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Note

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Access to β²-Amino Acids via Enantioselective 1,4-Arylation of β–Nitroacrylates Catalyzed by Chiral Rhodium Catalysts

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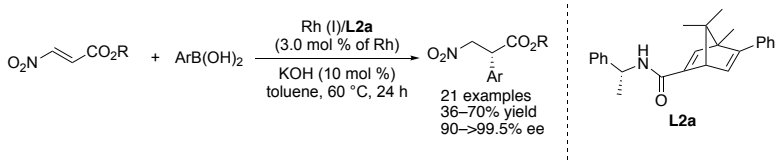
Supporting Information Placeholder



ABSTRACT: The highly enantioselective conjugate addition of a variety of arylboronic acids to β-nitroacrylates is reported to provide optically active α-aryl β-nitropropionates in up to 70% yields and >99.5% ee's, which are useful building blocks for preparing chiral β²-amino acids. The applicability of this transformation is demonstrated by converting **3aa** into the β²-amino acid **5** and transforming **3ap** to β-amino ester **7** via reduction and reductive *N*-alkylation. The latter compound is a precursor for preparing *ent*-ipatasertib.

The synthesis of chiral β-amino acids and derivatives thereof has attracted a great deal of interest[1] since they are crucial segments in numerous naturally occurring compounds of biological interest.[2] Amidst chiral β-amino acids, β²-amino acids (α-substituted-β-amino acids) are common building blocks in natural products and bioactive molecules (Figure 1). For example, bishyoscyamine (**1a**), an alkaloid isolated from *Anisodus acutangulus*, has an unusual dimeric tropane structure.[3a]

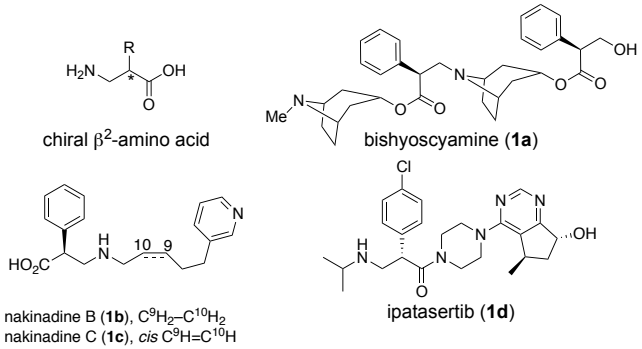


Figure 1. Compounds containing β²-amino acid moieties.

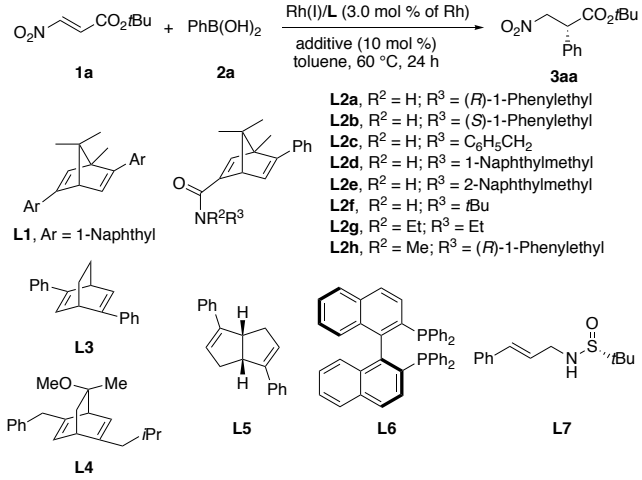
Nakinadines B (**1b**) and C (**1c**), which were isolated from the Okinawa marine sponge, *Amphimedon* sp. (SS-1059), were reported to show moderate *in vitro* cytotoxicity toward KB human epidermoid carcinoma and L1210 murine leukemia cells.[3b] Ipatasertib (**1d**) is an Akt inhibitor that is currently in clinical trials.[3c] In addition, β-peptides comprised of β²-amino acids exhibited inhibitory activity against viral infections[4a,b] and to have a specific affinity to the human somatostatin receptor 4 (hsst4) at the nano-molar level.[4c]

While the diastereoselective synthesis of β²-amino esters has been previously reported,[5] these preparations involved the aminomethylation of aldehydes[6a] and enals,[6b] respectively. Furthermore, the Rh-carbenoid induced C–H activation of *N*-substituted methylamines and their insertion into aryldiazoesters resulted in the one pot production of β²-amino esters.[6c] While the catalytic asymmetric hydrogenation of β²-enamides directly provided optically active β²-amino acids,[6d] the enantioselective hydrogenation of α-phthalimidylmethyl acrylates[6e] and α-aminomethyl acrylates[6f,g] readily gave rise to enantio-enriched β²-amino esters. Chiral β²-amino esters also can be synthesized by reducing the nitro group of α-substituted β-nitropropionates, which can be obtained by asymmetric transfer hydrogenation,[6h] or the hydrogenation[6i] of α-substituted β-nitroacrylates.

Since chiral α-substituted β-nitropropionates are crucial building blocks for the preparation of β²-amino acids and also appear to be cytotoxic,[7a] the development of an efficient synthetic route to α-substituted β-nitropropionates would be highly desirable. We envisaged that the asymmetric conjugate addition of carbon nucleophiles to prochiral β-nitroacrylates would offer a convenient and convergent access to α-chiral β-nitropropionates. In fact, the Cu(I)-catalyzed conjugate addition of dialkylzincs[7b] and trialkylaluminiums[7c] to β-nitroacrylates and the Pd(II)-catalyzed enantioselective arylation of β-nitroacrylamides[7d] gave 2-substituted-3-nitropropion-ates and -amides,

respectively, that were readily transformed into β^2-amino acids. In our recent studies,[8,9] a chiral Rh(I)/**L1** catalyst was found to have a high catalytic activity and enantioselectivity in the arylation of β-nitroolefins (S/C up to 1000).[8c] More recently, the same catalytic system was used for the enantioselective arylation of α-substituted β-nitroacrylates to access chiral $\beta^{2,2}$-amino acids.[8g] While β-nitroolefins[10] and α-substituted β-nitroacrylates[8g] were applicable acceptors in the Rh-catalyzed conjugate addition reactions,[11] the asymmetric arylation of β-nitroacrylates resulted in only moderate asymmetric induction when the diene ligand **L1** was used (Table 1, entry 1).[8g] At the same time, we also reported that chiral dienes **L2**, possessing an extra amide group, were effective ligands in achieving the highly selective arylation of *N*-DPP (diphenylphosphonyl) imines,[9c] as a result of the hydrogen bond donor ability of the amide group. Hence, we envisioned that hydrogen bond interactions between the NO_2 groups of nitroacrylates and the N−H bond of the chiral diene ligand **L2** would improve catalytic activity and enhance the degree of asymmetric induction associated with the conjugate addition[12] to β-nitroacrylates catalyzed by Rh(I)/**L2** catalysts, and we herein report our findings.

Table 1. Optimization of Reaction Conditions[a]



entry	additive	L	yield (%)[b]	ee (%)[c]
1	KOH	**L1**	31	83
2[d]	KHF_2	**L2a**	N.R.	N.D.
3[d]	KOH	**L2a**	45	90
4[e]	KOH	**L2a**	70	93
5[f]	KOH	**L2a**	68	90
6	KOH	**L2b**	50	93
7	KOH	**L2c**	24	86
8	KOH	**L2d**	45	85
9	KOH	**L2e**	50	88
10	KOH	**L2f**	26	91
11	KOH	**L2g**	73	74
12	KOH	**L2h**	53	80
13[g]	KOH	**L2a**	24	96
14[h]	KOH	**L2a**	36	70
15	LiOH	**L2a**	48	92
16	NaOH	**L2a**	48	96
17	$NaHCO_3$	**L2a**	47	96
18	K_2CO_3	**L2a**	42	96
19	KOH	**L3**	58	–65
20	KOH	**L4**	20	–17
21	KOH	**L5**	N.R.	N.D.
22	KOH	**L6**	N.R.	N.D.
23	KOH	**L7**	N.R.	N.D.

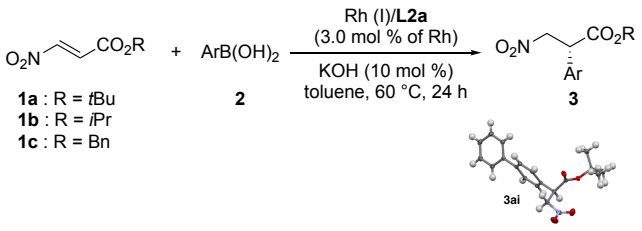
[a]Solutions of **1a** (0.2 mmol), **2a** (0.4 mmol, 2.0 equiv), $[RhCl(C_2H_4)_2]_2$ (1.5 mol %), **L** (3.6 mol %) and aq KHF_2 (3.0 M, 0.4 mL, 1.2 mmol) were stirred in toluene (1.0 mL) at 60 °C for 24 h. For other additives: 0.1 M, 0.2 mL, 0.02 mmol. [b]Isolated yield. N.R. denotes "no reaction" as judged by the ^{1}H NMR analysis of the crude products. [c]Determined by HPLC analysis. N.D. denotes "not determined." [d]At 40 °C. [e]10% of **1a** was left by analyzing the crude ^{1}H NMR spectrum. [f]At 80 °C for 12 h. [g]At 40 °C in ether. [h]At 40 °C in CH_2Cl_2.

Initial investigations involved the conjugate addition of *tert*-butyl nitroacrylate **1a** with phenylboronic acid (**2a**) (Table 1). While the desired product was not observed when the reaction was carried out in the presence of 3 mol % of Rh(I)/**L2a** under optimal reaction conditions for α-substituted β-nitroacrylates (entry 2), the desired product **3aa** was obtained in 45% yield and 90% ee when KHF_2 was replaced with KOH (entry 3). Conducting the reaction at 60 °C gave **3aa** in a gratifying 70% yield and 93% ee (entry 4), whereas the stereoselectivity decreased with the reaction run at 80 °C (entry 5). A subsequent ligand study revealed that, while high asymmetric induction was observed using both **L2a** and **L2b**, which were derived from (*R*)- and (*S*)-1-phenylethylamine respectively (entries 4 and 6), chiral diene ligands with *N*-benzyl (**L2c**), *N*-1-naphthylmethyl (**L2d**), *N*-2-naphthylmethyl (**L2e**), and *N*-*t*Bu (**L2f**) amides were found to be less efficient, giving **3aa** in 24–50% yield and 85–91% ee (entries 7–10). Conducting the asymmetric reaction with the *N*,*N*-diethyl amide ligand **L2g** and **L2h**, which is the *N*-Me analogue of **L2a**, provided compound **3aa** in 74% ee and 80% ee, respectively (entries 11 and 12), indicating the significance of hydrogen bond activation. The ensuing optimization with respect to solvents and additives resulted in no improvement in both catalytic reactivity and enantioselectivity (entries 13–18). This asymmetric transformation was also tested using chiral ligands that are known to be efficient in Rh(I)-catalyzed conjugate addition reactions. While chiral bicyclo[2.2.2]octadiene **L3**[13a] and **L4**[13b] gave **3aa** in moderate yield and ee (entries 19 and 20), no reaction was observed in the presence of chiral diene **L5**,[13c] which has a bicyclo[3.3.0] framework (entry 21). Similarly, the use of BINAP[13d] (**L6**, entry 22) and the sulfoxide-olefin hybrid ligand **L7**[13e] resulted in no desired product being produced (entry 23).

Table 2 summaries the outcome of asymmetric reactions of assorted arylboronic acids **2** with acceptors **1** under optimal reaction conditions that were presented in Table 1, entry 4. The use of methoxy-substituted phenylboronic acids (**2b**–**2d**) afforded enantio-enriched adducts **3ab**–**3ad** in 91–98% ee's and in 44–56% yields (entries 2–4). Similar results were observed when tolylboronic acids (**2e**–**2g**), 4-*t*Bu-phenylboronic acid (**2h**) and 4-biphenylboronic acid (**2i**) were used, producing adducts in 45–65% yields with 90–98% ee (entries 5–9). A single X-ray crystal analysis of **3ai** permitted the absolute configuration of newly formed chiral center to be determined as *R*.[14] 1-Naphthyl- and 2-naphthyl-boronic acids (**2j** and **2k**) were also applicable

in this asymmetric reaction, giving the corresponding adducts **3aj** and **3ak** in 65% and 45% yields with 93% and 94% ee, respectively (entries 10 and 11). While the steric hindrance of *ortho*-CF_3 substituent caused the chemical yield of compound **3al** to be decreased (entry 12), good chemical yields and high selectivity were found in the cases of its *meta*- and *para*-congeners (**2m** and **2n** in entries 13 and 14, respectively). Fluoro-, chloro- and dichloro-substituted phenylboronic acids are good reactions partners, providing addition products in 51–63% yields with 95–98% ee (entries 15–17). The scope of this method was further extended to acceptors with *i*Pr (**1b**) and Bn (**1c**) ester groups, which resulted in the formation of the corresponding products in 42–64% yield and 92–97% ee (entries 18–21).[23]

Table 2. Substrate Scope in Rh(I)/L2a-Catalyzed Asymmetric Conjugate Addition Reaction[a]

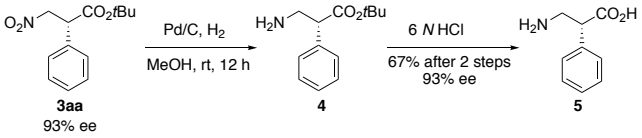


entry	1	Ar (2)	yield (%)[b]	ee (%)[c]
1[d]	**1a**	C_6H_5 (**2a**)	70 (52)(55) (**3aa**)	93
2[e]	**1a**	2-MeO-C_6H_4 (**2b**)	44 (**3ab**)	98
3	**1a**	3-MeO-C_6H_4 (**2c**)	56 (**3ac**)	94
4	**1a**	4-MeO-C_6H_4 (**2d**)	48 (**3ad**)	91
5	**1a**	2-Me-C_6H_4 (**2e**)	63 (**3ae**)	95
6	**1a**	3-Me-C_6H_4 (**2f**)	54 (**3af**)	92
7	**1a**	4-Me-C_6H_4 (**2g**)	45 (**3ag**)	90
8[e]	**1a**	4-*t*Bu-C_6H_4 (**2h**)	65 (**3ah**)	95
9	**1a**	4-Ph-C_6H_4 (**2i**)	57 (**3ai**)	98
10	**1a**	1-Naphthyl (**2j**)	65 (**3aj**)	93
11	**1a**	2-Naphthyl (**2k**)	45 (**3ak**)	94
12[e]	**1a**	2-CF_3-C_6H_4 (**2l**)	36 (**3al**)	>99.5
13	**1a**	3-CF_3-C_6H_4 (**2m**)	61 (**3am**)	98
14	**1a**	4-CF_3-C_6H_4 (**2n**)	67 (**3an**)	98
15	**1a**	4-F-C_6H_4 (**2o**)	63 (**3ao**)	96
16	**1a**	4-Cl-C_6H_4 (**2p**)	51 (**3ap**)	95
17	**1a**	3,4-Cl_2-C_6H_3 (**2q**)	51 (**3aq**)	98
18	**1b**	C_6H_5 (**2a**)	64 (**3ba**)	93
19	**1b**	1-Naphthyl (**2j**)	59 (**3bj**)	97
20	**1b**	4-F-C_6H_4 (**2n**)	43 (**3bn**)	96
21	**1c**	C_6H_5 (**2a**)	42 (**3ca**)	92

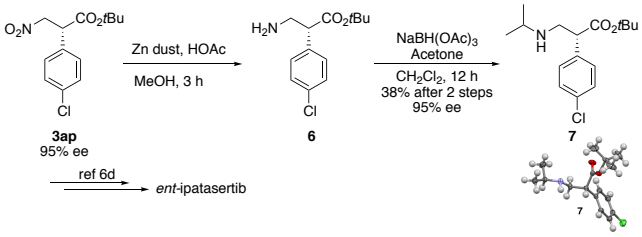
[a]Solutions of **1** (0.2 mmol), **2** (0.4 mmol, 2.0 equiv), $[RhCl(C_2H_4)_2]_2$ (1.5 mol %), **L2a** (3.6 mol %) and aq KOH (0.1 M, 0.2 mL, 0.02 mmol) were stirred in toluene (1.0 mL) at 60 °C for 24 h. [b]Isolated yield. [c]Determined by HPLC analysis. [d]Data in parenthesis was obtained from 2 mmole and 5.8 mmole (1.0 g) scale reactions, respectively. [e]An additional 3 mol % of Rh/**L2a** catalyst was added after 6 h.

The conversion of **3aa** into the corresponding amino acid further confirmed the utility of this method (Scheme 1). The hydrogenation of **3aa** in the presence of Pd/C[6h] proceeded smoothly to give the amino ester **4**, which was subsequently hydrolyzed in aq HCl to produce the β[2]-amino acid **5** in 67% over 2 steps. This method was also applicable for the preparation of a known precursor in the synthesis of an enantiomeric isomer of ipatasertib (Scheme 2).[3c,6d] The nitro group of **3ap** was reduced by means of Zn/HOAc to furnish the amine[15] which after a reductive *N*-alkylation reaction [acetone / $NaBH(OAc)_3$],[6d] gave a 38% yield of the amino ester **7** in a 2-step operation.

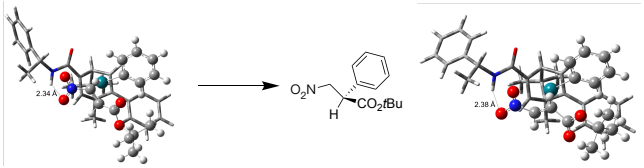
Scheme 1. Synthesis of β[2]-amino acid 5



Scheme 2. Synthesis of the *ent*-ipatasertib precursor 7



The stereochemical outcome was illustrated, in Figure 2, by carrying out DFT calculations using Gaussian 16 program[16] using hybrid B3LYP functional[17,18] in conjunction with 6-31G (d,p)[19] for the main group elements and LAN2LDZ basis set[20] for the Rh atom using toluene and the integral equation formalism variant of the polarizable continuum model (IEFPCM).[21] The results identified that the observed asymmetric reaction could be facilitated favorably via complex **8a**, in which the *tert*-butyl nitroacrylate **1a** was coordinated with the Rh-**L2a**-phenyl species via *Re*-face, by 4.6 kcal lower in energy than the corresponding *Si*-faced-coordinated complex **8b**. The steric repulsion between *tert*-butyl ester group and substituents of ligand backbone and the nitro group being hydrogen-bonded with the amide substituent[12j] accounted for the observed stereochemistry from *Re*-face addition.



8a (0.0 kcal mol^{-1}) **8b** (+4.6 kcal mol^{-1})

Figure 2. DFT-optimized putative transition structures for the asymmetric reaction to **1a**.

In summary, a highly enantioselective arylation of β-nitroacrylates was realized for the first time in the presence of Rh(I)-catalyst derived from the chiral diene ligand **L2a**. This method tolerated a variety of arylboronic acids as nucleophile donors and β-nitroacrylates as electrophiles, with addition products

being produced in up to 70% yield and >99.5% ee. The synthetic application of this asymmetric transformation was demonstrated by synthesizing β^2-amino acid **5** and β^2-amino ester **7**, a potential precursor for use in the synthesis of *ent*-ipatasertib.

Experimental section

General information

All commercial chemicals and solvents were reagent grade and were distilled before use. All reactions were carried out under an atmosphere of argon or nitrogen gas. Reactions were monitored by TLC using Merck 60 F 254 silica gel plates; zones were detected visually under ultraviolet irradiation (254 nm) or by spraying with $KMnO_4$ solution followed by heating with a heat gun or on a hot plate. Column chromatography was conducted over silica gel. NMR spectra were recorded at room temperature in deuterated solvents on Bruker spectrometers. Chemical shifts δ were recorded in parts per million (ppm) and were reported relative to the deuterated solvent signal for ^{13}C NMR spectroscopy, the residual ^1H-solvent signal for ^1H NMR spectroscopy. First order spin multiplicities are abbreviated as singlet (s), doublet (d), doublet of doublets (dd), septet (sep), and mutiplets are abbreviated as (m). High-resolution mass spectra were obtained using EI, ESI and FAB ionization methods. Optical rotations were measured on a Jasco P-2000 polarimeter. Enantiomeric excess was determined by HPLC analysis on a Chiralcel OD-H, or OJ-H and Chiralpak AD-H, or IB columns (Daicel Chemical Industries, Ltd). Substrates **1** were prepared according to the literature.[22] Boronic acids **2** that were commercially available were used as supplied and/or were prepared using methods reported in the literature.[23] Chiral diene ligands **L2** were prepared according to the reported procedure.[8a]

The following procedures were followed for the Rh-catalyzed asymmetric reactions: Under N_2 atmosphere, to a mixture of $[RhCl(C_2H_4)_2]_2$ (1.2 mg, 3.1 μmol, 3.0 mol % of Rh), chiral ligand **L2d** (2.58 mg, 7.2 μmol, 3.6 mol %), (*E*)-nitroacrylate **1** (0.2 mmol, 1.0 equiv) and arylboronic acid **2** (0.4 mmol, 3.0 equiv) were added toluene (1.0 mL) and aqueous KOH (0.1 M, 0.2 mL, 0.02 mmol, 0.1 equiv). The resulting mixture was heated to 60 °C for 24 h and the product mixture was concentrated *in vacuo* and the residue was purified by column chromatography over silica gel (hexanes / ethyl acetate = 20 / 1) to afford the desired products **3**.

(*R*)-*tert*-butyl 3-nitro-2-phenylpropanoate (3aa). Isolated as a colorless oil: 35.2 mg (0.2 mmol scale), 70% yield; 137 mg (1.0 mmol), 52% yield. The ee was determined on a Daicel Chiralpak IB column (250 mm) with hexanes / 2-propanol = 90 / 10, flow = 1.0 mL/min, wavelength = 220 nm. Retention times: 6.61 min [(*R*)-enantiomer], 9.47 min [(*S*)-enantiomer]. 93% ee. $[\alpha]_D^{28}$ +131.9 (*c* 1.00, $CHCl_3$). R_f 0.22 (hexanes / ethyl acetate, 20 / 1).^1H NMR (400 MHz, $CDCl_3$): δ 7.39–7.29 (m, 3H), 7.28–7.24 (m, 2H), 5.03 (dd, J = 14.8, 10.0 Hz, 1H), 4.49 (dd, J = 14.8, 5.2 Hz, 1H), 4.32 (dd, J = 10.0, 5.2 Hz, 1H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 133.9, 129.2, 128.4, 127.6, 82.5, 75.9, 49.7, 27.8. FT-IR (KBr, neat): $\tilde{\nu}$ 2980, 1726, 1556, 1370, 1254, 1210, 1152 cm^{-1}. HRMS (FAB/Magnetic Sector): *m/z* calcd for $C_{13}H_{18}NO_4^+$ $[M + H]^+$ 252.1236, found 252.1235.

(*R*)-*tert*-butyl 2-(2-methoxyphenyl)-3-nitropropanoate (3ab). Isolated as a colorless oil: 24.8 mg, 44% yield. The ee was determined on a Daicel Chiralcel OJ-H column (250 mm); detected at 220 nm; hexanes / 2-propanol, 90 / 10; flow = 1.0 mL/min; retention times: 10.51 min [(*R*)-enantiomer], 12.27 min [(*S*)-enantiomer]. 98% ee. $[\alpha]_D^{26}$ +77.1 (*c* 1.00, $CHCl_3$). R_f 0.17 (hexanes / ethyl acetate, 20 / 1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.26 (m, 1H), 7.15 (dd, J = 7.6, 1.6 Hz, 1H), 6.96–6.86 (m, 2H), 4.97 (dd, J = 14.4, 9.2 Hz, 1H), 4.64 (dd, J = 9.2, 5.2 Hz, 1H), 4.47 (dd, J = 14.4, 5.2, Hz, 1H), 3.83 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 156.7, 129.6, 129.3, 122.8, 120.9, 110.8, 82.0, 74.8, 55.3, 44.9, 27.8. FT-IR (KBr, neat): $\tilde{\nu}$ 2979, 2363, 1729, 1556, 1495, 1460, 1370, 1251, 1153 cm^{-1}. HRMS (EI/Magnetic Sector): *m/z* calcd for $C_{14}H_{19}NO_5^+$ $[M]^+$ 281.1263, found 281.1265.

(*R*)-*tert*-butyl 2-(3-methoxyphenyl)-3-nitropropanoate (3ac). Isolated as a colorless oil: 31.6 mg, 56% yield. The ee was determined on a Daicel Chiralpak IB column (250 mm); detected at 220 nm; hexanes / 2-propanol, 90 / 10; flow = 1.0 mL/min; retention times: 7.31 min [(*R*)-enantiomer], 20.93 min [(*S*)-enantiomer]. 94% ee. $[\alpha]_D^{26}$ +55.6 (*c* 1.00, $CHCl_3$). R_f 0.17 (hexanes / ethyl acetate, 20 / 1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.27 (dd, J = 8.0, 7.6 Hz, 1H), 6.89–6.77 (m, 3H), 5.02 (dd, J = 14.4, 10.4 Hz, 1H), 4.47 (dd, J = 14.4, 4.8 Hz, 1H), 4.29 (dd, J = 10.4, 4.8 Hz, 1H), 3.80 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 160.0, 135.2, 130.2, 119.9, 113.7, 113.6, 82.5, 75.9, 55.2, 49.6, 27.8. FT-IR (KBr, neat): $\tilde{\nu}$ 2982, 1727, 1601, 1586, 1556, 1492, 1371, 1258, 1219 cm^{-1}. HRMS (EI/Magnetic Sector): *m/z* calcd for $C_{14}H_{19}NO_5^+$ $[M]^+$ 281.1263, found 281.1263.

(*R*)-*tert*-butyl 2-(4-methoxyphenyl)-3-nitropropanoate (3ad). Isolated as a colorless oil: 27.0 mg, 48% yield. The ee was determined on a Daicel Chiralpak IB column (250 mm); detected at 220 nm; hexanes / 2-propanol, 90 / 10; flow = 1.0 mL/min; retention times: 9.17 min [(*R*)-enantiomer], 14.32 min [(*S*)-enantiomer]. 91% ee. $[\alpha]_D^{26}$ +55.7 (c 1.00, $CHCl_3$). R_f 0.17 (hexanes / ethyl acetate, 20 / 1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 4.99 (dd, J = 14.4, 10.0 Hz, 1H), 4.46 (dd, J = 14.4, 5.2 Hz, 1H), 4.26 (dd, J = 10.0, 5.2 Hz, 1H), 3.80 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 159.6, 128.9, 125.8, 114.6, 82.4, 76.1, 55.3, 48.9, 27.8. FT-IR (KBr, neat): $\tilde{\nu}$ 2979, 1725, 1610, 1556, 1513, 1369, 1303, 1252, 1152 cm^{-1}. HRMS (EI/Magnetic Sector): m/z calcd for $C_{14}H_{19}NO_5^+$ $[M]^+$ 281.1263, found 281.1265.

(*R*)-*tert*-butyl 3-nitro-2-(o-tolyl)propanoate (3ae). Isolated as a colorless oil: 33.5 mg, 63% yield. The ee was determined on a Daicel Chiralpak IB column (250 mm); detected at 220 nm; hexanes / 2-propanol, 90 / 10; flow = 1.0 mL/min; retention times: 6.85 min [(*R*)-enantiomer], 17.57 min [(*S*)-enantiomer]. 95% ee. $[\alpha]_D^{26}$ +75.9 (*c* 1.00, $CHCl_3$). R_f 0.3 (hexanes / ethyl acetate, 20 / 1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.24–7.12 (m, 4H), 5.03 (dd, J = 14.4, 10.0 Hz, 1H), 4.62 (dd, J = 10.0, 4.8 Hz, 1H), 4.42 (dd, J = 14.4, 4.8 Hz, 1H), 2.44 (s, 3H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 136.4, 132.4, 131.2, 128.2, 126.7, 126.4, 82.4, 75.2, 45.4, 27.8, 19.6. FT-IR (KBr, neat): $\tilde{\nu}$ 2979, 1727, 1556, 1370, 1253, 1152 cm^{-1}. HRMS (EI/Magnetic Sector): *m/z* calcd for $C_{14}H_{19}NO_4^+$ $[M]^+$ 265.1314, found 265.1313.

(*R*)-*tert*-butyl 3-nitro-2-(*m*-tolyl)propanoate (3af). Isolated as a colorless oil: 28.7 mg, 54% yield. The ee was determined on a Daicel Chiralpak IB column (250 mm); detected at 220 nm; hexanes / 2-propanol, 90 / 10; flow = 1.0 mL/min; retention times: 5.36 min [(*R*)-enantiomer], 7.52 min [(*S*)-enantiomer]. 92% ee. $[\alpha]_D^{26}$ +59.0 (*c* 1.00, $CHCl_3$). R_f 0.3 (hexanes / ethyl acetate, 20 / 1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.25–7.21 (m, 1H),

7.13 (d, J = 7.6 Hz, 1H), 7.06–7.03 (m, 2H), 5.02 (dd, J = 14.4, 10.0 Hz, 1H), 4.46 (dd, J = 14.4, 4.8 Hz, 1H), 4.28 (dd, J = 10.0, 4.8 Hz, 1H), 2.35 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 139.0, 133.7, 129.15, 129.05, 128.5, 124.7, 82.4, 76.0, 49.6, 27.8, 21.3. FT-IR (KBr, neat): $\tilde{\nu}$ 2981, 1726, 1556, 1370, 1252, 1150 cm^{-1}. HRMS (EI/Magnetic Sector): *m/z* calcd for $C_{14}H_{19}NO_4^+$ $[M]^+$ 265.1314, found 265.1316.

(*R*)-*tert*-butyl 3-nitro-2-(*p*-tolyl)propanoate (3ag). Isolated as a colorless oil: 23.9 mg, 45% yield. The ee was determined on a Daicel Chiralpak IB column (250 mm); detected at 220 nm; hexanes / 2-propanol, 90 / 10; flow = 1.0 mL/min; retention times: 6.51 min [(*R*)-enantiomer], 10.64 min [(*S*)-enantiomer]. 90% ee. $[\alpha]_D^{26}$ +54.0 (*c* 1.00, $CHCl_3$). R_f 0.3 (hexanes / ethyl acetate, 20 / 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, J = 8.6 Hz, 2H), 7.14 (d, J = 8.6 Hz, 2H), 5.01 (dd, J = 14.4, 10.0 Hz, 1H), 4.46 (dd, J = 14.4, 5.2 Hz, 1H), 4.28 (dd, J = 10.0, 5.2 Hz, 1H), 2.33 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 138.3, 130.8, 129.9, 127.6, 82.4, 76.1, 49.3, 27.8, 21.1. FT-IR (KBr, neat): $\tilde{\nu}$ 2980, 1727, 1514, 1416, 1371, 1253, 1210, 1153 cm^{-1}. HRMS (EI/Magnetic Sector): *m/z* calcd for $C_{14}H_{19}NO_4^+$ $[M]^+$ 265.1314, found 265.1314.

(*R*)-*tert*-butyl 2-(4-(*tert*-butyl)phenyl)-3-nitropropanoate (3ah). Isolated as a colorless oil: 40.0 mg, 65% yield. The ee was determined on a Daicel Chiralpak IB column (250 mm); detected at 220 nm; hexanes / 2-propanol, 90 / 10; flow = 1.0 mL/min; retention times: 4.96 min [(*R*)-enantiomer], 14.72 min [(*S*)-enantiomer]. 95% ee. $[\alpha]_D^{26}$ +48.7 (*c* 1.00, $CHCl_3$). R_f 0.37 (hexanes / ethyl acetate, 20 / 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J = 8.6 Hz, 2H), 7.18 (d, J = 8.6 Hz, 2H), 5.01 (dd, J = 14.8, 10.4 Hz, 1H), 4.46 (dd, J = 14.8, 4.8 Hz, 1H), 4.29 (dd, J = 10.4, 4.8 Hz, 1H), 1.43 (s, 9H) 1.31 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 151.4, 130.7, 127.4, 126.1, 82.4, 76.1, 49.3, 34.6, 31.2, 27.8. FT-IR (KBr, neat): $\tilde{\nu}$ 2966, 1727, 1555, 1369, 1252, 1152 cm^{-1}. HRMS (EI/Magnetic Sector): *m/z* calcd for $C_{17}H_{25}NO_4^+$ $[M]^+$ 307.1784, found 307.1782.

(*R*)-*tert*-butyl 2-([1,1'-biphenyl]-4-yl)-3-nitropropanoate (3ai). Isolated as an off-white solid: 37.3 mg, 57% yield. The ee was determined on a Daicel Chiralpak IB column (250 mm); detected at 220 nm; hexanes / 2-propanol, 90 / 10; flow = 1.0 mL/min; retention times: 11.28 min [(*R*)-enantiomer], 11.87 min [(*S*)-enantiomer]. 98% ee. $[\alpha]_D^{26}$ +67.0 (*c* 1.00, $CHCl_3$). M.p. 84–86 ºC. R_f 0.17 (hexanes / ethyl acetate, 20 / 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61–7.55 (m, 4H), 7.48–7.42 (m, 2H), 7.40–7.31 (m, 3H), 5.07 (dd, J = 14.4, 10.4 Hz, 1H), 4.53 (dd, J = 14.4, 5.2 Hz, 1H), 4.37 (dd, J = 10.4, 5.2 Hz, 1H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 141.4, 140.2, 132.8, 128.8, 128.2, 127.9, 127.6, 127.0, 82.6, 75.9, 49.4, 27.8. FT-IR (KBr, neat): $\tilde{\nu}$ 2978, 1727, 1556, 1487, 1413, 1370, 1253, 1152 cm^{-1}. HRMS (EI/Magnetic Sector): *m/z* calcd for $C_{19}H_{21}NO_4^+$ $[M]^+$ 327.1471, found 327.1472.

(*R*)-*tert*-butyl 2-(naphthalen-1-yl)-3-nitropropanoate (3aj). Isolated as a colorless oil: 39.2 mg, 65% yield. The ee was determined on a Daicel Chiralpak IB column (250 mm); detected at 220 nm; hexanes / 2-propanol, 90 / 10; flow = 1.0 mL/min; retention times: 11.01 min [(*R*)-enantiomer], 28.53 min [(*S*)-enantiomer]. 93% ee. $[\alpha]_D^{26}$ +124.5 (*c* 1.00, $CHCl_3$). R_f 0.35 (hexanes / ethyl acetate, 20 / 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.64–7.52 (m, 2H), 7.49–7.37 (m, 2H), 5.23–5.12 (m, 2H) 4.55 (d, J = 10.8 Hz, 1H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 134.2, 130.9, 130.1, 129.2, 129.1, 127.1, 126.2, 125.4, 125.3, 122.4, 82.7, 75.5, 45.4, 27.8. FT-IR (KBr, neat): $\tilde{\nu}$ 2978, 1726, 1556, 1513, 1370, 1254, 1153 cm^{-1}. HRMS (EI/Magnetic Sector): *m/z* calcd for $C_{17}H_{19}NO_4^+$ $[M]^+$ 301.1314, found 301.1315.

(*R*)-*tert*-butyl 2-(naphthalen-2-yl)-3-nitropropanoate (3ak). Isolated as an off-white solid: 27.2 mg, 45% yield. The ee was determined on a Daicel Chiralpak AD-H column (250 mm); detected at 220 nm; hexanes / 2-propanol, 90 / 10; flow = 1.0 mL/min; retention times: 9.36 min [(*S*)-enantiomer], 10.16 min [(*R*)-enantiomer]. 94% ee. $[\alpha]_D^{26}$ +66.0 (*c* 1.00, $CHCl_3$). M.p. 88–90 ºC. R_f 0.35 (hexanes / ethyl acetate, 20 / 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89–7.79 (m, 3H), 7.74–7.72 (m, 1H), 7.55–7.48 (m, 2H), 7.37 (dd, J = 8.4, 2.0 Hz, 1H), 5.14 (dd, J = 14.8, 10.0 Hz, 1H), 4.58 (dd, J = 14.8, 5.2 Hz, 1H), 4.50 (dd, J = 10.0, 5.2 Hz, 1H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 133.4, 133.0, 131.2, 129.1, 127.9, 127.7, 127.2, 126.7, 126.6, 125.1, 82.6, 76.0, 49.8, 27.8. FT-IR (KBr, neat): $\tilde{\nu}$ 2979, 1726, 1555, 1370, 1252, 1218, 1151 cm^{-1}. HRMS (EI/Magnetic Sector): *m/z* calcd for $C_{17}H_{19}NO_4^+$ $[M]^+$ 301.1314, found 301.1314.

(*R*)-*tert*-butyl 3-nitro-2-(2-(trifluoromethyl)phenyl)propanoate (3al). Isolated as a colorless oil: 23.0 mg, 36% yield. The ee was determined on a Daicel Chiralpak IB column (250 mm); detected at 220 nm; hexanes / 2-propanol, 90 / 10; flow = 1.0 mL/min; retention times: 5.84 min [(*R*)-enantiomer], 6.19 min [(*S*)-enantiomer]. 99.5% ee. $[\alpha]_D^{26}$ +75.9 (*c* 1.00, $CHCl_3$). R_f 0.25 (hexanes / ethyl acetate, 20 / 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.0 Hz, 1H), 7.56 (dd, J = 8.0, 7.2 Hz, 1H), 7.50–7.41 (m, 2H), 4.98 (dd, J = 14.8, 10.4 Hz, 1H), 4.79 (dd, J = 10.4, 4.0, Hz, 1H), 4.41 (dd, J = 14.8, 4.0 Hz, 1H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 132.5, 129.2 (q, J = 30.0 Hz), 128.61, 128.55, 127.0 (q, J = 6.0 Hz), 124.0 (q, J = 272.0 Hz), 83.0, 75.3, 45.3, 27.7. FT-IR (KBr, neat): $\tilde{\nu}$ 2980, 1730, 1561, 1376, 1314, 1255, 1156 cm^{-1}. HRMS (FAB/Magnetic Sector): *m/z* calcd for $C_{14}H_{17}F_3NO_4^+$ $[M + H]^+$ 320.1110, found 320.1108.

(*R*)-*tert*-butyl 3-nitro-2-(3-(trifluoromethyl)phenyl)propanoate (3am). Isolated as a colorless oil: 39.1 mg, 61% yield. The ee was determined on a Daicel Chiralpak IB column (250 mm); detected at 220 nm; hexanes / 2-propanol, 90 / 10; flow = 1.0 mL/min; retention times: 6.43 min [(*R*)-enantiomer], 7.65 min [(*S*)-enantiomer]. 98% ee. $[\alpha]_D^{26}$ +62.0 (*c* 1.00, $CHCl_3$). R_f 0.25 (hexanes / ethyl acetate, 20 / 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 7.2 Hz, 1H), 7.56–7.42 (m, 3H), 5.05 (dd, J = 14.4, 9.6 Hz, 1H), 4.53 (dd, J = 14.4, 5.6 Hz, 1H), 4.40 (dd, J = 9.6, 5.6 Hz, 1H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 135.0, 131.7 (q, J = 32.0 Hz), 131.2, 129.8, 125.4 (q, J = 3.0 Hz), 124.8 (q, J = 3.0 Hz), 123.7 (q, J = 271.0 Hz), 83.2, 75.6, 49.4, 27.7. FT-IR (KBr, neat): $\tilde{\nu}$ 2980, 1729, 1562, 1372, 1330, 1256, 1154 cm^{-1}. HRMS (FAB/Magnetic Sector): *m/z* calcd for $C_{14}H_{17}F_3NO_4^+$ $[M + H]^+$ 320.1110, found 320.1110.

(*R*)-*tert*-butyl 3-nitro-2-(4-(trifluoromethyl)phenyl)propanoate (3an). Isolated as a colorless oil: 42.8 mg, 67% yield. The ee was determined on a Daicel Chiralpak IB column (250 mm); detected at 220 nm; hexanes / 2-propanol, 90 / 10; flow = 1.0 mL/min; retention times: 7.01 min [(*R*)-enantiomer], 9.25 min [(*S*)-enantiomer]. 98% ee. $[\alpha]_D^{26}$ +62.4 (*c* 1.00, $CHCl_3$). R_f 0.25 (hexanes / ethyl acetate, 20 / 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 5.04 (dd, J = 14.8, 9.6 Hz, 1H), 4.52 (dd, J = 14.8, 5.6 Hz, 1H), 4.40 (dd, J = 9.6, 5.6 Hz, 1H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 137.9, 130.9 (q, J = 33.0 Hz), 128.3, 126.2 (q,

J = 4.0 Hz), 123.8 (q, J = 270.0 Hz), 83.2, 75.6, 49.5, 27.7. FT-IR (KBr, neat): $\tilde{\nu}$ 2982, 1729, 1561, 1421, 1372, 1326, 1256, 1154 cm^{-1}. HRMS (FAB/Magnetic Sector): *m/z* calcd for $C_{14}H_{17}F_3NO_4^+$ $[M + H]^+$ 320.1110, found 320.1110.

(*R*)-*tert*-butyl 2-(4-fluorophenyl)-3-nitropropanoate (3ao). Isolated as a colorless oil: 33.9 mg, 63% yield. The ee was determined on a Daicel Chiralcel OD-H column (250 mm); detected at 220 nm; hexanes / 2-propanol, 90 / 10; flow = 1.0 mL/min; retention times: 10.27 min [(*S*)-enantiomer], 10.91 min [(*R*)-enantiomer]. 96% ee. $[\alpha]_D^{26}$ +64.8 (*c* 1.00, $CHCl_3$). R_f 0.22 (hexanes / ethyl acetate, 20 / 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.21 (m, 2H), 7.09–7.02 (m, 2H), 5.00 (dd, J = 14.4, 10.0 Hz, 1H), 4.48 (dd, J = 14.4, 5.2, Hz 1H), 4.31 (dd, J = 10.0, 5.2 Hz, 1H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 165.1 (d, J = 246.0 Hz), 129.7, 129.5 (d, J = 8.0 Hz), 116.2 (d, J = 22.0 Hz), 82.7, 75.9, 48.9, 27.7. FT-IR (KBr, neat): $\tilde{\nu}$ 2983, 1728, 1605, 1157, 1510, 1418, 1372, 1228, 1152 cm^{-1}. HRMS (EI/Magnetic Sector): *m/z* calcd for $C_{13}H_{16}FNO_4^+$ $[M]^+$ 269.1063, found 269.1062.

(*R*)-butyl 2-(4-chlorophenyl)-3-nitropropanoate (3ap). Isolated as an off-white solid: 29.3 mg, 51% yield. The ee was determined on a Daicel Chiralpak IB column (250 mm); detected at 220 nm; hexanes / 2-propanol, 90 / 10; flow = 1.0 mL/min; retention times: 7.47 min [(*R*)-enantiomer], 10.11 min [(*S*)-enantiomer]. 95% ee. $[\alpha]_D^{26}$ +67.5 (*c* 1.00, $CHCl_3$). M.p. 60–62 ºC. R_f 0.27 (hexanes / ethyl acetate, 20 / 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 5.00 (dd, J = 14.4, 10.0 Hz, 1H), 4.48 (dd, J = 14.4, 5.4 Hz, 1H), 4.30 (dd, J = 10.0, 5.4 Hz, 1H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 134.5, 132.4, 129.5, 129.2, 82.9, 75.7, 49.1, 27.8. FT-IR (KBr, neat): $\tilde{\nu}$ 2980, 1726, 1556, 1492, 1370, 1254, 1152 cm^{-1}. HRMS (EI/Magnetic Sector): *m/z* calcd for $C_{13}H_{16}ClNO_4^+$ $[M]^+$ 285.0768, found 285.0768.

(*R*)-*tert*-butyl 2-(3,4-dichlorophenyl)-3-nitropropanoate (3aq). Isolated as a colorless oil: 32.7 mg, 51% yield. The ee was determined on a Daicel Chiralpak IB column (250 mm); detected at 220 nm; hexanes / 2-propanol, 90 / 10; flow = 1.0 mL/min; retention times: 8.03 min [(*R*)-enantiomer], 15.57 min [(*S*)-enantiomer]. 98% ee. $[\alpha]_D^{26}$ +61.8 (*c* 1.00, $CHCl_3$). R_f 0.25 (hexanes / ethyl acetate, 20 / 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.12 (dd, J = 8.4, 2.4 Hz, 1H), 4.99 (dd, J = 14.8, 9.6 Hz, 1H), 4.49 (dd, J = 14.8, 5.6 Hz, 1H), 4.28 (dd, J = 9.6, 5.6 Hz, 1H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 134.0, 133.4, 132.9, 131.2, 129.9, 127.1, 83.3, 75.5, 48.8, 27.8. FT-IR (KBr, neat): $\tilde{\nu}$ 2981, 1729, 1556, 1472, 1371, 1253, 1153 cm^{-1}. HRMS (EI/Magnetic Sector): *m/z* calcd for $C_{13}H_{15}Cl_2NO_4^+$ $[M]^+$ 319.0378, found 319.0380.

(*R*)-isopropyl 3-nitro-2-phenylpropanoate (3ba). Isolated as a colorless oil: 30.4 mg, 64% yield. The ee was determined on a Daicel Chiralpak IB column (250 mm); detected at 220 nm; hexanes / 2-propanol, 90 / 10; flow = 1.0 mL/min; retention times: 9.04 min (*R*), 17.65 min (*S*). 93% ee. $[\alpha]_D^{28}$ +118.1 (*c* 1.00, $CHCl_3$). R_f 0.3 (hexanes / ethyl acetate, 20 / 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.24 (m, 5H), 5.13–5.00 (m, 2H), 4.53 (dd, J = 14.8, 5.2 Hz, 1H), 4.38 (dd, J = 10.0, 5.2 Hz, 1H), 1.27 (d, J = 6.2 Hz, 3H), 1.13 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 133.5, 129.3, 128.5, 127.8, 75.8, 69.6, 49.0, 21.6, 21.3. FT-IR (KBr, neat): $\tilde{\nu}$ 2987, 2360, 1729, 1697, 1557, 1376, 1251, 1203, 1178 cm^{-1}. HRMS (EI/Magnetic Sector): *m/z* calcd for $C_{12}H_{15}NO_4^+$ $[M]^+$ 237.1001, found 237.1000.

(*R*)-isopropyl 2-(naphthalen-1-yl)-3-nitropropanoate (3bj). Isolated as a colorless oil: 33.9 mg, 59% yield. The ee was determined on a Daicel Chiralcel OJ-H column (250 mm); detected at 220 nm; hexanes / 2-propanol, 90 / 10; flow = 1.0 mL/min; retention times: 23.04 min [(*R*)-enantiomer], 28.56 min [(*S*)-enantiomer]. 96% ee. $[\alpha]_D^{26}$ +210.5 (*c* 1.00, $CHCl_3$). R_f 0.2 (hexanes / ethyl acetate, 20 / 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.64–7.51 (m, 2H), 7.47–7.41 (m, 1H), 7.39–7.35 (m, 1H), 5.28–5.16 (m, 2H), 5.11 (sep, J = 6.4 Hz, 1H), 4.64–4.51 (m, 1H), 1.27 (d, J = 6.4 Hz, 3H), 1.09 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 134.2, 130.9, 129.7, 129.3, 129.2, 127.2, 126.2, 125.5, 125.4, 122.3, 75.4, 69.8, 44.8, 21.6, 21.2. FT-IR (KBr, neat): $\tilde{\nu}$ 2983, 1728, 1645, 1557, 1522, 1418, 1376, 1319, 1253, 1203, 1144 cm^{-1}. HRMS (EI/Magnetic Sector): *m/z* calcd for $C_{16}H_{17}NO_4^+$ $[M]^+$ 287.1158, found 287.1159.

(*R*)-isopropyl 3-nitro-2-(4-(trifluoromethyl)phenyl)propanoate (3bn). Isolated as a colorless oil: 22.0 mg, 43% yield. The ee was determined on a Daicel Chiralpak IB column (250 mm); detected at 220 nm; hexanes / 2-propanol, 90 / 10; flow = 1.0 mL/min; retention times: 7.17 min [(*R*)-enantiomer], 11.15 min [(*S*)-enantiomer]. 96% ee. $[\alpha]_D^{26}$ +117.6 (*c* 1.00, $CHCl_3$). R_f 0.17 (hexanes / ethyl acetate, 20 / 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.22 (m, 2H), 7.10–7.02 (m, 2H), 5.10–5.01 (m, 2H), 4.53 (dd, J = 14.4, 5.2 Hz, 1H), 4.37 (dd, J = 10.0, 5.2 Hz, 1H), 1.27 (d, J = 6.4 Hz, 3H), 1.13 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 162.7 (*d*, J = 247.0 Hz), 129.6 (*d*, J = 8.0 Hz), 129.3 (*d*, J = 3.0 Hz), 116.3 (*d*, J = 22.0 Hz), 75.8, 69.8, 48.3, 21.6, 21.3. FT-IR (KBr, neat): $\tilde{\nu}$ 2989, 1731, 1621, 1560, 1421, 1377, 1326, 1254, 1205 cm^{-1}. HRMS (EI/Magnetic Sector): *m/z* calcd for $C_{12}H_{14}FNO_4^+$ $[M]^+$ 255.0907, found 255.0908.

(*R*)-benzyl 3-nitro-2-phenylpropanoate (3ca). Isolated as an off-white solid: 24.0 mg, 42% yield. The ee was determined on a Daicel Chiralpak IB column (250 mm); detected at 220 nm; hexanes / 2-propanol, 90 / 10; flow = 1.0 mL/min; retention times: 13.89 min [(*R*)-enantiomer], 26.77 min [(*S*)-enantiomer]. 92% ee. $[\alpha]_D^{28}$ +98.2 (*c* 1.00, $CHCl_3$). M.p. 50–52 ºC. R_f 0.2 (hexanes / ethyl acetate, 20 / 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.18 (m, 10H), 5.22 (d, J = 12.4 Hz, 1H), 5.12 (d, J = 12.4 Hz, 1H), 5.11 (dd, J = 14.4, 10.0 Hz, 1H), 4.56 (dd, J = 14.8, 5.2 Hz, 1H), 4.48 (dd, J = 10.0, 5.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 135.1, 133.1, 129.4, 128.7, 128.6, 128.4, 128.01, 127.96, 75.7, 67.5, 48.8. FT-IR (KBr, neat): $\tilde{\nu}$ 3036, 1737, 1557, 1498, 1455, 1416, 1377, 1247, 1195 cm^{-1}. HRMS (EI/Magnetic Sector): *m/z* calcd for $C_{16}H_{15}NO_4^+$ $[M]^+$ 285.1001, found 285.1001.

General procedures for the synthesis of β²-amino acids

A 10 mL round bottle flask charged with **3aa** (50.3 mg, 0.2 mmol), and Pd/C (20 mg, 5wt%, 10%, 0.01 mmol) was evacuated and backed filled with H_2. MeOH (2 mL) was then added. After being stirred at rt for 12 h, the mixture was filtered through a pad of Celite® and the volatile was removed at reduced pressure, followed by the addition of 6 *N* HCl (10 mL). The mixture was heated to reflux, and it was cooled to rt after 12 h. The aqueous layer was extracted with ether (20 mLx3), and the aqueous layer was concentrated to give ammonium salt of compound **5** as a white solid. The solid was purified and neutralized by column chromatography on silica gel (eluting with

IPA/MeOH/NH_4OH, 5/2/1) to give **5** (22.1 mg, 67%) as a white solid.

(*R*)-3-amino-2-phenylpropanoic acid (5).[25] $[\alpha]_D^{25}$ +80.7 (*c* 0.22, H_2O) M.p. 204–206 ºC. ^{1}H NMR (400 MHz, D_2O): δ 7.48–7.32 (m, 5H), 3.80 (dd, J = 7.6, 7.6 Hz, 1H), 3.47 (dd, J = 12.8, 7.6 Hz, 1H), 3.29 (dd, J = 12.8, 7.6 Hz, 1H). ^{13}C NMR (100 MHz, D_2O): δ 178.3, 137.2, 129.3, 128.2, 128.0, 51.4, 42.3. HRMS (ESI/Q-TOF): *m/z* calcd for $C_9H_{10}NO_2^-$ $[M]^-$ 164.0717, found 164.0711.

To a 15 mL round bottle flask were added **3ap** (108.6 mg, 0.38 mmol), Zn dust (99.2 mg, 1.52 mmol), and MeOH (4 mL). At 0 °C, AcOH (4 mL) was added and the mixture was stirred for additional 3 h. Ethyl acetate (10 mL) was added after the mixture was warmed to rt. The whole mixture was neutralized with $NaHCO_{3(aq)}$, and the aqueous layer was separated, and extracted with ethyl acetate (10 mLx3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated at reduced pressure to give the crude mixture. To this mixture were added $NaBH(OAc)_3$, and CH_2Cl_2 (2 mL) under Ar atmosphere. The mixture was added anhydrous acetone (22 μL, 0.3 mmol), and after being stirred for overnight, the mixture was neutralized with 5 % $NaOH_{(aq)}$. The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated at reduced pressure to give the crude mixture, which was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 3/7) to give **7** (47.3 mg, 38%) as a white solid.

***tert*-butyl (*R*)-2-(4-chlorophenyl)-3-(isopropylamino)propanoate (7)**. The ee was determined on a Daicel Chiralpak OJ-H column (250 mm); detected at 220 nm; hexanes / 2-propanol, 90 / 10; flow = 1.0 mL/min; retention times: 3.46 min [(*R*)-enantiomer], 4.88 min [(*S*)-enantiomer]. 95% ee. $[\alpha]_D^{29}$ +15.2 (*c* 1.00, $CHCl_3$). M.p. 61–63 ºC. R_f 0.37 (hexanes / ethyl acetate, 3/ 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 3.64 (dd, J = 8.4, 6.8 Hz, 1H), 3.17 (dd, J = 12.0, 8.4 Hz, 1H), 2.84–2.73 (m, 2H), 1.39 (s, 9H), 1.37–1.25 (m, 1H), 1.03 (d, J = 6.4 Hz, 3H), 1.01 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 136.5, 133.1, 129.3, 128.8, 81.1, 52.6, 50.2, 48.3, 27.9, 22.9, 22.8. FT-IR (KBr, neat): $\tilde{\nu}$ 2968, 2931, 2869, 1724, 1506, 1491, 1367, 1257, 1147 cm^{-1}. HRMS (ESI/Q-TOF): *m/z* calcd for $C_{16}H_{25}NO_2Cl^+$ $[M+H]^+$298.1574, found 298.1577.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information containing HPLC chromatograms, and NMR spectra of addition products is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. β-Peptides: From Structure to Function. *Chem. Rev*. **2001**, *101*, 3219–3213. (b) Liu, M.; Sibi, M. P. Recent Advances in the Stereoselective Synthesis of β-Amino Acids. *Tetrahedron*, **2002**, *58*, 7991–8035. (c) Lelais, G.; Seebach, D. β²-Amino Acids—Syntheses, Occurrence in Natural Products, and Components of β-Peptides. *Biopolymers* **2004**, *76*, 206–243. (d) Davies, S. G.; Smith, A. D.; Price, P. D. The Conjugate Addition of Enantiomerically Pure Lithium Amides as Homochiral Ammonia Equivalents: Scope, Limitations and Synthetic Applications. *Tetrahedron: Asymmetry* **2005**, *16*, 2833–2891. (e) Juaristi, E.; Soloshonok, V. A. Eds. *Enantioselective Synthesis of β-Amino Acids*, 2nd ed., Wiley-VCH: Weinheim, **2005**. (f) Liljeblad, A.; Kanerva, L. T. Biocatalysis as a Profound Tool in the Preparation of Highly Enantiopure β-Amino Acids. *Tetrahedron*, **2006**, *62*, 5831–5854. (g) Haldar, D. Recent Developments in the Synthesis of Amino Acids and Analogues for Foldamers Study. *Curr. Org. Synth.* **2008**, *5*, 61–80.

(2) Kudo, F.; Miyanaga, A.; Eguchi, T. *Nat. Prod. Rep.* **2014**, *31*, 1056.

(3) (a) Geng, C.-A.; Ma, Y.-B.; Chen, J.-J. Bishyoscyamine, One Unusual Dimeric Tropane Alkaloid from *Anisodus Acutangulus*. *Chin. Chem. Lett.* **2013**, *24*, 236–238. (b) Nishi, T.; Kubota, T.; Fromont, J.; Sasaki, T.; Kobayashi, J. Nakinadines B–F: New Pyridine Alkaloids with a β-Amino Acid Moiety from Sponge Amphimedon sp. *Tetrahedron*, **2008**, *64*, 3127–3132. (c) Blake, J. F.; Xu, R.; Bencsik, J. R.; Xiao, D.; Kallan, N. C.; Schlachter, S.; Mitchell, I. S.; Spencer, K. L.; Banka, A. L.; Wallace, E. M.; Gloor, S. L.; Martinson, M.; Woessner, R. D.; Vigers, G. P. A.; Brandhuber, B. J.; Liang, J.; Safina, B. S.; Li, J.; Zhang, B.; Chabot, C.; Do, S.; Lee, L.; Oeh, J.; Sampath, D.; Lee, B. B.; Lin, K.; Liederer, B. M.; Skelton, N. J. Discovery and Preclinical Pharmacology of a Selective ATP-Competitive Akt Inhibitor (GDC-0068) for the Treatment of Human Tumors. *J. Med. Chem.* **2012**, *55*, 8110–8127.

(4) (a) Stephens, O. M.; Kim, S.; Welch, B. D.; Hodsdon, M. E.; Kay, M. S.; Schepartz, A. Inhibiting HIV Fusion with a β-Peptide Foldamer. *J. Am. Chem. Soc*. **2005**, *127*, 13126–13127. (b) English, E. P.; Chumanov, R. S.; Gellman, S. H.; Compton, T. Rational Development of β-Peptide Inhibitors of Human Cytomegalovirus Entry. *J. Biol. Chem.* **2006**, *281*, 2661–2667. (c) Gademann, K.; Kimmerlin, T.; Hoyer, D.; Seebach, D. Peptide Folding Induces High and Selective Affinity of a Linear and Small β-Peptide to the Human Somatostatin Receptor 4. *J. Med. Chem*. **2001**, *44*, 2460–2468.

(5) (a) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. New Procedure for the Direct Generation of Titanium Enolates. Diastereoselective Bond Constructions with Representative Electrophiles. *J. Am. Chem. Soc*. **1990**, *112*, 8215–8216. (b) Hintermann, T.; Seebach, D. Synthesis of a β-Hexapeptide from (*R*)-2-Aminomethylalkanoic Acids and Structural Investigations. *Synlett* **1997**, 437–438. (c) Beddow, J. E.; Davies, S. G.; Smith, A. D.; Russell, A. J. Asymmetric Synthesis of 2-Alkyl- and 2-aryl-3-aminopropionic acids (β²-Amino Acids) from (*S*)-*N*-Acryloyl-5,5-dimethyloxazolidin-2-one SuperQuat Derivatives. *Chem. Commun*. **2004**, 2778–2779. (d) Tessier, A.; Lahmar, N.; Pytkowicz, J.; Brigaud, T. Highly Diastereoselective Synthetic Route to Enantiopure β²-Amino Acids and γ-Amino Alcohols Using a Fluorinated Oxazolidine (Fox) as Chiral Auxiliary. *J. Org. Chem.* **2008**, *73*, 3970–3973.

(6) (a) Chi, Y.; Gellman, S. H. Enantioselective Organocatalytic Aminomethylation of Aldehydes: A Role for Ionic Interactions and Efficient Access to β²-Amino Acids. *J. Am. Chem. Soc*. **2006**, *128*, 6804–6805. (b) Xu, J.; Chen, X.; Wang, M.; Zheng, P.; Song, B.-A.; Chi, Y. R. Aminomethylation of Enals through Carbene and Acid Cooperative Catalysis: Concise Access to β²-Amino Acids. *Angew. Chem. Int. Ed.* **2015**, *54*, 5161–5165. (c) Davies, H. M. L.; Venkataramani, C. Catalytic Enantioselective Synthesis of β²-Amino Acids. *Angew. Chem. Int. Ed.* **2002**, *41*, 2197–2199. (d) Remarchuk, T.; Babu, S.; Stults, J.; Zanotti-Gerosa, A.; Roseblade, S.; Yang, S.; Huang, P.; Sha, C.; Wang, Y. An Efficient Catalytic Asymmetric Synthesis of a β²-Amino Acid on Multikilogram Scale. *Org. Process Res. Dev.* **2014**, *18*, 135–141. (e) Huang, H.; Liu, X.; Deng, J.; Qiu, M.; Zheng, Z. Rhodium-Catalyzed Enantioselective Hydrogenation of β-Phthalimide Acrylates to

Synthesis of β²-Amino Acids. *Org. Lett.* **2006**, *8*, 3359–3362. (f) Qiu, L.; Prashad, M.; Hu, B.; Prashad, K.; Repic, O.; Blacklock, T. J.; Kwong, F. Y.; Kok, S. H. L.; Lee, H. W.; Chan, A. S. C. Enantioselective Hydrogenation of α-Aminomethylacrylates Containing a Free N–H Group for the Synthesis of β-Amino Acid Derivatives. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104,* 16787–16792. (g) Guo, Y.; Shao, G.; Li, L.; Wu, W.; Li, R.; Li, J.; Song, J.; Qiu, L.; Prashad, M.; Kwong, F. Y. A General Approach to the Synthesis of β²-Amino Acid Derivatives via Highly Efficient Catalytic Asymmetric Hydrogenation of α-Aminomethylacrylates. *Adv. Synth. Catal.* **2010**, *352,* 1539–1553. (h) Martin, N. J. A.; Chen, X.; List, B. Organocatalytic Asymmetric Transferhydrogenation of β-Nitroacrylates: Accessing β²-Amino Acids. *J. Am. Chem. Soc.* **2008**, *130*, 13862–13863. (i) Li, S.; Xiao, T.; Li, D.; Zhang, X. First Iridium-Catalyzed Highly Enantioselective Hydrogenation of β-Nitroacrylates. *Org. Lett.* **2015**, *17*, 3782–3785.

(7) (a) Csuk, R.; Heller, L.; Siewert, B.; Gutnov, A.; Seidelmann, O.; Wendisch, V. β-Nitro Substituted Carboxylic Acids and Their Cytotoxicity. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4011–4013. (b) Eilitz, U.; Leßmann, F.; Seidelmann, O.; Wendisch, V. Stereoselective Synthesis of β²-Amino Acids by Michael Addition of Diorgano Zinc Reagents to Nitro Acrylates. *Tetrahedron: Asymmetry* **2003**, *14*, 189–191. (c) Eilitz, U.; Leßmann, F.; Seidelmann, O.; Wendisch, V. Stereoselective Michael Addition of Trimethyl Aluminium to Nitro Acrylates: A Route to 2-Methyl-3-amino Propionic Acid. *Tetrahedron: Asymmetry* **2003**, *14*, 3095–3097. (d) Petri, A.; Seidelmann, O.; Eilitz, U.; Leßmann, F.; Reißmann, S.; Wendisch, V. *Tetrahedron Lett.* **2014**, *55*, 267.

(8) (a) Wei, W.-T.; Yeh, J.-Y.; Kuo, T.-S.; Wu, H.-L. Highly Enantioselective Rhodium-Catalyzed Asymmetric 1,4-Addition Reactions of Arylboronic Acids to Acyclic α,β-Unsaturated Compounds: The Formal Synthesis of (−)-Indatraline. *Chem. Eur. J.* **2011**, *17*, 11405–11409. (b) Liu, C.-C.; Janmanchi, D.; Chen, C.-C.; Wu, H.-L. Expanding the C_1-Symmetric Bicyclo[2.2.1]heptadiene Ligand Family: Highly Enantioselective Synthesis of Cyclic β-Aryl-Substituted Carbonyl Compounds. *Eur. J. Org. Chem.* **2012**, 2503–2507. (c) Huang, K.-C.; Gopula, B.; Kuo, T.-S.; Chiang, C.-W.; Wu, P.-Y.; Henschke, J. P.; Wu, H.-L. Rhodium-Catalyzed Asymmetric Addition of Arylboronic Acids to β-Nitroolefins: Formal Synthesis of (*S*)-SKF 38393. *Org. Lett.* **2013**, *15*, 5730–5733. (d) Gopula, B.; Tsai, Y.-F.; Kuo, T.-S.; Wu, P.-Y.; Henschke, J. P.; Wu, H.-L. Rhodium/Chiral Diene Complexes in the Catalytic Asymmetric Arylation of β-Pyrazol-1-yl Acrylates. *Org. Lett.* **2015**, *17*, 1142–1145. (e) Gopula, B.; Yang, S.-H.; Kuo, T.-S. Hsieh, J.-C.; Wu, P.-Y.; Henschke, J. P.; Wu, H.-L. Direct Synthesis of Chiral 3-Arylsuccinimides by Rhodium- Catalyzed Enantioselective Conjugate Addition of Arylboronic Acids to Maleimides. *Chem. Eur. J.* **2015**, *21*, 11050–11055. (f) Fang, J.-H.; Chang, C.-A.; Gopula, B.; Kuo, T.-S.; Wu, P.-Y.; Henschke, J. P.; Wu, H.-L. Rhodium-Catalyzed Enantioselective Arylation of *N*-Substituted α,β-Unsaturated γ-Lactams: Preparation of Chiral 4-Aryl-2- Pyrrolidones. *Asian J. Org. Chem.* **2016**, *5*, 481–485. (g) Fang, J.-H.; Jian, J.-H.; Chang, H.-C.; Kuo, T.-S.; Lee, W.-Z.; Wu, P.-Y.; Wu, H.-L. Synthesis of Quaternary-Carbon-Containing β²,²-Amino Acids by the Rh^{I}-Catalyzed Enantioselective Arylation of α-Substituted β-Nitroacrylates. *Chem. Eur. J.* **2017**, 23, 1830–1838.

(9) (a) Gopula, B.; Chiang, C.-W.; Lee, W.-Z.; Kuo, T.-S.; Wu, P.-Y.; Henschke, J. P.; Wu, H.-L. Highly Enantioselective Rh-Catalyzed Alkenylation of Imines: Synthesis of Chiral Allylic Amines via Asymmetric Addition of Potassium Alkenyltrifluoroborates to *N*-Tosyl Imines. *Org. Lett.* **2014**, *16*, 632–635. (b) Chen, C.-C.; Gopula, B.; Syu, J.-F.; Pan, J.-H.; Kuo, T.-S.; Wu, P.-Y.; Henschke, J. P.; Wu, H.-L. Enantioselective and Rapid Rh-Catalyzed Arylation of *N*-Tosyl- and *N*-Nosylaldimines in Methanol. *J. Org. Chem.* **2014**, *79*, 8077–8085. (c) Syu, J. F.; Lin, H. Y.; Cheng, Y.-Y.; Tsai, Y.-C.; Ting, Y.-C.; Kuo, T.-S.; Janmanchi, D.; Wu, P.-Y.; Henschke, J. P.; Wu, H.-L. Design and Synthesis of Chiral Diene Ligands for Rh^{I}-Catalyzed Enantioselective Arylation of *N*-DPP-protected Aldimines: Synthesis of the Antifungal Agent Bifonazole. *Chem. Eur. J.* **2017**, *23*, 14515–14522.

(10) (a) Wang, Z. G.; Feng, C. G.; Zhang, S. S.; Xu, M. H.; Lin, G. Q. Rhodium-Catalyzed Asymmetric Conjugate Addition of Organoboronic Acids to Nitroalkenes Using Chiral Bicyclo[3.3.0] Diene Ligands. *Angew. Chem. Int. Ed.* **2010**, *49*, 5780–5783. (b) Lang, F.; Chen,; Li, L.; Xing, J.; Han, F.; Cun, L.; Liao, J. Rhodium-catalyzed Highly Enantioselective Addition of Arylboronic Acids to 2-Nitrostyrenes by *tert*-Butanesulfinylphosphine Ligand. *Chem. Eur. J.* **2011**, *17*, 5242–5245. (c) Xing, J.; Chen, G.; Cao, P.; Liao, J. Rhodium-Catalyzed Asymmetric Addition of Arylboronic Acids to Indolylnitroalkenes. *Eur. J. Org. Chem.* **2012**, 1230–1236. (d) Xue, F.; Wang, D. P.; Li, X. C.; Wan, B. S. Rhodium-Catalyzed Asymmetric Conjugate Addition of Arylboronic Acids to Nitroalkenes Using Olefin–Sulfoxide Ligands. *J. Org. Chem.* **2012**, *77*, 3071–3081.

(11) (a) Hayashi, T.; Yamasaki, K. Rhodium-Catalyzed Asymmetric 1,4-Addition and Its Related Asymmetric Reactions. *Chem. Rev*. **2003**, *103*, 2829–2844. (b) Tang, P.; Dong, H.-Q.; Lin, G.-Q. Rhodium-Catalyzed Asymmetric Arylation. *ACS Catal*. **2012**, *2*, 95–119. (c) Glorius, F. Chiral Olefin Ligands—New "Spectators" in Asymmetric Catalysis. *Angew. Chem. Int. Ed.* **2004**, *43*, 3364–3366. (d) Defieber, C.; Grützmacher, H.; Carreira, E. M. Chiral Olefins as Steering Ligands in Asymmetric Catalysis. *Angew. Chem. Int. Ed.* **2008**, 47, 4482–4502. (e) Shintani, R.; Hayashi, T. Chiral Diene Ligands for Asymmetric Catalysis. *Aldrichimica Acta* **2009**, *42*, 31–38.

(12) For some selected references on hydrogen bond-mediated selectivity in transition metal catalysis: (a) Das, S.; Incarvito, C. D.; Crabtree, R. H.; Brudvig, G. W. Molecular Recognition in the Selective Oxygenation of Saturated C-H Bonds by a Dimanganese Catalyst. *Science* **2006**, *312*, 1941–1943. (b) Fackler, P.; Berthold, C.; Voss, F.; Bach, T. Hydrogen-Bond-Mediated Enantio- and Regioselectivity in a Ru-Catalyzed Epoxidation Reaction. *J. Am. Chem. Soc.* **2010**, *132*, 15911–15913. (c) Fackler, P.; Huber, S. M.; Bach, T. Enantio- and Regioselective Epoxidation of Olefinic Double Bonds in Quinolones, Pyridones, and Amides Catalyzed by a Ruthenium Porphyrin Catalyst with a Hydrogen Bonding Site. *J. Am. Chem. Soc.* **2012**, *134*, 12869–12878. (d) Hyster, T. K.; Knorr, L.; Ward, T. R.; Rovis, T. Biotinylated Rh(III) Complexes in Engineered Streptavidin for Accelerated Asymmetric C–H Activation. *Science* **2012**, *338*, 500–503. (e) Gellrich, U.; Seiche, W.; Keller, M.; Briet, B. Mechanistic Insights into a Supramolecular Self-Assembling Catalyst System: Evidence for Hydrogen Bonding during Rhodium-Catalyzed Hydroformylation. *Angew. Chem. Int. Ed.* **2012**, *51*, 11033–11038. (f) Dydio, P.; Reek, J. H. N. Supramolecular Control of Selectivity in Hydroformylation of Vinyl Arenes: Easy Access to Valuable β-Aldehyde Intermediates. *Angew. Chem. Int. Ed.* **2013**, *52*, 3878–3882. (g) Dydio, P.; Detz, R. J.; Reek, J. H. N. Precise Supramolecular Control of Selectivity in the Rh-Catalyzed Hydroformylation of Terminal and Internal Alkenes. *J. Am. Chem. Soc.* **2013**, *135*, 10817–10828. (h) Arai, T.; Ogawa, H.; Awata, A.; Sato, M.; Watanabe, M.; Yamanaka, M. PyBidine–Cu(OTf)$_2$-Catalyzed Asymmetric [3+2] Cycloaddition with Imino Esters: Harmony of Cu–Lewis Acid and Imidazolidine-NH Hydrogen Bonding in Concerto Catalysis. *Angew. Chem. Int. Ed.* **2015**, *54*, 1595–1599. (i) Hatano, M.; Nishimura, T. Hydroxoiridium/Chiral Diene Complexes as Effective Catalysts for Asymmetric Annulation of α-Oxo- and Iminocarboxamides with 1,3-Dienes. *Angew. Chem. Int. Ed.* **2015**, *54*, 10949–10952. (j) Miyaura, H.; Nishino, K.; Yasukawa, T.; Kobayashi, S. *Chem. Sci.* **2017**, *8*, 8362–8372.

(13) (a) Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T. Preparation of C_2-Symmetric Bicyclo[2.2.2]octa-2,5-diene Ligands and Their Use for Rhodium-Catalyzed Asymmetric 1,4-Addition of Arylboronic Acids. *J. Org. Chem.* **2005**, *70*, 2503–2508. (b) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. Asymmetric Synthesis of 3,3-Diarylpropanals with Chiral Diene−Rhodium Catalysts. *J. Am. Chem. Soc*. **2005**, *127*, 10850–10851. (c) Helbig, S.; Sauer, S.; Cramer, N.; Laschat, S.; Baro, A. Frey, W. Chiral Bicyclo[3.3.0]octa-2,5-dienes as Steering Ligands in Substrate-Dependent Rhodium-Catalyzed 1,4-Addition of Arylboronic Acids to Enones. *Adv. Synth. Catal*. **2007**, *349*, 2331–2337. (d) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. Rhodium-Catalyzed Asymmetric 1,4-Addition of Aryl- and Alkenylboronic Acids to Enones. *J. Am. Chem. Soc.* **1998**, *120*, 5579–5580. (e) Jin, S.-S.; Wang, H.; Zhu, T.-S.; Xu, M.-H. Design of *N*-Cinnamyl Sulfinamides as New Sulfur-containing Olefin Ligands for Asymmetric Catalysis: Achieving Structural Simplicity with a Categorical Linear Framework. *Org. Biomol. Chem.* **2012**, 10, 1764–1768.

(14) CCDC 1820488 (compound **3ai**) and 1820490 (compound **7**) contain the supplementary crystallographic data for this paper. The data

can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/structures/

(15) Wahba, A. E.; Hamann, M. T. Reductive *N*-Alkylation of Nitroarenes: A Green Approach for the *N*-Alkylation of Natural Products. *J. Org. Chem.* **2012**, *77*, 4578–4585.

(16) Frisch, M. J. et al.; *Guassian 16*, Revison A.03, Gaussian, Inc., Wallingford CT, 2016.

(17) Becke, A. D. Density-functional Exchange-energy Approximation with Correct Asymptotic Behavior. *Phys. Rev. A* **1988**, *38*, 3098–3100.

(18) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti Correlation-energy Formula into a Functional of the Electron Density. *Phys. Rev. B* **1988**, *37*, 785–789.

(19) Andrae, D.; Häussermann, U.; Dolg, M.; Stoll, H.; Preuss, H. Energy-adjusted *ab initio* Pseudopotentials for the Second and Third Row Transition Elements. *Theor. Chim. Acta* **1990**, *77*, 123–141.

(20) Hay, P. J.; Wadt, W. R. *Ab initio* Effective Core Potentials for Molecular Calculations. Potentials for K to Au Including the Outermost Core Orbitals. *J. Chem. Phys.* **1985**, *82*, 299–310.

(21) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999–3094.

(22) (a) Ishikawa, H.; Suzuki, T.; Hayashi, Y. High-Yielding Synthesis of the Anti-Influenza Neuramidase Inhibitor (−)-Oseltamivir by Three "One-Pot" Operations. *Angew. Chem. Int. Ed.* **2009**, *48*, 1304–1307. (b) Yoshida, M.; Masaki, E.; Ikehara, H.; Hara, S. Enantioselective Synthesis of Gabapentin Analogues via Organocatalytic Asymmetric Michael Addition of α-Branched Aldehydes to β-Nitroacrylates. *Org. Biomol. Chem.* **2012**, *10*, 5289–5297. (c) Mukherjee, S.; Corey, E. J. [4 + 2] Cycloaddition Reactions Catalyzed by a Chiral Oxazaborolidinium Cation. Reaction Rates and Diastereo-, Regio-, and Enantioselectivity Depend on Whether Both Bonds Are Formed Simultaneously. *Org. Lett.* **2010**, *12*, 1024–1027.

(23) Paraskar, A. S.; Sudalai, A. Co-catalyzed Reductive Cyclization of Azido and Cyano Substituted α,β-Unsaturated Esters with $NaBH_4$: Enantioselective Synthesis of (*R*)-Baclofen and (*R*)-Rolipram. *Tetrahedron* **2006**, *62*, 4907–4916.

(24) In all cases being tested, recovery of unreacted starting materials accounts for the moderate chemical yields.

(25) Gianolio, E.; Mohan, R.; Berkessel, A. Enantiopure *N*-Benzyloxycarbonyl-β²-amino Acid Allyl Esters from Racemic β-Lactams by Dynamic Kinetic Resolution Using *Candida Antarctica* Lipase. *Adv. Synth. Catal.* **2016**, *358*, 30. No erosion of ee was observed by comparing the optical rotation of compound **5** ($[\alpha]_D^{25}$ +80.7 (*c* 0.22, H_2O); 93% ee) with reported data ($[\alpha]_D^{20}$ +82 (*c* 0.2, H_2O), 95% ee) listed in above reference.