and enantioselectivities of the allylic amination reaction (entries 4, 5, Table 1). Finally, Et_3N was found as the best choice of base in terms of yield, regioselectivity and enantioselectivity (94% yield, b : l = 97 : 3, 99% ee, entry 6, Table 1). Notably, excellent ee could also be obtained in the reaction without additional base but the yield was slightly decreased (entry 7, Table 1). Various solvents (such as dioxane, CH_2Cl_2, CH_3CN, toluene, and Et_2O) were well tolerated and THF afforded the best results (entries 8–12, Table 1).

Table 2 Screening of various chiral phosphoramidite ligands[a]



Entry	L	Yield[b] (**3aa** + **4aa**, %)	**3aa**/**4aa**[c]	ee[d] (%)
1	**L1**	Trace	—	—
2	**L2**	Trace	—	—
3	**L3**	94	97 : 3	99
4[e]	**L3**	Trace	—	—
5	**L4**	26	75 : 25	12

[a] Reaction conditions: $[Ir(dbcot)Cl]_2$/**L**/**1a**/**2a**/Et_3N = 0.02/0.04/1.0/1.1/1.1, 0.1 M of **1a** in THF. [b] Isolated yield. [c] Determined by ^1H NMR of the crude reaction mixture. [d] Determined by HPLC analysis. [e] $[Ir(cod)Cl]_2$ was employed instead of $[Ir(dbcot)Cl]_2$.

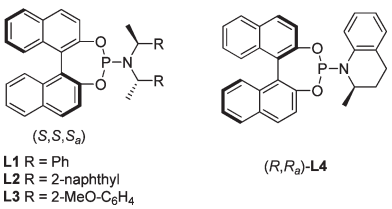
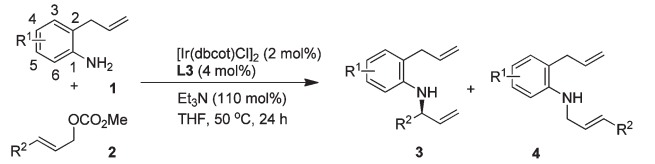


Fig. 2 Chiral phosphoramidite ligands.

Next, several readily available chiral phosphoramidite ligands were examined as summarized in Table 2. Phosphoramidite ligands **L1** and **L2** (Fig. 2), varying the substituents on the phenyl ring of amine moiety, only afforded trace amount of products (entries 1, 2, Table 2). Low yield and enantioselectivity were obtained when **L4** was used (entry 5, Table 2). We also found that the proper choice of iridium precursor is critical. Only a trace amount of desired products was observed when $[Ir(cod)Cl]_2$ was employed instead of $[Ir(dbcot)Cl]_2$ in the presence of **L3** (entry 4, Table 2).

Under the optimal reaction conditions (that is, 2 mol% of $[Ir(dbcot)Cl]_2$, 4 mol% of **L3**, 110 mol% of Et_3N, 0.2 mmol of **1**, 0.22 mmol of **2** in THF at 50 °C, entry 3, Table 2), substrate scope of the Ir-catalyzed enantioselective allylic amination reaction was explored (Table 3). Substrates bearing either an electron-donating group (4-MeO, entry 2, Table 3) or electron-withdrawing group (4-Cl, 3-Cl, entries 3, 4, Table 3) on the phenyl ring of the cinnamyl methyl carbonates were well tolerated and led to their corresponding amination products in excellent yields (81–99%) and enantioselectivities (92–99% ee). Notably, *o*-methoxy substituted cinnamyl methyl carbonate also reacted smoothly but the yield, regio- and enantioselectivity were decreased slightly (entry 5, Table 3). Reaction with the hetero-aromatic substituted carbonate such as 2-thienyl allylic carbonate occurred with the same level of regio- and enantioselectivity (entry 6, Table 3). It is worth mentioning that even the alkyl substituted allylic carbonates were well tolerated (entries 7, 8, Table 3). On the other hand, it was found that reactions with substrates bearing both electron-donating and electron-withdrawing groups on the phenyl ring of 2-allylanilines all

Table 3 Substrate scope of Ir-catalyzed allylic amination with 2-allylanilines[a]



Entry	R^1, R^2	Yield[b] (**3** + **4**, %)	**3**/**4**[c]	ee[d] (%)
1	H, C_6H_5	94	97 : 3	**3aa** 99
2	H, 4-MeO-C_6H_4	99	98 : 2	**3ab** 92
3	H, 4-Cl-C_6H_4	81	98 : 2	**3ac** 99
4	H, 3-Cl-C_6H_4	99	93 : 7	**3ad** 98
5	H, 2-MeO-C_6H_4	86	90 : 10	**3ae** 86
6	H, 2-thienyl	97	96 : 4	**3af** 96
7	H, *c*-C_3H_5	86	92 : 8	**3ag** 92
8	H, Et	74	96 : 4	**3ah** 96
9	4-F, C_6H_5	96	98 : 2	**3ba** 96
10	4-Br, C_6H_5	94	99 : 1	**3ca** 99
11	4-Me, C_6H_5	65	97 : 3	**3da** 99
12	3,5-$(MeO)_2$, C_6H_5	61	99 : 1	**3ea** 99

[a] Reaction conditions: [Ir(dbcot)Cl]$_2$/**L3**/**1**/**2**/Et_3N = 0.02/0.04/1.0/1.1/1.1, 0.1 M of **1** in THF. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] Determined by HPLC analysis.

proceeded with excellent enantioselective control. The yields of substrates with electron-donating groups were comparably lower than their electron-withdrawing counterparts (entries 9–12, Table 3).

With these highly enantioenriched amination products in hand, then the synthesis of 1-benzazepine derivatives was examined. This was achieved in a two-step process including protection with trifluoroacetic anhydride and then a RCM reaction with **Zhan-1B** as catalyst (2 mol%). **Zhan-1B** was chosen as the appropriate catalyst rather than other conventional ring-closing-metathesis catalysts based on our previous work.[14,17] The results are summarized in Table 4. In general, 1-benzazepine derivatives were obtained in good yields without notable loss of enantiomeric purity.

The resulting 1-benzazepines could further undergo versatile transformations. For example, the double bond of the enantioenriched 1-benzazepine **5aa** could be easily hydrogenated with Pd/C in methanol at room temperature in almost quantitative yield (eqn (1)). The convenient cleavage of the trifluoroacetyl group of **5aa** with $NaBH_4$ makes it particularly appealing for further transformation with **7** as an optically active secondary amine (eqn (2)).[19] In these two cases, the enantiomeric purity could be well preserved. The absolute configuration of **5ca** was assigned to be (*S*) by X-ray crystallographic analysis (Fig. 3).

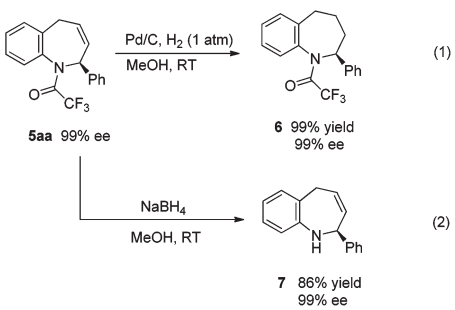
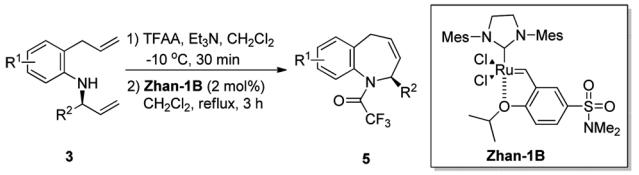


Table 4 Synthesis of enantioenriched 1-benzazepine derivatives[a]



Entry	**3** R^1, R^2	**5**, yield[b] (%)	ee[c,d] (%)
1	**3aa** H, C_6H_5	**5aa**, 75	99 (99)
2	**3ab** H, 4-MeO-C_6H_4	**5ab**, 75	94 (92)
3	**3ac** H, 4-Cl-C_6H_4	**5ac**, 99	99 (99)
4	**3ad** H, 3-Cl-C_6H_4	**5ad**, 92	95 (98)
5	**3ae** H, 2-MeO-C_6H_4	**5ae**, 83	84 (86)
6	**3af** H, 2-thienyl	**5af**, 96	98 (96)
7	**3ag** H, *c*-C_3H_5	**5ag**, 99	92 (92)
8	**3ah** H, Et	**5ah**, 75	94 (96)
9	**3ba** 4-F, C_6H_5	**5ba**, 83	96 (96)
10	**3ca** 4-Br, C_6H_5	**5ca**, 72	98 (99)
11	**3da** 4-Me, C_6H_5	**5da**, 88	99 (99)
12	**3ea** 3,5-$(MeO)_2$, C_6H_5	**5ea**, 84	98 (99)

[a] (1) Reaction conditions: **3**/TFAA/Et_3N = 1.0/1.5/2.0, 0.1 M of **3** in CH_2Cl_2; (2) 0.004 mmol of **Zhan-1B** in 2 mL of CH_2Cl_2. [b] Isolated yield. [c] Determined by HPLC analysis. [d] ee of **3** is given in parentheses.

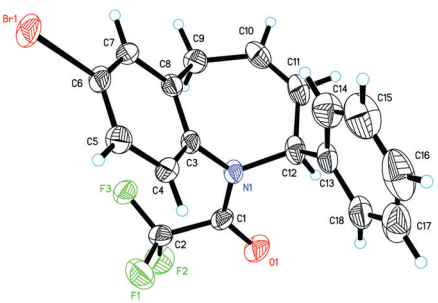


Fig. 3 X-Ray crystal structure of (*S*)-**5ca** [CCDC 859342] (thermal ellipsoids are set at 30% probability).

Conclusions

In summary, we have successfully developed an efficient method for the synthesis of enantioenriched 1-benzazepine derivatives by employing Ir-catalyzed asymmetric allylic amination with 2-allylanilines and a subsequent RCM reaction. The current methodology features high enantioselectivity and ready availability of the starting materials, which make it particularly attractive in organic synthesis.

Experiment section

General

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). Data for ^1H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, br s = broad singlet, coupling constant(s) in Hz, integration). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm).

The phosphoramidite ligands,[20] the substituted allylic carbonates,[21] and the substituted 2-allylanilines[22] were prepared according to known procedures.

General procedure for the Ir-catalyzed allylic amination

A flame-dried Schlenk tube was cooled to room temperature and filled with argon. To this flask were added $[Ir(dbcot)Cl]_2$ (3.5 mg, 0.004 mmol, 2 mol%), phosphoramidite ligand **L3** (4.8 mg, 0.008 mmol, 4 mol%), THF (0.5 mL) and *n*-propylamine (0.5 mL). The reaction mixture was heated at 50 °C for 0.5 h, and the color of the solution was changed from orange to light yellow. Then the reaction mixture was cooled to room temperature, and the solvent was removed *in vacuo*. To the same flask, 2-allylaniline derivative **1** (0.20 mmol), allylic carbonate **2** (0.22 mmol), Et_3N (22.2 mg, 0.22 mmol) and THF (2 mL) were added. The reaction mixture was stirred at 50 °C. After the reaction was complete (monitored by TLC), the crude reaction mixture was filtered through celite and washed with EtOAc. The solvents were removed under reduced pressure. Then the crude residue was purified by silica gel column chromatography (petroleum ether : EtOAc = 100 : 1) to afford the product **3**.

3aa. Pale yellow oil, R_f = 0.8 (petroleum ether : EtOAc = 10 : 1), b : l = 97 : 3, 94% yield, 99% ee [Daicel Chiralcel OJ-H, hexane : 2-propanol = 99 : 1, v = 0.5 mL min^{-1}, λ = 254 nm, t (major) = 20.40 min, t (minor) = 27.88 min]; $[\alpha]_D^{20}$ + 20.5 (c 1.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 3.34 (d, J = 6.0 Hz, 2H), 4.18 (br s, 1H), 4.90–5.00 (m, 1H), 5.03–5.28 (m, 4H), 5.87–6.10 (m, 2H), 6.52 (d, J = 8.7 Hz, 1H), 6.67 (t, J = 7.5 Hz, 1H), 6.99–7.11 (m, 2H), 7.21–7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.8, 60.4, 111.8, 115.8, 116.4, 117.3, 123.5, 127.0, 127.3, 127.5, 128.7, 129.8, 136.0, 139.2, 141.9, 145.1; IR (thin film): ν_{max} (cm^{-1}) = 3424, 1636, 1604, 1586, 1451, 1314, 1261, 1027, 919, 799, 748, 701; MS (EI, *m*/*z*, rel. intensity) 249 (M^+, 16), 117 (100); HRMS (EI) calcd for $C_{18}H_{19}N$ (M^+): 249.1517. Found: 249.1519.

3ab. Pale yellow oil, R_f = 0.5 (petroleum ether : EtOAc = 10 : 1), b : l = 98 : 2, 99% yield, 92% ee [Daicel Chiralcel OD-H, hexane : 2-propanol = 99 : 1, v = 0.5 mL min^{-1}, λ = 254 nm, t (minor) = 14.43 min, t (major) = 16.96 min]; $[\alpha]_D^{20}$ + 14.0 (c 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 3.32 (d, J = 6.0 Hz, 2H), 3.78 (s, 3H), 4.12 (br s, 1H), 4.88–4.93 (m, 1H), 5.05–5.24 (m, 4H), 5.88–6.05 (m, 2H), 6.54 (d, J = 8.8 Hz, 1H), 6.71 (t, J = 7.2 Hz, 1H), 6.86 (d, J = 7.6 Hz, 2H), 7.01–7.08 (m, 2H), 7.26 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.8, 55.2, 59.8, 111.8, 114.0, 115.5, 116.4, 117.2, 123.4, 127.5, 128.1, 129.7, 134.0, 136.0, 139.4, 145.2, 158.8; IR (thin film): ν_{max} (cm^{-1}) = 3421, 2834, 1636, 1605, 1507, 1246, 1174, 1034, 994, 918, 825, 747; MS (EI, *m*/*z*, rel. intensity) 279 (M^+, 16), 147 (100); HRMS (EI) calcd for $C_{19}H_{21}NO$ (M^+): 279.1623. Found: 279.1622.

3ac. Pale yellow oil, R_f = 0.8 (petroleum ether : EtOAc = 10 : 1), b : l = 98 : 2, 81% yield, 99% ee [Daicel Chiralcel OD-H, hexane : 2-propanol = 99 : 1, v = 0.5 mL min^{-1}, λ = 254 nm, t (major) = 15.51 min, t (minor) = 16.51 min]; $[\alpha]_D^{20}$ + 47.1 (c 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 3.34 (d, J = 6.0 Hz, 2H), 4.15 (br s, 1H), 4.89–4.96 (m, 1H), 5.06–5.25 (m, 4H), 5.89–6.04 (m, 2H), 6.45 (d, J = 7.6 Hz, 1H), 6.68 (t, J = 7.2 Hz, 1H), 6.99–7.09 (m, 2H), 7.24–7.33 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.8, 59.8, 111.8, 116.3, 116.4, 117.6, 123.6, 127.5, 128.3, 128.8, 129.9, 132.9, 136.0, 138.8, 140.4, 144.9; IR (thin film): ν_{max} (cm^{-1}) = 3423, 3079, 1636, 1506, 1490, 1313, 1261, 1090, 995, 919, 811, 747; MS (EI, *m*/*z*, rel. intensity) 283 (M^+, 23), 115 (100); HRMS (EI) calcd for $C_{18}H_{18}NCl$ (M^+): 283.1128. Found: 283.1127.

3ad. Pale yellow oil, R_f = 0.7 (petroleum ether : EtOAc = 10 : 1), b : l = 93 : 7, 99% yield, 98% ee [Daicel Chiralcel OD-H, hexane : 2-propanol = 99 : 1, v = 0.5 mL min^{-1}, λ = 254 nm, t (major) = 14.99 min, t (minor) = 22.17 min]; $[\alpha]_D^{20}$ + 50.1 (c 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 3.36 (d, J = 6.0 Hz, 2H), 4.18 (br s, 1H), 4.89–4.97 (m, 1H), 5.07–5.27 (m, 4H), 5.91–6.06 (m, 2H), 6.46 (d, J = 8.0 Hz, 1H), 6.69 (t, J = 7.2 Hz, 1H), 7.01–7.09 (m, 2H), 7.20–7.31 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.8, 60.1, 111.8, 116.5, 117.7, 123.6, 125.1, 127.1, 127.5, 127.6, 129.9, 134.5, 136.0, 138.7, 144.2, 144.9; IR (thin film): ν_{max} (cm^{-1}) = 3423, 3078, 1636, 1588, 1507, 1312, 1253, 996, 920, 785, 747; MS (EI, *m*/*z*, rel. intensity) 283 (M^+, 33), 115 (100); HRMS (EI) calcd for $C_{18}H_{18}NCl$ (M^+): 283.1128. Found: 283.1124.

3ae. Pale yellow oil, R_f = 0.5 (petroleum ether : EtOAc = 10 : 1), b : l = 90 : 10, 86% yield, 86% ee [Daicel Chiralcel OD-H, hexane : 2-propanol = 99 : 1, v = 0.5 mL min^{-1}, λ = 254 nm, t (minor) = 25.26 min, t (major) = 33.71 min]; $[\alpha]_D^{20}$ + 17.7 (c 1.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 3.34 (d, J = 6.3 Hz, 2H), 3.84 (s, 3H), 4.36 (br s, 1H), 5.05–5.28 (m, 4H), 5.33–5.45 (m, 1H), 5.88–6.13 (m, 2H), 6.53 (d, J = 8.1 Hz, 1H), 6.64 (t, J = 7.5 Hz, 1H), 6.84–6.94 (m, 2H), 6.99–7.10 (m, 2H), 7.18–7.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.8, 54.3, 55.4, 110.6, 111.6, 114.8, 116.2, 117.0, 120.8, 123.5, 127.5, 128.3, 129.7, 129.8, 136.1, 138.8, 145.2, 156.8; IR (thin film): ν_{max} (cm^{-1}) = 3432, 2929, 1637, 1603, 1508, 1491, 1242, 996, 919, 755; MS (EI, *m*/*z*, rel. intensity) 279 (M^+, 17), 147 (100); HRMS (EI) calcd for $C_{19}H_{21}NO$ (M^+): 279.1623. Found: 279.1620.

3af. Pale yellow oil, R_f = 0.8 (petroleum ether : EtOAc = 10 : 1), b : l = 96 : 4, 97% yield, 96% ee [Daicel Chiralcel OD-H, hexane : 2-propanol = 99 : 1, v = 0.5 mL min^{-1}, λ = 254 nm, t (major) = 14.20 min, t (minor) = 15.45 min]; $[\alpha]_D^{20}$ + 46.5 (c 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 3.33 (d, J = 6.0 Hz, 2H), 4.20–4.22 (m, 1H), 5.07–5.13 (m, 2H), 5.24–5.35 (m, 3H), 5.91–6.00 (m, 1H), 6.06 (ddd, J = 17.2, 10.4, 6.0 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.72 (t, J = 7.6 Hz, 1H), 6.95–7.01 (m, 2H), 7.06–7.12 (m, 2H), 7.21–7.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.7, 56.0, 111.9, 116.4, 116.5, 117.8, 123.8, 124.4, 124.7, 126.9, 127.5, 130.0, 135.9, 138.4, 144.8, 146.5; IR (thin film): ν_{max} (cm^{-1}) = 3416, 3076, 1636, 1586, 1311, 1253, 993, 920, 747, 699; MS (EI, *m*/*z*, rel. intensity) 255 (M^+, 10), 123 (100); HRMS (EI) calcd for $C_{16}H_{17}NS$ (M^+): 255.1082. Found: 255.1080.

3ag. Pale yellow oil, R_f = 0.8 (petroleum ether : EtOAc = 10 : 1), b : l = 92 : 8, 86% yield, 92% ee [Daicel Chiralcel OD-H,

hexane : 2-propanol = 99 : 1, v = 0.5 mL min^{-1}, λ = 254 nm, t (minor) = 8.34 min, t (major) = 9.50 min]; $[\alpha]_D^{20}$ − 18.0 (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.19–0.40 (m, 2H), 0.45–0.61 (m, 2H), 0.96–1.10 (m, 1H), 3.21–3.31 (m, 1H), 3.34 (d, J = 6.0 Hz, 2H), 4.06 (br s, 1H), 5.07–5.27 (m, 4H), 5.82 (ddd, J = 16.2, 10.5, 5.7 Hz, 1H), 5.90–6.05 (m, 1H), 6.55 (d, J = 8.1 Hz, 1H), 6.66 (t, J = 7.5 Hz, 1H), 6.95–7.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.5, 3.2, 16.8, 36.8, 59.9, 111.6, 115.0, 116.3, 116.9, 123.2, 127.4, 129.7, 136.2, 138.7, 145.9; IR (thin film): ν_{max} (cm^{-1}) = 3413, 3005, 1604, 1507, 1314, 995, 916, 745; MS (EI, m/z, rel. intensity) 213 (M^+, 41), 81 (100); HRMS (EI) calcd for $C_{15}H_{19}N$ (M^+): 213.1517. Found: 213.1514.

3ah. Pale yellow oil, R_f = 0.8 (petroleum ether : EtOAc = 10 : 1), b : l = 96 : 4, 74% yield, 96% ee [Daicel Chiralcel OD-H, hexane : 2-propanol = 99 : 1, v = 0.5 mL min^{-1}, λ = 254 nm, t (minor) = 16.41 min, t (major) = 18.89 min]; $[\alpha]_D^{20}$ + 5.4 (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, J = 7.2 Hz, 3H), 1.57–1.70 (m, 2H), 3.31 (d, J = 6.3 Hz, 2H), 3.65–3.84 (m, 2H), 5.04–5.24 (m, 4H), 5.73 (ddd, J = 16.5, 10.5, 5.4 Hz, 1H), 5.88–6.03 (m, 1H), 6.60 (d, J = 7.8 Hz, 1H), 6.65 (t, J = 7.5 Hz, 1H), 7.03 (d, J = 7.5 Hz, 1H), 7.11 (t, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.3, 28.6, 36.9, 56.9, 111.3, 115.0, 116.3, 116.7, 123.1, 127.5, 129.9, 136.3, 139.8, 145.7; IR (thin film): ν_{max} (cm^{-1}) = 3430, 2963, 1636, 1605, 1512, 1462, 1316, 1260, 1094, 1018, 917, 801, 747; MS (EI, m/z, rel. intensity) 201 (M^+, 28), 172 (100); HRMS (EI) calcd for $C_{14}H_{19}N$ (M^+): 201.1517. Found: 201.1513.

3ba. Pale yellow oil, R_f = 0.8 (petroleum ether : EtOAc = 10 : 1), b : l = 98 : 2, 96% yield, 96% ee [Daicel Chiralcel OD-H, hexane : 2-propanol = 99 : 1, v = 0.5 mL min^{-1}, λ = 254 nm, t (major) = 16.08 min, t (minor) = 19.18 min]; $[\alpha]_D^{20}$ + 45.4 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.29 (d, J = 6.0 Hz, 2H), 3.98 (br s, 1H), 4.85–4.91 (m, 1H), 5.05–5.27 (m, 4H), 5.86–6.06 (m, 2H), 6.43 (dd, J = 9.2, 4.8 Hz, 1H), 6.72 (dt, J = 8.4, 3.2 Hz, 1H), 6.79 (dd, J = 9.2, 2.8 Hz, 2H), 7.20–7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.4, 61.0, 112.7, 112.8, 113.1, 113.4, 115.8, 116.3, 116.5, 117.0, 125.3, 125.4, 126.9, 127.4, 128.7, 135.1, 139.3, 141.4, 141.8, 154.4, 156.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −128.0 (m); IR (thin film): ν_{max} (cm^{-1}) = 3418, 1639, 1509, 1261, 1218, 1027, 922, 867, 803, 701; MS (EI, m/z, rel. intensity) 267 (M^+, 20), 117 (100); HRMS (EI) calcd for $C_{18}H_{18}NF$ (M^+): 267.1423. Found: 267.1422.

3ca. Pale yellow oil, R_f = 0.9 (petroleum ether : EtOAc = 10 : 1), b : l = 99 : 1, 94% yield, 99% ee [Daicel Chiralcel OD-H, hexane : 2-propanol = 99 : 1, v = 0.5 mL min^{-1}, λ = 254 nm, t (minor) = 10.88 min, t (major) = 11.97 min]; $[\alpha]_D^{20}$ + 3.5 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.27 (d, J = 6.4 Hz, 2H), 4.14–4.16 (m, 1H), 4.90 (t, J = 5.2 Hz, 1H), 5.05–5.24 (m, 4H), 5.84–5.94 (m, 1H), 6.00 (ddd, J = 16.8, 10.4, 6.0 Hz, 1H), 6.37 (d, J = 8.8 Hz, 1H), 7.10 (dd, J = 8.4, 2.4 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 7.22–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.3, 60.4, 109.1, 113.4, 116.0, 117.1, 125.6, 126.9, 127.5, 128.7, 130.0, 132.2, 135.0, 138.8, 141.3, 144.1; IR (thin film): ν_{max} (cm^{-1}) = 3429, 2963, 1637, 1594, 1499, 1261, 1096, 1025, 921, 802, 701; MS (EI, m/z, rel. intensity) 327 (M^+, 19), 117(100); HRMS (EI) calcd for $C_{18}H_{18}NBr$ (M^+): 327.0623. Found: 327.0626.

3da. Pale yellow oil, R_f = 0.8 (petroleum ether : EtOAc = 10 : 1), b : l = 97 : 3, 65% yield, 99% ee [Daicel Chiralcel OD-H, hexane : 2-propanol = 99 : 1, v = 0.5 mL min^{-1}, λ = 254 nm, t (major) = 12.71 min, t (minor) = 13.65 min]; $[\alpha]_D^{20}$ + 13.5 (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.21 (s, 3H), 3.32 (d, J = 6.0 Hz, 2H), 4.04 (br s, 1H), 4.92–4.93 (m, 1H), 5.04–5.29 (m, 4H), 5.87–6.09 (m, 2H), 6.44 (d, J = 7.8 Hz, 1H), 6.81–6.90 (m, 2H), 7.21–7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 36.8, 60.6, 112.1, 115.7, 116.3, 123.7, 126.5, 127.0, 127.2, 127.8, 128.6, 130.6, 136.1, 139.4, 142.1, 142.9; IR (thin film): ν_{max} (cm^{-1}) = 3414, 2962, 1636, 1617, 1512, 1452, 1309, 1261, 1026, 919, 803, 701; MS (EI, m/z, rel. intensity) 263 (M^+, 42), 117 (100); HRMS (EI) calcd for $C_{19}H_{21}N$ (M^+): 263.1674. Found: 263.1678.

3ea. Pale yellow oil, R_f = 0.8 (petroleum ether : EtOAc = 5 : 1), b : l = 99 : 1, 61% yield, 99% ee [Daicel Chiralcel OD-H, hexane : 2-propanol = 99 : 1, v = 0.5 mL min^{-1}, λ = 254 nm, t (minor) = 18.60 min, t (major) = 27.43 min]; $[\alpha]_D^{20}$ + 13.4 (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.36 (d, J = 5.7 Hz, 2H), 3.65 (s, 3H), 3.75 (s, 3H), 4.25 (br s, 1H), 4.92–4.95 (m, 1H), 4.97–5.07 (m, 2H), 5.15–5.28 (m, 2H) 5.78–6.09 (m, 4H), 7.20–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.8, 54.9, 55.7, 60.6, 88.0, 91.4, 103.7, 114.8, 115.8, 126.9, 127.3, 128.7, 136.4, 139.3, 142.0, 147.0, 158.2, 159.6; IR (thin film): ν_{max} (cm^{-1}) = 3423, 2999, 1605, 1513, 1452, 1203, 1144, 1064, 995, 916, 806, 701; MS (EI, m/z, rel. intensity) 309 (M^+, 25), 117 (100); HRMS (EI) calcd for $C_{20}H_{23}NO_2$ (M^+): 309.1729. Found: 309.1730.

General procedure for the trifluoroacetylation/RCM of 3

To a solution of amine **3** (0.2 mmol) and Et_3N (60.6 mg, 0.6 mmol) in CH_2Cl_2 (2 mL) was added dropwise trifluoroacetic anhydride (42.3 μL, 0.3 mmol) at −10 °C. The mixture was stirred at this temperature for 30 min. The reaction was quenched with $NaHCO_3$ (aq.) and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (petroleum ether : EtOAc = 20 : 1) to afford the desired products, to which in CH_2Cl_2 (2 mL) was added **Zhan-1B** catalyst (2.9 mg, 0.004 mmol) under an argon atmosphere. The mixture was refluxed for 3 h. Then the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether : EtOAc = 20 : 1) to afford the desired product **5**.

5aa. White solid, R_f = 0.6 (petroleum ether : EtOAc = 10 : 1), 75% yield, 99% ee [Daicel Chiralcel OD-H, hexane : 2-propanol = 99 : 1, v = 0.5 mL min^{-1}, λ = 254 nm, t (major) = 12.07 min, t (minor) = 13.51 min]; $[\alpha]_D^{20}$ − 204.8 (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.12 (dd, J = 16.5, 8.1 Hz, 1H), 3.87 (ddd, J = 16.5, 5.7, 2.7 Hz, 1H), 5.61 (dt, J = 12.0, 3.6 Hz, 1H), 6.17–6.28 (m, 1H), 6.31 (d, J = 7.8 Hz, 1H), 6.81–6.89 (m, 1H), 7.00–7.16 (m, 3H) 7.26–7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.6, 58.1, 116.4 (q, J = 286.9 Hz), 126.4, 126.5, 127.3, 128.2, 128.3, 128.5, 128.9, 129.1, 130.2, 135.1, 137.0, 140.0, 156.5 (q, J = 34.3 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.5; IR (thin film): ν_{max} (cm^{-1}) = 2962, 1696, 1495, 1413,

1187, 1146, 800, 747, 734, 671; ESI-MS: 317 (M^+); HRMS (ESI) calcd for $C_{18}H_{14}F_3NO$ (M^+): 317.1027. Found: 317.1025; m.p. 119–121 °C.

5ab. White solid, R_f = 0.4 (petroleum ether : EtOAc = 10 : 1), 75% yield, 94% ee [Daicel Chiralcel OD-H, hexane : 2-propanol = 99 : 1, v = 0.5 mL min^{-1}, λ = 254 nm, t (minor) = 24.41 min, t (major) = 29.08 min]; $[\alpha]_D^{20}$ − 181.2 (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.10 (dd, J = 16.8, 9.0 Hz, 1H), 3.75 (s, 3H), 3.85 (dd, J = 17.1, 3.0 Hz, 1H), 5.58 (dt, J = 11.7, 3.9 Hz, 1H), 6.01–6.13 (m, 1H), 6.34 (d, J = 8.1 Hz, 1H), 6.63–6.74 (m, 3H), 6.84–7.00 (m, 3H) 7.16–7.24 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.5, 55.1, 57.6, 113.4, 116.3 (q, J = 286.9 Hz), 126.1, 126.5, 127.7, 128.4, 129.1, 130.1, 130.3, 135.1, 140.0, 156.4 (q, J = 34.9 Hz), 159.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.6; IR (thin film): ν_{max} (cm^{-1}) = 2998, 2960, 1729, 1694, 1260, 1152, 1071, 1038, 798, 734; ESI-MS: 347 (M^+); HRMS (ESI) calcd for $C_{19}H_{16}F_3NO_2$ (M^+): 347.1133. Found: 347.1131; m.p. 93–94 °C.

5ac. White solid, R_f = 0.7 (petroleum ether : EtOAc = 10 : 1), 99% yield, 99% ee [Daicel Chiralcel OD-H, hexane : 2-propanol = 99 : 1, v = 0.5 mL min^{-1}, λ = 254 nm, t (minor) = 25.22 min, t (major) = 33.79 min]; $[\alpha]_D^{20}$ − 194.7 (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.13 (dd, J = 16.5, 8.7 Hz, 1H), 3.86 (dd, J = 16.8, 3.0 Hz, 1H), 5.57 (dt, J = 11.7, 4.2, 3.0 Hz, 1H), 6.05–6.18 (m, 1H), 6.34 (d, J = 7.5 Hz, 1H), 6.64–6.73 (m, 1H), 6.86–7.03 (m, 3H) 7.10–7.29 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.5, 57.3, 116.3 (q, J = 286.8 Hz), 126.7, 126.9, 127.0, 128.4, 128.6, 129.3, 130.2, 130.3, 134.3, 134.8, 135.5, 139.9, 156.6 (q, J = 35.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.6; IR (thin film): ν_{max} (cm^{-1}) = 2963, 1691, 1493, 1412, 1260, 1185, 1151, 1088, 1019, 795, 763, 734; ESI-MS: 351 (M^+); HRMS (ESI) calcd for $C_{18}H_{13}ClF_3NO_2$ (M^+): 351.0638. Found: 351.0637; m.p. 136–138 °C.

5ad. Yellow oil, R_f = 0.6 (petroleum ether : EtOAc = 10 : 1), 92% yield, 95% ee [Daicel Chiralcel OD-H, hexane : 2-propanol = 99 : 1, v = 0.5 mL min^{-1}, λ = 254 nm, t (major) = 15.56 min, t (minor) = 17.02 min]; $[\alpha]_D^{20}$ − 92.1 (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.14 (dd, J = 16.8, 8.4 Hz, 1H), 3.86 (ddd, J = 16.5, 6.0, 2.7 Hz, 1H), 5.57 (ddd, J = 12.0, 4.5, 3.3 Hz, 1H), 6.07–6.19 (m, 1H), 6.36 (d, J = 7.8 Hz, 1H), 6.64–6.72 (m, 1H), 6.86–7.03 (m, 3H) 7.13 (t, J = 7.8 Hz, 1H), 7.18–7.30 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.5, 57.5, 116.3 (q, J = 286.4 Hz), 126.6, 126.7, 127.1, 127.2, 128.6, 128.7, 129.1, 129.4, 129.5, 130.2, 134.2, 134.8, 139.0, 139.9, 156.2 (q, J = 35.4 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.6; IR (thin film): ν_{max} (cm^{-1}) = 2962, 2925, 1691, 1494, 1409, 1260, 1182, 1150, 1016, 801, 788, 733; ESI-MS: 351 (M^+); HRMS (ESI) calcd for $C_{18}H_{13}ClF_3NO_2$ (M^+): 351.0638. Found: 351.0642.

5ae. White solid, R_f = 0.4 (petroleum ether : EtOAc = 10 : 1), 83% yield, 84% ee [Daicel Chiralcel OD-H, hexane : 2-propanol = 99 : 1, v = 1.0 mL min^{-1}, λ = 254 nm, t (major) = 7.31 min, t (minor) = 8.47 min]; $[\alpha]_D^{20}$ − 159.8 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05 (dd, J = 17.2, 8.4 Hz, 1H), 3.81–3.89 (ddd, J = 17.6, 5.2, 1.6 Hz, 1H), 3.82 (s, 3H), 5.54 (ddd, J = 11.6, 4.8, 3.3 Hz, 1H), 5.97–6.03 (m, 1H), 6.31 (d, J = 8.0 Hz, 1H), 6.47–6.49 (m, 2H), 6.76–6.83 (m, 3H) 7.02–7.12 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.2, 53.0, 55.4, 110.0, 116.5 (q, J = 287.0 Hz), 119.7, 124.6, 126.5, 126.6, 127.6, 128.5, 128.8, 129.4, 129.6, 130.0, 136.0, 139.4, 155.4 (q, J = 34.8 Hz), 157.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −68.3; IR (thin film): ν_{max} (cm^{-1}) = 2944, 1688, 1491, 1430, 1246, 1189, 1149, 1111, 1026, 753, 731; ESI-MS: 348 (M^+ + 1); HRMS (ESI) calcd for $C_{19}H_{16}F_3NO_2$ (M^+): 347.1133. Found: 347.1134; m.p. 94–95 °C.

5af. Yellow oil, R_f = 0.6 (petroleum ether : EtOAc = 10 : 1), 96% yield, 98% ee [Daicel Chiralcel OD-H, hexane : 2-propanol = 99 : 1, v = 0.5 mL min^{-1}, λ = 254 nm, t (major) = 17.22 min, t (minor) = 19.87 min]; $[\alpha]_D^{20}$ − 140.0 (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.13 (dd, J = 16.5, 8.4 Hz, 1H), 3.83 (ddd, J = 17.1, 6.9, 3.3 Hz, 1H), 5.70 (ddd, J = 11.7, 4.2, 3.3 Hz, 1H), 6.01–6.10 (m, 1H), 6.57 (d, J = 7.8 Hz, 1H), 6.68 (d, J = 3.3 Hz, 1H), 6.80–6.81 (m, 2H), 6.97–7.03 (m, 1H), 7.16–7.26 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.6, 53.1, 116.3 (q, J = 286.4 Hz), 126.4, 126.5, 126.6, 126.7, 127.3, 127.8, 128.6, 129.2, 130.0, 135.2, 139.8, 140.1, 156.3 (q, J = 36.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.6; IR (thin film): ν_{max} (cm^{-1}) = 2962, 1696, 1496, 1413, 1259, 1188, 1145, 1017, 852, 709; ESI-MS: 324 (M^+ + 1); HRMS (ESI) calcd for $C_{16}H_{12}F_3NO_2S$ (M^+): 323.0592. Found: 323.0594.

5ag. Yellow oil, R_f = 0.7 (petroleum ether : EtOAc = 10 : 1), 99% yield, 92% ee [Daicel Chiralcel OJ-H, hexane : 2-propanol = 99 : 1, v = 0.5 mL min^{-1}, λ = 254 nm, t (minor) = 18.96 min, t (major) = 20.62 min]; $[\alpha]_D^{20}$ − 16.1 (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.42–0.56 (m, 5H), 3.03 (dd, J = 15.3, 7.2 Hz, 1H), 3.74 (dd, J = 16.8, 3.3 Hz, 1H), 4.59 (br s, 1H), 5.54–5.59 (m, 1H), 5.77–5.84 (m, 1H), 7.20–7.35 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.0, 4.7, 14.4, 31.6, 59.8, 116.4 (q, J = 287.4 Hz), 124.5, 126.5, 126.7, 128.5, 128.7, 129.3, 129.9, 135.8, 140.3, 156.4 (q, J = 35.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.5; IR (thin film): ν_{max} (cm^{-1}) = 2962, 1698, 1604, 1500, 1418, 1260, 1209, 1152, 1101, 1022, 799, 734; ESI-MS: 281 (M^+); HRMS (ESI) calcd for $C_{15}H_{14}F_3NO$ (M^+): 281.1027. Found: 281.1023.

5ah. Yellow oil, R_f = 0.7 (petroleum ether : EtOAc = 10 : 1), 75% yield, 94% ee [Daicel Chiralcel OJ-H, hexane : 2-propanol = 99 : 1, v = 0.5 mL min^{-1}, λ = 254 nm, t (major) = 18.68 min, t (minor) = 22.25 min]; $[\alpha]_D^{20}$ − 87.2 (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (t, J = 7.5 Hz, 3H), 1.14–1.16 (m, 2H), 3.13 (dd, J = 16.8, 8.7 Hz, 1H), 3.70–3.95 (m, 1H), 5.41–5.50 (m, 1H), 5.61 (d, J = 11.4 Hz, 1H), 5.91 (t, J = 10.8 Hz, 1H), 7.30–7.51 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.8, 26.0, 31.5, 56.4, 116.4 (q, J = 286.7 Hz), 124.3, 126.8, 128.9, 129.3, 129.4, 129.6, 135.1, 140.8, 157.0 (q, J = 35.1 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −67.2; IR (thin film): ν_{max} (cm^{-1}) = 2968, 1695, 1496, 1417, 1186, 1148, 851, 759, 729, 672; ESI-MS: 269 (M^+); HRMS (ESI) calcd for $C_{14}H_{14}F_3NO$ (M^+): 269.1027. Found: 269.1030.

5ba. White solid, R_f = 0.7 (petroleum ether : EtOAc = 10 : 1), 83% yield, 96% ee [Daicel Chiralcel OJ-H, hexane : 2-propanol = 99 : 1, v = 0.5 mL min^{-1}, λ = 254 nm, t (minor) = 13.15 min, t (major) = 14.30 min]; $[\alpha]_D^{20}$ − 215.0 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08 (dd, J = 16.4, 8.4 Hz, 1H), 3.78 (dd, J = 16.4, 3.2 Hz, 1H), 5.63 (ddd, J = 11.6, 4.4, 3.2 Hz, 1H), 6.04–6.08 (m, 1H), 6.25–6.29 (m, 1H), 6.57–6.62 (m, 1H), 6.68–6.71 (m, 1H) 6.93 (dd, J = 8.4, 2.8 Hz, 1H), 6.97–7.00 (m, 2H), 7.10–7.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.4, 58.0, 113.1, 113.3, 115.4, 115.6, 116.6 (q, J = 287.2 Hz), 125.9, 127.6, 128.2, 128.4, 128.7, 128.9, 131.0, 131.0, 131.8, 131.9,

136.8, 142.5, 142.6, 156.6 (q, J = 35.2 Hz), 161.1, 163.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.6, −112.2 (m); IR (thin film): ν_{max} (cm^{-1}) = 2962, 1695, 1497, 1260, 1210, 1208, 1179, 1144, 1017, 780, 699; ESI-MS: 336 (M^+ + 1); HRMS (ESI) calcd for $C_{18}H_{13}F_4NONa$ (M^+ + Na): 358.0826. Found: 358.0826; m.p. 74–76 °C.

5ca. White solid, R_f = 0.7 (petroleum ether : EtOAc = 10 : 1), 72% yield, 98% ee [Daicel Chiralcel OJ-H, hexane : 2-propanol = 99 : 1, ν = 0.5 mL min^{-1}, λ = 254 nm, t (major) = 12.13 min, t (minor) = 13.00 min]; $[\alpha]_D^{20}$ − 125.7 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (dd, J = 16.8, 8.8 Hz, 1H), 3.78 (ddd, J = 16.8, 6.0, 3.2 Hz, 1H), 5.57 (ddd, J = 11.6, 7.6, 4.4 Hz, 1H), 5.98–6.05 (m, 1H), 6.12 (d, J = 8.4 Hz, 1H), 6.64–6.66 (m, 1H), 6.95 (d, J = 7.2 Hz, 2H), 7.00 (dd, J = 8.4, 2.4 Hz, 1H), 7.13–7.21 (m, 3H), 7.32 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.2, 57.9, 116.2 (q, J = 287.0 Hz), 123.1, 125.8, 127.5, 128.4, 128.5, 128.8, 129.6, 131.5, 131.6, 134.2, 136.7, 142.1, 156.4 (q, J = 35.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −68.1; IR (thin film): ν_{max} (cm^{-1}) = 2961, 1699, 1487, 1418, 1262, 1189, 1102, 1081, 813, 699; ESI-MS: 418 (M^+ + Na); HRMS (ESI) calcd for $C_{18}H_{13}F_3NONa$ (M^+ + Na): 418.0025. Found: 418.0020; m.p. 178–180 °C.

5da. White solid, R_f = 0.6 (petroleum ether : EtOAc = 10 : 1), 88% yield, 99% ee [Daicel Chiralcel OJ-H, hexane : 2-propanol = 99 : 1, ν = 0.5 mL min^{-1}, λ = 254 nm, t (major) = 9.83 min, t (minor) = 10.94 min]; $[\alpha]_D^{20}$ − 206.4 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 3.05 (dd, J = 17.2, 7.2 Hz, 1H), 3.82 (ddd, J = 16.4, 6.0, 2.8 Hz, 1H), 5.59 (ddd, J = 11.2, 4.0, 2.8 Hz, 1H), 6.05–6.11 (m, 1H), 6.19 (d, J = 8.0 Hz, 1H), 6.67–6.72 (m, 2H), 6.97–6.99 (m, 3H), 7.15–7.24 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 31.5, 58.1, 116.4 (q, J = 287.2 Hz), 126.6, 127.0, 127.3, 128.1, 128.2, 129.0, 129.2, 130.0, 132.4, 137.2, 139.1, 139.7, 156.7 (q, J = 34.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −68.2; IR (thin film): ν_{max} (cm^{-1}) = 2962, 1682, 1503, 1417, 1260, 1211, 1179, 1017, 798, 753, 698; ESI-MS: 332 (M^+ + 1); HRMS (ESI) calcd for $C_{19}H_{16}F_3NONa$ (M^+ + Na): 354.1076. Found: 354.1083; m.p. 121–123 °C.

5ea. White solid, R_f = 0.6 (petroleum ether : EtOAc = 10 : 1), 84% yield, 98% ee [Daicel Chiralcel OJ-H, hexane : 2-propanol = 99 : 1, ν = 0.5 mL min^{-1}, λ = 254 nm, t (major) = 11.96 min, t (minor) = 12.89 min]; $[\alpha]_D^{20}$ − 200.5 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.26 (ddd, J = 17.2, 6.8, 3.2 Hz, 1H), 3.38 (s, 3H), 3.68 (dd, J = 16.8, 8.8 Hz, 1H), 3.80 (s, 3H), 5.42 (br s, 1H), 5.60 (ddd, J = 11.2, 4.4, 3.2 Hz, 1H), 6.05–6.11 (m, 1H), 6.37 (d, J = 2.4 Hz, 1H), 6.66–6.68 (m, 1H), 7.01–7.04 (m, 2H), 7.14–7.24 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 55.3, 55.7, 58.1, 99.4, 106.4, 116.4 (q, J = 287.1 Hz), 121.0, 127.1, 127.4, 128.2, 129.0, 136.7, 137.1, 156.3, 156.5 (q, J = 35.5 Hz), 158.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −68.3; IR (thin film): ν_{max} (cm^{-1}) = 2961, 1682, 1610, 1588, 1457, 1261, 1195, 1145, 1112, 948, 802, 700; ESI-MS: 378 (M^+ + 1); HRMS (ESI) calcd for $C_{20}H_{19}F_3NO_3$ (M^+ + 1): 378.1312. Found: 378.1327; m.p. 81–83 °C.

Procedure for the hydrogenation of 5aa

To a solution of **5aa** (11.2 mg, 0.04 mmol) in MeOH (2 mL) was added 10% Pd/C (3.5 mg, 0.004 mmol) under Ar atmosphere. Then the reactor was charged with 1 atm of H_2 and then the reaction mixture was stirred at room temperature. When **5aa** was fully consumed (monitored by TLC), the reaction mixture was filtered through a celite pad. After removal of the solvent, the residue was purified by silica gel column chromatography (petroleum ether : EtOAc = 20 : 1) to give **6** (11.3 mg, 99% yield).

6 Colorless oil, R_f = 0.5 (petroleum ether : EtOAc = 10 : 1), 99% ee [Daicel Chiralcel OD-H, hexane : 2-propanol = 99 : 1, ν = 0.5 mL min^{-1}, λ = 254 nm, t (major) = 7.42 min, t (minor) = 8.81 min]; $[\alpha]_D^{20}$ − 69.9 (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61–1.6 (m, 4H), 2.69–2.77 (m, 1H), 2.93–3.04 (m, 1H), 5.42 (dd, J = 12.0, 3.3 Hz, 1H), 7.06–7.09 (m, 1H), 7.25–7.41 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 29.1, 29.2, 60.1, 116.1 (q, J = 286.8 Hz), 126.9, 127.2, 127.3, 127.8, 128.4, 129.0, 129.4, 129.7, 134.9, 138.8, 140.8, 156.8 (q, J = 35.9 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −68.9; IR (thin film): ν_{max} (cm^{-1}) = 2958, 1693, 1491, 1453, 1202, 1180, 1024, 800, 699; ESI-MS: 319 (M^+); HRMS (ESI) calcd for $C_{18}H_{16}F_3NO$ (M^+): 319.1184. Found: 319.1183.

Procedure for the deprotection of 5aa

To a solution of **5aa** (38.3 mg, 0.12 mmol) in MeOH (2 mL) was added $NaBH_4$ (27.5 mg, 0.72 mmol) under argon atmosphere. The resulting mixture was stirred at room temperature. When **5aa** was fully consumed (monitored by TLC), the solvent was evaporated under reduced pressure. Then the residue was purified by silica gel column chromatography (petroleum ether : EtOAc = 20 : 1) to give **7** (22.9 mg, 86% yield).

7 White solid, R_f = 0.4 (petroleum ether : EtOAc = 10 : 1), 99% ee [Daicel Chiralcel OD-H, hexane : 2-propanol = 99 : 1, ν = 0.5 mL min^{-1}, λ = 254 nm, t (major) = 16.74 min, t (minor) = 25.15 min]; $[\alpha]_D^{20}$ − 65.0 (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.35 (dd, J = 15.9, 5.4 Hz, 1H), 3.74–3.81 (m, 1H), 4.85 (br s, 1H), 5.47 (d, J = 10.2 Hz, 1H), 5.92–5.95 (m, 1H), 6.66 (d, J = 7.5 Hz, 1H), 6.89–6.94 (m, 1H), 7.02–7.11 (m, 2H), 7.27–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.6, 62.8, 121.8, 122.3, 125.5, 127.1, 127.6, 128.5, 128.7, 130.8, 135.7, 143.5, 146.9; IR (thin film): ν_{max} (cm^{-1}) = 3317, 2959, 2924, 1599, 1490, 1470, 1258, 1092, 1018, 838, 799, 757, 700; MS (EI): 221 (M^+); HRMS (EI) calcd for $C_{16}H_{15}N$ (M^+): 221.1204. Found: 221.1203; m.p. 122–123 °C.

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Notes and references

1 For a book chapter:T. L. Gilchrist, in *Heterocyclic Chemistry*, 3rd edn, Addison Wesley, Essex, England, 1997, p. 414.
2 (*a*) T. Kametani and K. Fukumoto, *Heterocycles*, 1975, **3**, 931; (*b*) M. Kawase, S. Saito and N. Motohashi, *Int. J. Antimicrob. Agents*, 2000, **14**, 193; (*c*) V. Kouznetsov, A. Palma and C. Ewert, *Curr. Org. Chem.*, 2001, **5**, 519.

3 H. Ogawa, H. Yamashita, K. Kondo, Y. Yamamura, H. Miyamoto, K. Kan, K. Kitano, M. Tanaka, K. Nakaya, S. Nakamura, T. Mori, M. Tominaga and Y. Yabuuchi, *J. Med. Chem.*, 1996, **39**, 3547.

4 K. Kondo, H. Ogawa, H. Yamashita, H. Miyamoto, M. Tanaka, K. Nakaya, K. Kitano, Y. Yamamura, S. Nakamura, T. Onogawa, T. Mori and M. Tominaga, *Bioorg. Med. Chem.*, 1999, **7**, 1743.

5 A. Palma, A. F. Yépes, S. M. Leal, C. A. Coronado and P. Escobar, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2360.

6 Selected examples: (*a*) M. Qadir, J. Cobb, P. W. Sheldrake, N. Whittall, A. J. P. White, K. K. Hii, P. N. Horton and M. B. Hursthouse, *J. Org. Chem.*, 2005, **70**, 1545; (*b*) M. Seto, K. Aikawa, N. Miyamoto, Y. Aramaki, N. Kanzaki, K. Takashima, Y. Kuze, Y. Iizawa, M. Baba and M. Shiraishi, *J. Med. Chem.*, 2006, **49**, 2037; (*c*) D. Boeglin, D. Bonnet and M. Hibert, *J. Comb. Chem.*, 2007, **9**, 487; (*d*) V. Singh and S. Batra, *Eur. J. Org. Chem.*, 2007, 2970; (*e*) S. Kotha and V. R. Shah, *Eur. J. Org. Chem.*, 2008, 1054; (*f*) R. Abonia, P. Cuervo, B. Insuasty, J. Quiroga, M. Nogueras and J. Cobo, *Eur. J. Org. Chem.*, 2008, 4684.

7 Selected examples of asymmetric synthesis of 1-benzazepine: (*a*) R. A. Bunce, L. B. Johnson and E. M. Holt, *J. Heterocycl. Chem.*, 2004, **41**, 563; (*b*) S. L. Gómez Ayala, E. Stashenko, A. Palma, A. Bahsas and J. M. Amaro-Luis, *Synlett*, 2006, 2275; (*c*) A. F. Yépez, A. Palma, E. Stashenko, A. Bahsas and J. M. Amaro-Luis, *Tetrahedron Lett.*, 2006, **47**, 5825; (*d*) O. Hara, T. Koshizawa, K. Makino, I. Kunimune, A. Namiki and Y. Hamada, *Tetrahedron*, 2007, **63**, 6170; (*e*) C. Li, X. Li and R. Hong, *Org. Lett.*, 2009, **11**, 4036; (*f*) D.-J. Cheng, H.-B. Wu and S.-K. Tian, *Org. Lett.*, 2011, **13**, 5636.

8 For reviews: (*a*) H. Miyabe and Y. Takemoto, *Synlett*, 2005, 1641; (*b*) R. Takeuchi and S. Kezuka, *Synthesis*, 2006, 3349; (*c*) G. Helmchen, A. Dahnz, P. Dübon, M. Schelwies and R. Weihofen, *Chem. Commun.*, 2007, 675; (*d*) G. Helmchen, in *Iridium Complexes in Organic Synthesis*, ed. L. A. Oro and C. Claver, Wiley-VCH, Weinheim, Germany, 2009, p. 211; (*e*) J. F. Hartwig and L. M. Stanley, *Acc. Chem. Res.*, 2010, **43**, 1461; (*f*) J. F. Hartwig and M. J. Pouy, *Top. Organomet. Chem.*, 2011, **34**, 169; (*g*) W.-B. Liu, J.-B. Xia and S.-L. You, *Top. Organomet. Chem.*, 2012, **38**, 155.

9 Selected examples: (*a*) J. P. Janssen and G. Helmchen, *Tetrahedron Lett.*, 1997, **38**, 8025; (*b*) K. Tissot-Croset, D. Polet and A. Alexakis, *Angew. Chem., Int. Ed.*, 2004, **43**, 2426; (*c*) A. Alexakis and D. Polet, *Org. Lett.*, 2004, **6**, 3529; (*d*) T. Graening and J. F. Hartwig, *J. Am. Chem. Soc.*, 2005, **127**, 17192; (*e*) S. Streiff, C. Welter, M. Schelwies, G. Lipowsky, N. Miller and G. Helmchen, *Chem. Commun.*, 2005, 2957; (*f*) D. J. Weix and J. F. Hartwig, *J. Am. Chem. Soc.*, 2007, **129**, 7720.

10 Selected examples: (*a*) T. Ohmura and J. F. Hartwig, *J. Am. Chem. Soc.*, 2002, **124**, 15164; (*b*) C. Shu and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2004, **43**, 4794; (*c*) I. Lyothier, C. Defieber and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2006, **45**, 6204; (*d*) C. Defieber, M. A. Ariger, P. Moriel and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2007, **46**, 3139; (*e*) M. Ueda and J. F. Hartwig, *Org. Lett.*, 2010, **12**, 92; (*f*) S. Zheng, N. Gao, W. Liu, D. Liu, X. Zhao and T. Cohen, *Org. Lett.*, 2010, **12**, 4454; (*g*) J. F. Teichert, M. Fañanás-Mastral and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2011, **50**, 688; (*h*) M. Gärtner, S. Mader, K. Seehafer and G. Helmchen, *J. Am. Chem. Soc.*, 2011, **133**, 2072; (*i*) N. Gao, S. Zheng, W. Yang and X. Zhao, *Org. Lett.*, 2011, **13**, 1514; (*j*) W. Huang, S. Zheng, J. Tang and X. Zhao, *Org. Biomol. Chem.*, 2011, **9**, 7897.

11 Selected examples: (*a*) C. A. Kiener, C. Shu, C. Incarvito and J. F. Hartwig, *J. Am. Chem. Soc.*, 2003, **125**, 14272; (*b*) C. Shu, A. Leitner and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2004, **43**, 4797; (*c*) H. Miyabe, A. Matsumura, K. Moriyama and Y. Takemoto, *Org. Lett.*, 2004, **6**, 4631; (*d*) B. P. Bondzic, A. Farwick, J. Liebich and P. Eilbracht, *Org. Biomol. Chem.*, 2008, **6**, 3723.

12 (*a*) H. He, X.-J. Zheng, Y. Li, L.-X. Dai and S.-L. You, *Org. Lett.*, 2007, **9**, 4339; (*b*) W.-B. Liu, H. He, L.-X. Dai and S.-L. You, *Org. Lett.*, 2008, **10**, 1815; (*c*) W.-B. Liu, H. He, L.-X. Dai and S.-L. You, *Synthesis*, 2009, 2076; (*d*) J.-B. Xia, W.-B. Liu, T.-M. Wang and S.-L. You, *Chem.–Eur. J.*, 2010, **16**, 6442; (*e*) Q.-L. Xu, L.-X. Dai and S.-L. You, *Org. Lett.*, 2010, **12**, 800; (*f*) Q.-L. Xu, W.-B. Liu, L.-X. Dai and S.-L. You, *J. Org. Chem.*, 2010, **75**, 4615; (*g*) Q.-F. Wu, H. He, W.-B. Liu and S.-L. You, *J. Am. Chem. Soc.*, 2010, **132**, 11418; (*h*) J.-B. Xia, C.-X. Zhuo and S.-L. You, *Chin. J. Chem.*, 2010, **28**, 1525; (*i*) Q.-F. Wu, W.-B. Liu, C.-X. Zhuo, Z.-Q. Rong, K.-Y. Ye and S.-L. You, *Angew. Chem., Int. Ed.*, 2011, **50**, 4455; (*j*) C.-X. Zhuo, W.-B. Liu, Q.-F. Wu and S.-L. You, *Chem. Sci.*, 2012, **3**, 205.

13 H. He, W.-B. Liu, L.-X. Dai and S. L. You, *Angew. Chem., Int. Ed.*, 2010, **49**, 1496.

14 K.-Y. Ye, H. He, W.-B. Liu, L.-X. Dai and S. L. You, *J. Am. Chem. Soc.*, 2011, **133**, 19006.

15 P. A. Evans, J. E. Robinson and K. K. Moffett, *Org. Lett.*, 2001, **3**, 3269.

16 (*a*) C. Welter, R. M. Moreno, S. Streiff and G. Helmchen, *Org. Biomol. Chem.*, 2005, **3**, 3266; (*b*) R. Weihofen, O. Tverskoy and G. Helmchen, *Angew. Chem., Int. Ed.*, 2006, **45**, 5546; (*c*) A. Dahnz and G. Helmchen, *Synlett*, 2006, 697; (*d*) O. V. Singh and H. Han, *J. Am. Chem. Soc.*, 2007, **129**, 774; (*e*) J. H. Lee, S. Shin, J. Kang and S.-g. Lee, *J. Org. Chem.*, 2007, **72**, 7443.

17 We recently realized the synthesis of enantioenriched 2*H*-chromene and 2,5-dihydrobenzo[*b*]oxepine derivatives *via* Ir-catalyzed allylic etherification/RCM: H. He, K.-Y. Ye, Q.-F. Wu, L.-X. Dai and S.-L. You, *Adv. Synth. Catal.*, 2012, **354**, DOI: 10.1002/adsc.201100809, in press.

18 S. Spiess, C. Welter, G. Franck, J.-P. Taquet and G. Helmchen, *Angew. Chem., Int. Ed.*, 2008, **47**, 7652.

19 Z. H. Kudzin, P. Lyzwa, J. Luczak and G. Andrijewski, *Synthesis*, 1997, 44.

20 (*a*) A. Alexakis, S. Rosset, J. Allamand, S. March, F. Guillen and C. Benhaim, *Synlett*, 2001, 1375; (*b*) R. Naasz, L. A. Arnold, A. J. Minnaard and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2001, **40**, 927; (*c*) D. Polet and A. Alexakis, *Synthesis*, 2004, 2586.

21 P. G. M. Wuts, S. W. Ashford, A. M. Anderson and J. R. Atkins, *Org. Lett.*, 2003, **5**, 1483.

22 (*a*) K. C. Nicolaou, A. J. Roecker, R. Hughes, R. van Summeren, J. A. Pfefferkorn and N. Winssinger, *Bioorg. Med. Chem.*, 2003, **11**, 465; (*b*) D. M. Schultz and J. P. Wolfe, *Org. Lett.*, 2010, **12**, 1028.