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Synthesis and utilization of trifluoromethylated amino alcohol ligands for the enantioselective Reformatsky reaction and addition of diethylzinc to *N*-(diphenylphosphinoyl)imine

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ABSTRACT

A series of trifluoromethylated amino alcohol ligands, which had been designed and conveniently prepared, were successfully applied in the enantioselective Reformatsky reaction and addition of diethylzinc to *N*-(diphenylphosphinoyl)imine, respectively. The influence of the substituents on C-3 position and the amino moiety on the enantioselectivity has been carefully investigated. In the best cases, ligand **1b** exhibited good selectivity for the enantioselective Reformatsky reaction in 86% ee and ligand **12d** provided excellent enantioselectivity in the addition of diethylzinc to *N*-(diphenylphosphinoyl)imine with 95% ee.

1. Introduction

Organozinc reagents are useful synthetic intermediates as a result of their convenient synthesis and high tolerance toward functional groups.[1] Nucleophilic addition of organozinc reagents to aldehydes and imines are very important reactions in organic synthesis. The design of economical and efficient chiral ligands for highly enantioselective transformations has been one of the major projects in asymmetric synthesis.[2] Recently, the study of trifluoromethylated ligands has attracted more and more attention[3] due to the fact that both the strong electron-withdrawing property[4] and steric bulkiness[5] of the trifluoromethyl group may play an essential role for rate enhancement and stereocontrol. For example, Nelson group successfully developed the enantioselective cross aldol reaction with the CF_3-containing Al(III) triamine complex as catalyst.[3d] The CF_3-containing molybdenum alkylidene complexes were also utilized in asymmetric ring-closing metathesis.[3b] What mostly interests us is that, in 2002, Katagiri and Uneyama found that a type of trifluoromethylated amino alcohols ligands (Fig. 1) promoted the unexpectedly higher aggregation of the diethylzinc species, the extent of which correlated well to the asymmetric induction in the reaction with benzaldehyde.[3h] In addition, these trifluoromethylated amino alcohols were used as the chiral ligands for enantioselective Reformatsky reaction with up to 90% ee.[3i] These results prompted us to design and synthesize novel trifluoromethylated amino alcohol ligands for enantioselective nucleophilic addition reactions of organozinc reagents to aldehydes and imines.

Figure 1. The trifluoromethylated amino alcohol ligands.

Katagiri and Uneyama's trifluoromethylated amino alcohols ligands were some optically pure *N*-monosubstituted or *N*,*N*-disubstituted 1,1,1-trifluoromethyl-3-amino-propan-2-ols (Fig. 1).[3i] We proposed that an additional stereocenter at C-3 position would improve the enantioselectivities of nucleophilic addition reactions of organozinc reagents to aldehydes and imines. Thus, we designed a series of novel trifluoromethylated amino alcohol ligands, which possessed an additional substitution group at C-3 position. Most importantly, these novel trifluoromethylated amino alcohol ligands would be conveniently accessed from readily available amino acids. Herein, we would like to describe the synthesis of new trifluoromethylated amino alcohol ligands, and further evaluate these ligands as promoters for the enantioselective Reformatsky reactions and addition of diethylzinc to *N*-(diphenylphosphinoyl)imine.

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2. Results and discussion

2.1. Synthesis and evaluation of novel trifluoromethylated amino alcohol ligands for the enantioselective Reformatsky reaction

The Reformatsky reaction is one of the most synthetically useful methods for the preparation of β-hydroxyesters.[6] Attainment of high stereoselectivity of the reaction would be a key issue for further extension of its applicability. Until now, a wide range of chiral ligands has been applied to this reaction,[3i,7] but high enantioselectivities were hard to be achieved. Figure 2 outlined the designed trifluoromethylated amino alcohol ligands **1a**–**f**, **2a**, **b**, and **3a**, **b**. These ligands could be grouped into three types. Ligands **1a**–**f** featured that a methyl group occupied the C-3 position and the amino group was alkylated by the different straight-chain or cyclic groups (or the amino group was naked). For the ligands **2a**, **b**, an *iso*-propyl group or *sec*-butyl group possessed the C-3 position and the amino groups were alkylated with two methyl groups. In the ligands **3a**, **b**, the rigidity of ligands was improved by connecting C-3 position and amino group into the pyrrolidine ring. All of these ligands could be easily prepared starting from some reported intermediates in a straightforward fashion.

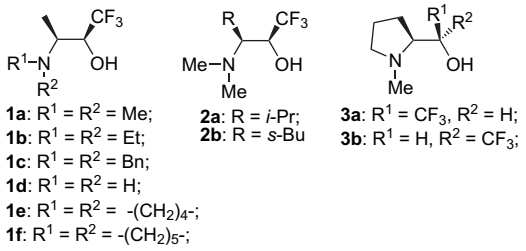
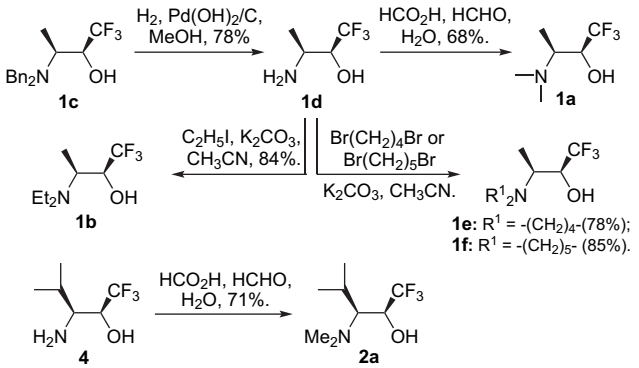


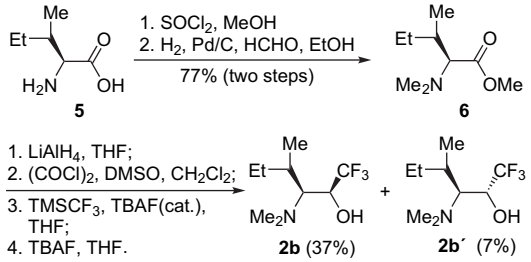
Figure 2. Novel trifluoromethylated amino alcohol ligands.

The ligand **1c** was prepared according to the reported literature (Scheme 1).[8] Hydrogenolysis of the compound **1c** with $Pd(OH)_2/C$ as catalyst produced the debenzylated primary amine alcohol **1d** in 78% yield. The *N*,*N*-dimethylated derivative **1a** was accessed from the compound **1d** by refluxing with $HCO_2H/HCHO$.[9] Exposure of the compound **1d** to different alkyl halides with K_2CO_3/CH_3CN as base system afforded the cyclic tertiary amines **1e**, **1f** and acyclic tertiary amine **1b**. In addition, treatment of trifluoromethylated primary amine **4**[8] with $HCO_2H/HCHO$ under refluxing condition could conveniently provide another trifluoromethylated amino alcohol ligand **2a**.



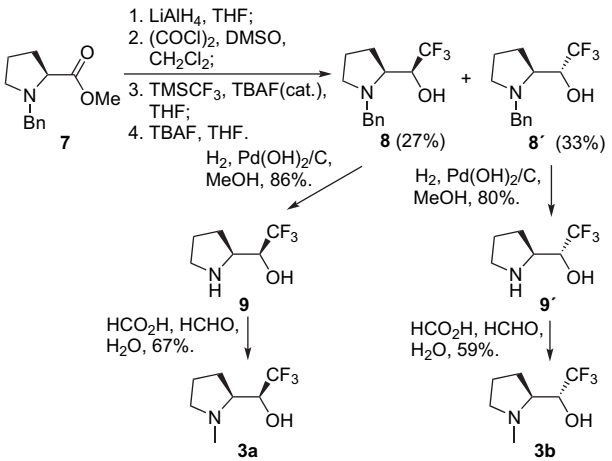
Scheme 1.

Starting from the natural amino acid L-isoleucine **5**, the ligand **2b** was conveniently synthesized (Scheme 2). Thus, treatment of compound **5** with $SOCl_2$/MeOH delivered the corresponding methyl ester hydrochloride, which was subsequently hydrogenated in the presence of aqueous formaldehyde to give the ester **6**. Reduction of the ester **6** with $LiAlH_4$ followed by Swern oxidation furnished the corresponding aldehyde, which was subjected to Ruppert–Prakash reagent ($TMSCF_3$) in the presence of TBAF[10] to afford the mixture of trifluoromethylated amino alcohols **2b** and **2b′**. During the four steps from the ester **6** to the compounds **2b** and **2b′**, all the intermediates were subjected to the next step without further isolation after work-up. The ratio of the diastereoisomers **2b** and **2b′** was 5.5:1 according to ^{19}F NMR and they could be readily separated on silica gel chromatography. The stereochemistry of the isomers **2b** (2*S*,3*S*) and **2b′** (2*R*,3*S*) was assigned on the basis of their ^1H NMR characteristics. The signal (3.83 ppm) of the methine proton at C-2 in the isomer **2b′** appeared upfield relative to that of the compound **2b** (3.97 ppm), and the vicinal coupling constant (5.7 Hz) between protons at C-2 and C-3 for the isomer **2b′** is larger than that of the compound **2b** (4.8 Hz). These data are coincident with those described for the reported 1,2-amino alcohols.[8,11]



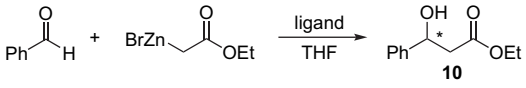
Scheme 2.

Synthesis of the L-prolinal ligands **3a** and **3b** commenced with the methyl ester **7**,[12] itself available from the L-proline (Scheme 3). Reduction of the compound **7** with $LiAlH_4$ followed by Swern oxidation gave the aldehyde, which was further subjected to $TMSCF_3$/TBAF to afford the diastereoisomers **8** and **8′** in 60% total yield. The isomers **8** and **8′** could be easily separated on silica gel chromatography. The dr and stereochemistry of compounds **8** and **8′** were determined on the basis of ^{19}F NMR and ^1H NMR spectral data, respectively. Removal of the benzyl group in the isomer **8** via hydrogenation with $Pd(OH)_2/C$ as catalyst yielded the amino alcohol **9** in 86% yield, which was further methylated to provide the



Scheme 3.

Table 1
Reformatsky reaction promoted by various trifluoromethylated amino alcohol ligands



Entry	Ligand	Temp (°C)	Yield[a] (%)	ee % (config.)[b,c]
1	**1a**	0	<5	n.d.[d]
2	**1a**	20	32	n.d.[d]
3	**1a**	40	87	83 (*R*)
4	**1b**	40	89	86 (*R*)
5	**1c**	40	85	39 (*R*)
6	**1d**	40	76	49 (*R*)
7	**1e**	40	88	82 (*R*)
8	**1f**	40	90	76 (*R*)
9	**2a**	40	92	58 (*R*)
10	**2b**	40	82	49 (*R*)
11	**3a**	40	94	82 (*R*)
12	**3b**	40	90	74 (*S*)

[a] Yield of isolated product after flash chromatography.
[b] Determined by HPLC analysis on a chiral column (ChiralCel OD).
[c] The absolute stereochemistry was assigned by comparison with the reported optical rotation.[13]
[d] n.d.=not determined.

trifluoromethylated pyrrolidine ligand **3a** in 67% yield. The isomer ligand **3b** was prepared from the alcohol **8′** in 47% total yield over two steps using the same procedures.

With all the desired trifluoromethylated amino alcohols **1a–f**, **2a**, **b**, and **3a**, **b** in hand, the Reformatsky reaction between PhCHO and $BrZnCH_2CO_2Et$ was used to evaluate these ligands. The results are summarized in Table 1. First of all, the temperature was a key for the Reformatsky reaction. Using the ligand **1a** as catalyst, little reactant was consumed when the reaction was carried out at 0 °C (entry 1), while this reaction can generate the desired alcohol **10** in 32% yield at 20 °C (entry 2). The yield could be further improved to 87% when the reaction was performed at 40 °C and the product **10** was provided in 83% ee (entry 3). Compared to the *N*,*N*-dimethyl 1,1,1-trifluoromethyl-3-amino-propan-2-ol ligand used in Katagiri and Uneyama group (80% yield, 81% ee),[3i] our ligand *N*,*N*-dimethyl 1,1,1-trifluoromethyl-3-amino-butan-2-ol **1a** gave almost the same result (87% yield, 83% ee) except that the reaction temperature was lower (reflux THF vs 40 °C). The ligand **1b** with substitution of ethyl group for methyl group in **1a** afforded the better enantioselectivity (86% ee) and yield (89%) (entry 4). This enantioselectivity was as high as the best record, which has been attained. However, the enantioselectivity decreased significantly when the methyl or ethyl groups in ligand **1a** or **1b** were replaced with the benzyl groups in ligand **1c** (entry 5), which demonstrated that substitution of large steric hindrance at amino group was disadvantageous for the enantioselectivity. The ligand **1d** with no protecting group on amino group only provide the product in 49% ee although the yield did not change significantly (76%) (entry 6). Interestingly, the enantioselectivities were obtained in 82 and 76% ee, respectively, if the ligands **1e** and **1f** were utilized (entries 7 and 8). The replacement of methyl at C-3 position with large steric *iso*-propyl or *sec*-butyl would resulted in the significant decrease in enantioselectivities (entries 9 and 10), which unambiguously indicated that the substitution group at C-3 position played an important role on the enantioselectivity (entries 9 and 10 vs entry 3) and the large steric group at C-3 position was unbeneficial. To our delight, usage of the ligands **3a**, **b**, which featured that C-3 position and amino group were jointed into the pyrrolidine ring, also delivered the product **10** in 82 and 74% ee, respectively (entries 11 and 12). The opposite configurations of the product **10** were induced by the ligands **3a** and **3b**, which showed that the chirality resulted from the configurations of the carbon bonded to the hydroxyl group.

2.2. Synthesis and evaluation of the trifluoromethylated amino alcohol ligands for the highly enantioselective addition of diethylzinc to *N*-(diphenylphosphinoyl)imine

Chiral amines are widely used in the synthesis of natural products and physiologically active substances, in chiral separation, and in asymmetric synthesis as chiral auxiliaries.[14,15] An attractive and direct access to the chiral amines was the enantioselective addition of organometallic reagents to imines.[16] Among the organometallic reagents, dialkylzinc reagents are very useful since organozinc reagents bearing several functional groups could be easily available,[17] and their usage would lead to a lot of polyfunctionalized compounds. Since Soai and co-workers reported that an ephedrine derivative was used as a chiral ligand in the addition of diethylzinc to *N*-(diphenylphosphinoyl)imines,[18a] enantioselective alkylations of *N*-diphenylphosphinoyl arylimines with dialkylzinc reagents catalyzed by amino alcohols,[18] hydroxyoxazolines,[19] and copper,[20] zirconium[21] or nickel[22] complexes have been described. Of all the reported chiral amino alcohol ligands, the conformationally restricted and structurally rigid artificial amino alcohols generally exhibit higher enantioselectivities than those simple and flexible analogues. Although a lot of chiral amino alcohols possessing different substitution on amino group and carbon chain were synthesized and evaluated, no concerned description was given to the influence of fluorine substitution on enantioselectivity. As the trifluoromethylated amino alcohol ligand **11** had been proved successful in the enantioselective alkylation of PhCHO with Et_2Zn in our aforementioned description,[3h] it was reasonable to use our trifluoromethylated amino alcohol ligand **1f** as the promoter in the enantioselective addition of Et_2Zn to imines (Fig. 3). What is more, the presence of an aromatic ring in the nitrogen substituent of the amino alcohol ligands seems to be important to the enantioselectivity. So two types of simple trifluoromethylated amino alcohols featuring a *N*-benzyl group and different groups occupying the C-3 position were designed as ligands to promote the enantioselective addition of Et_2Zn to imines (Fig. 3). The first type of ligands **12a–e** has flexible structure, while the second type of ligands **8** and **8′** is conformationally restricted with the prolinol skeleton.

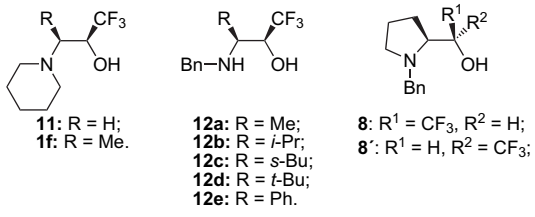
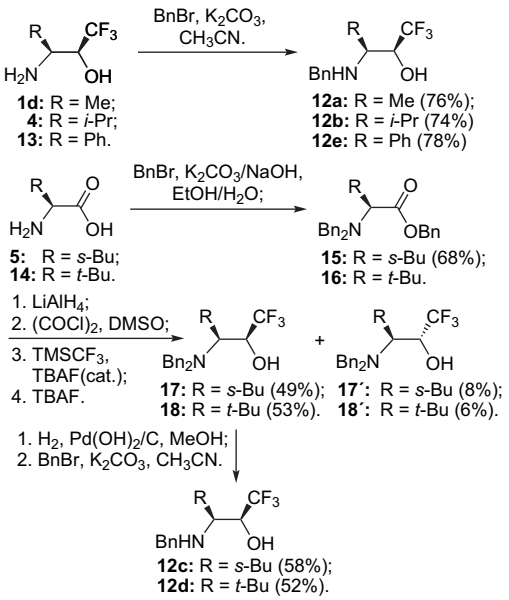


Figure 3. Trifluoromethylated amino alcohol ligands for the addition of diethylzinc to imines.

The synthesis of the ligands **12a**, **12b**, and **12e** was accomplished in high yield from the aforementioned intermediates **1d**, **4**, and **13**[8] via treatment with $BnBr/K_2CO_3$ in CH_3CN, respectively (Scheme 4). Ligands **12c** and **12d** were prepared beginning from the readily available L-isoleucine **5** and L-tert-leucine **14**, respectively. Thus, treatment of the compound **5** with $BnBr/K_2CO_3$/NaOH produced the benzyl ester **15** in 68% yield. Reduction of the compound **15** with $LiAlH_4$, followed by Swern oxidation and trifluoromethylation provided the diastereoisomers **17** and **17′** in a ratio of 6.3:1. The two isomers **17** and **17′** were easily separated on silica gel chromatography and the stereochemistry was also determined on the basis of ^1H NMR. Hydrogenolysis of the major isomer **17** with $Pd(OH)_2/C$ as catalyst gave the primary amine intermediate, which was then subjected to treatment with $BnBr/K_2CO_3$ to afford the ligand **12c** in

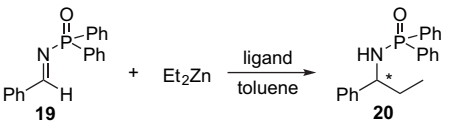
58% total yield. By the same producers, the ligand **12d** was prepared from L-tert-leucine **14** through the intermediate benzyl ester **16**.[23]



Scheme 4.

Then, the trifluoromethylated amino alcohol ligands, **1f**, **8**, **8′**, and **12a–e** were evaluated for the addition of diethylzinc to *N*,*N*-diphenylphosphinoyl benzalimine **19**. The results are summarized in Table 2. The piperidinyl derivative **1f** showed a decrease of the enantioselectivity compared to ligand **12a** (entries 1 and 2), from which it could be concluded that the aryl substituent in ligands **12a** had an obvious effect on the enantioselectivity of this reaction. The possibility of using a substoichiometric amount of the ligand was then investigated. The enantioselectivity dropped down from 92 to 87% ee when the amount of ligand **12a** was reduced from 1.0 to 0.5 equiv (entries 2 and 3). The rigid ligand **8** exhibited lower enantioselectivity than the flexible ligand **12a** (entries 3 and 4). The difference of chirality of the carbon bonded to the hydroxyl group between compounds **8** and **8′** also resulted in different configurations of the product **20** (compare entries 4 and 5). With the different substituent groups at the C-3 position, all the other ligands **12b–e** were efficient and high enantioselectivities were obtained for the titled reaction (entries 6–9). Ligands **12b**, **12c**, **12d**, and **12e** catalyzed the reaction in excellent enantioselectivities of 94, 94, 95, and 90% ee, respectively. These results indicated that the enantioselectivity was not very sensitive to the steric hindrance of the substituent group at the C-3 position.

Table 2
Addition of diethylzinc to *N*-(diphenylphosphinoyl)imine promoted by trifluoromethylated amino alcohol ligands



19 **20**

Entry	Ligand	Ligand (equiv)	Yield[a]	ee %[b] (config.[c])
1	**1f**	1.0	92	87 (*R*)
2	**12a**	1.0	89	92 (*R*)
3	**12a**	0.5	90	87 (*R*)
4	**8**	0.5	79	70 (*R*)
5	**8′**	0.5	87	65 (*S*)
6	**12b**	1.0	90	94 (*R*)
7	**12c**	1.0	91	94 (*R*)
8	**12d**	1.0	92	95 (*R*)
9	**12e**	1.0	95	90 (*R*)

[a] Yield of isolated product after flash chromatography.
[b] Determined by HPLC analysis on a chiral column (ChiralCel OD).
[c] Configuration was determined as described in Ref. 18d.

3. Conclusion

A set of trifluoromethylated amino alcohol ligands have been conveniently prepared from commercially available amino acids, and were successfully applied in the enantioselective Reformatsky reaction and enantioselective addition of diethylzinc to *N*-(diphenylphosphinoyl)imine, respectively. Usage of the ligand **1b** afforded the good enantioselectivity for Reformatsky reaction with up to 86% ee. Ligands **12b**, **12c**, and **12d** gave excellent enantioselectivity for the addition of diethylzinc to *N*-(diphenylphosphinoyl)imine in 94, 94, and 95% ee, respectively. These successful examples using trifluoromethylated amino alcohol ligands to promote the title reactions illustrated that a large family of chiral compounds containing a trifluoromethylated amino alcohol moiety had the potential to be developed as useful ligands. Further studies to use these trifluoromethylated amino alcohol ligands and develop novel trifluoromethylated ligands in other asymmetric catalytic reactions are currently in progress in our laboratory.

4. Experimental

4.1. General information

All reagents were used as received from commercial sources, unless specified otherwise, or prepared as described in the literature. Reactions requiring anhydrous conditions were performed in vacuum heat-dried glassware under nitrogen atmosphere. Reaction mixtures were stirred magnetically. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM300 spectrometer. ^{19}F NMR spectra was recorded on a Bruker AM300 spectrometer ($FCCl_3$ as outside standard and low field is positive). Chemical shifts (δ) are reported in parts per million and coupling constants (J) are in hertz. The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. All the melting points and optical rotations are uncorrected. The enantiomeric excesses were determined by HPLC analysis on Chiralpak OD column.

4.2. Synthesis of chiral ligands for the enantioselective Reformatsky reactions

*4.2.1. (2S,3S)-3-(Dimethylamino)-1,1,1-trifluoro-2-butanol (**1a**)*

A mixture of (2*S*,3*S*)-3-amino-1,1,1-trifluoro-2-butanol **1d** (572 mg, 4.00 mmol), formic acid (2.00 mL), and 37% aqueous formaldehyde (2.00 mL) was heated at reflux overnight. The reaction was then cooled to room temperature rendered alkaline with 20% aqueous NaOH until Dragendorff test was negative, then extracted with ethyl ether. The combined organic phase was washed with brine, dried over $NaSO_4$, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH=15:1) to give compound **1a** (465 mg, 68%) as a white solid: mp 178–180 °C; $[\alpha]_D^{28}$ +25.7 (*c* 1.08, MeOH); ^{1}H NMR (300 MHz, MeOH-d_4) δ 4.35 (dq, J=7.8, 1.8 Hz, 1H), 3.26 (dq, J=6.9, 1.8 Hz, 1H), 2.56 (s, 6H), 1.25 (d, J=7.8 Hz, 3H); ^{13}C NMR (75.5 MHz, MeOH-d_4) δ 126.7 (q, J_{C-F}=282.7 Hz), 70.1 (q, J_{C-F}=29.1 Hz), 59.3, 41.2, 8.6; ^{19}F NMR (282 MHz, MeOH-d_4) δ −79.8 (d, J=8.5 Hz, 3F); MS (ESI) m/z 172.1 $(M+H)^+$; IR (thin film) 3175, 2963, 2702, 1465, 1279, 1161, 1059, 904 cm^{-1}. Anal. Calcd for $C_6H_{12}F_3NO$: C, 42.10; H, 7.07; N, 8.18. Found: C, 41.67; H, 6.82; N, 7.93.

4.2.2. (2S,3S)-3-(Diethylamino)-1,1,1-trifluoro-2-butanol (**1b**)

Ethyl iodide (0.53 mL, 6.60 mmol), potassium carbonate (1037 mg, 7.50 mmol), and **1d** (429 mg, 3.00 mmol) were added to acetonitrile (20 mL) and heated at reflux for 24 h. The reaction was then cooled to room temperature, filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH=25:1) to give compound **1b** (502 mg, 84%) as a clear oil: $[\alpha]_D^{27}$ +50.7 (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (dq, *J*=8.1, 5.1 Hz, 1H), 3.48 (s, 1H), 3.12 (m, 1H), 2.55 (m, 4H), 1.15 (dd, *J*=7.2, 1.5 Hz, 3H), 1.04 (t, *J*=7.2 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 125.2 (q, J_{C-F}=284.8 Hz), 70.2 (q, J_{C-F}=29.1 Hz), 54.8, 43.9, 13.3, 9.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ −74.2 (d, *J*=8.5 Hz, 3F); MS (ESI) *m*/*z* 200.2 $(M+H)^+$; IR (thin film) 3421, 2977, 2826, 1458, 1388, 1274, 1166, 885 cm^{-1}; HRMS calcd for $C_8H_{17}F_3NO$ $(M+H)^+$: 200.1266. Found: 200.1257.

4.2.3. (2S,3S)-3-(1-Pyrrolidinyl)-1,1,1-trifluoro-2-butanol (**1e**)

1,4-Dibromobutane (0.39 mL, 3.30 mmol), potassium carbonate (1037 mg, 7.50 mmol), and **1d** (429 mg, 3.00 mmol) were added to acetonitrile (20 mL) and heated at reflux for 24 h. The reaction was then cooled to room temperature, filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH=20:1) to give compound **1e** (461 mg, 78%) as a white solid: mp 55–57 °C; $[\alpha]_D^{24}$ +33.7 (*c* 0.66, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.79 (s, 1H), 4.13 (dq, *J*=8.1, 2.4 Hz, 1H), 2.67 (m, 5H), 1.83 (m, 4H), 1.21 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 125.0 (q, J_{C-F}=283.3 Hz), 69.9 (q, J_{C-F}=28.2 Hz), 59.9, 52.1, 22.9, 12.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.5 (d, *J*=7.9 Hz, 3F); MS (ESI) *m*/*z* 198.1 $(M+H)^+$; IR (thin film) 2973, 2831, 1771, 1462, 1278, 1131, 1027, 900 cm^{-1}. Anal. Calcd for $C_8H_{14}F_3NO$: C, 48.73; H, 7.16; N, 7.10. Found: C, 48.74; H, 7.11; N, 6.86.

4.2.4. (2S,3S)-3-(1-Piperidinyl)-1,1,1-trifluoro-2-butanol (**1f**)

1,5-Dibromopentane (0.45 mL, 3.30 mmol), potassium carbonate (1037 mg, 7.50 mmol), and **1d** (429 mg, 3.00 mmol) were added to acetonitrile (20 mL) and heated at reflux for 24 h. The reaction was then cooled to room temperature, filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH=25:1) to give compound **1f** (538 mg, 85%) as a white solid: mp 87–89 °C; $[\alpha]_D^{27}$ +21.8 (*c* 1.12, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.99 (dq, *J*=8.1, 1.5 Hz, 1H), 3.79 (s, 1H), 2.90 (dq, *J*=6.9, 4.5 Hz, 1H), 2.61 (m, 2H), 2.47 (m, 2H), 1.59 (m, 4H), 1.44 (m, 2H), 1.15 (dd, *J*=7.5, 1.5 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 125.2 (q, J_{C-F}=282.5 Hz), 69.6 (q, J_{C-F}=28.9 Hz), 59.4, 50.9, 26.2, 24.3, 9.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.1 (d, *J*=7.9 Hz, 3F); MS (ESI) *m*/*z* 212.4 $(M+H)^+$; IR (thin film) 2940, 2820, 1444, 1260, 1159, 1039, 883, 754 cm^{-1}. Anal. Calcd for $C_9H_{16}F_3NO$: C, 51.18; H, 7.64; N, 6.63. Found: C, 50.84; H, 7.52; N, 6.49.

4.2.5. (2S,3S)-3-(Dimethylamino)-1,1,1-trifluoro-4-methyl-2-pentanol (**2a**)

A mixture of compound **4** (684 mg, 4.00 mmol), formic acid (2 mL), and 37% aqueous formaldehyde (2 mL) was heated at reflux overnight. The reaction was then cooled to room temperature rendered alkaline with 20% aqueous NaOH until Dragendorff test was negative, then extracted with ethyl ether. The combined organic phase was washed with brine, dried over $NaSO_4$, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate=10:1) to give compound **2a** (565 mg, 71%) as a clear oil: $[\alpha]_D^{28}$ +9.1 (*c* 0.98, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.14 (s, 1H), 3.95 (dq, *J*=7.8, 1.5 Hz, 1H), 2.49 (s, 6H), 2.44 (d, *J*=4.5 Hz, 1H), 2.18 (m, 1H), 1.05 (d, *J*=6.3 Hz, 3H), 0.98 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 125.4 (q, J_{C-F}=284.8 Hz), 72.2, 67.9 (q, J_{C-F}=29.1 Hz), 42.9, 27.6, 22.7, 20.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.6 (d, *J*=9.0 Hz, 3F); MS (ESI) *m*/*z* 200.3 $(M+H)^+$; IR (thin film) 3423, 2962, 2784, 1463, 1295, 1085, 944, 703 cm^{-1}; HRMS calcd for $C_8H_{17}F_3NO$ $(M+H)^+$: 200.1265. Found: 200.1257.

4.2.6. N,N-Dimethyl-L-isoleucine methyl ester (**6**)

A suspension of L-isoleucine (3.933 g, 30.00 mmol) in methanol (60 mL) was cooled to 0 °C. Thionyl chloride (2.40 mL, 33.00 mmol) was added dropwise and then the cooling bath was removed. The clear mixture was left at room temperature for 1 day. The solvent was then removed by rotary evaporation and the crude product (4.998 g, 92%) was crystallized from isopropanol/hexane. A mixture of the above methyl ester hydrochloride (4.998 g, 27.60 mmol), 37% aqueous formaldehyde (16.47 mL, 220.80 mmol), and 10% Pd/C (2400 mg) was stirred in ethanol (450 mL) under hydrogen at room temperature overnight. The filtrate was evaporated, dissolved in chloroform, washed with 2 M NaOH, dried over $NaSO_4$, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate=3:2) to give compound **6** (4.014 g, 77% for two steps) as a clear oil: $[\alpha]_D^{27}$ −28.0 (*c* 1.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H), 2.87 (d, *J*=9.6 Hz, 1H), 2.29 (s, 6H), 1.82 (m, 1H), 1.66 (m, 1H), 1.14 (m, 1H), 0.91 (m, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.9, 72.4, 50.2, 41.4, 33.1, 25.0, 15.4, 10.3; MS (ESI) *m*/*z* 174.2 $(M+H)^+$; IR (thin film) 2967, 2789, 1733, 1457, 1258, 1150, 996, 775 cm^{-1}. Anal. Calcd for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.08. Found: C, 62.27; H, 10.85; N, 7.95.

4.2.7. (2S,3S)-3-(Dimethylamino)-1,1,1-trifluoro-4-methyl-2-hexanol (**2b**) and (2R,3S)-3-(dimethylamino)-1,1,1-trifluoro-4-methyl-2-hexanol (**2b′**)

To a suspension of lithium aluminum hydride (1.020 g, 27.50 mmol) in dry THF (32 mL) was added compound **6** (2.162 g, 12.50 mmol) in dry THF (10 mL) at 0 °C, and the mixture was warmed to room temperature. After 3 h of being stirred, the mixture was cooled to 0 °C, excess hydride was quenched with EtOAc, and then a 10% NaOH aqueous solution was slowly added. Finally, the mixture was filtered and washed with EtOAc. The filtrates were concentrated in vacuo to give the crude reduction product (1.598 g, 88%). The crude product was subjected to the next step without purification. To a stirred solution of oxalyl chloride (1.32 mL, 15.13 mmol) in dry CH_2Cl_2 (32 mL) cooled to −78 °C under nitrogen was added dropwise of DMSO (2.24 mL, 31.47 mmol). After 15 min, a solution of the above reduction product (1.598 g, 11.01 mmol) in dry CH_2Cl_2 (32 mL) was added and the mixture was stirred for 30 min at −78 °C before addition of triethylamine (4.48 mL, 32.14 mmol). Then, the reaction was allowed to reach the room temperature under stirring for 45 min and the mixture quenched with water. The aqueous phase was extracted with CH_2C1_2, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$) and then concentrated to give the crude oxidation product (1.411 g, 79% for two steps). The crude product was subjected to the next step without purification. To a solution of $TMSCF_3$ (2.19 mL, 14.79 mmol) in dry THF (30 mL) were added a solution of the above oxidation product (1.411 g, 9.86 mmol) in dry THF (20 mL) and TBAF (0.50 mL, 1.0 M in THF, 0.50 mmol) cooled to 0 °C under nitrogen. The mixture was stirred at that temperature until the reaction was complete. Subsequently, TBAF (2.00 mL, 1.0 M in THF, 2.00 mmol) was added, the reaction mixture was stirred at room temperature for 1 h, and quenched by addition of aqueous saturated NH_4Cl solution. The THF was removed and the aqueous phase was extracted with diethyl ether. The combined organic phase was washed with brine, dried over $NaSO_4$, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate=20:1) to give compounds **2b** (984 mg, 37% for four steps) and **2b′** (180 mg, 7% for four steps) as clear oils. Compound **2b**: $[\alpha]_D^{26}$ +8.2 (*c* 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (s, 1H), 3.97 (dq, *J*=7.2, 4.8 Hz, 1H), 2.57 (dd, *J*=10.8, 4.8 Hz, 1H), 2.46 (s, 6H), 1.93

(m, 1H), 1.62 (m, 1H), 1.12 (m, 1H), 0.93 (m, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 125.4 (q, J_{C-F}=283.7 Hz), 69.7, 68.0 (q, J_{C-F}=29.1 Hz), 42.8, 33.3, 27.9, 16.3, 10.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.8 (d, J=7.1 Hz, 3F); MS (ESI) m/z 214.2 $(M+H)^+$; IR (thin film) 3438, 2969, 2783, 1460, 1271, 1128, 1083, 703 cm^{-1}. Anal. Calcd for $C_9H_{18}F_3NO$: C, 50.69; H, 8.51; N, 6.57. Found: C, 51.06; H, 8.81; N, 6.20. Compound **2b′**: $[\alpha]_D^{26}$ +10.6 (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.43 (s, 1H), 3.83 (dq, J=7.2, 5.7 Hz, 1H), 2.61 (dd, J=5.7, 4.5 Hz, 1H), 2.41 (s, 6H), 1.78 (m, 1H), 1.44 (m, 1H), 1.23 (m, 1H), 0.94 (m, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 125.5 (q, J_{C-F}=281.8 Hz), 66.2 (q, J_{C-F}=30.4 Hz), 64.9, 42.5, 33.8, 28.1, 15.8, 12.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ −77.0 (d, J=7.1 Hz, 3F); MS (ESI) m/z 214.3 $(M+H)^+$; IR (thin film) 3428, 2969, 2802, 1465, 1273, 1165, 1133, 692 cm^{-1}; HRMS calcd for $C_9H_{19}F_3NO$ $(M+H)^+$: 214.1411. Found: 214.1413.

4.2.8. (S)-2-[(S)-1-Benzyl-2-pyrrolidinyl]-1,1,1-trifluoro-2-ethanol (**8**) and (R)-2-[(S)-1-benzyl-2-pyrrolidinyl]-1,1,1-trifluoro-2-ethanol (**8′**)

By use of the same procedures as that described for **2b** and **2b′**, compound **7** (9.820 g, 44.81 mmol) was converted to compound **8** (3.126 g, 27% for four steps) and compound **8′** (3.785 g, 33% for four steps) as clear oils. Compound **8**: $[\alpha]_D^{27}$ −67.3 (*c* 0.51, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 5H), 4.11 (dq, J=7.8, 2.4 Hz, 1H), 3.96 (d, J=12.9 Hz, 1H), 3.49 (s, 1H), 3.42 (d, J=12.9 Hz, 1H), 3.00 (m, 1H), 2.91 (dt, J=7.2, 2.1 Hz, 1H), 2.34 (dd, J=13.8, 9.3 Hz, 1H), 2.10 (m, 1H), 1.79 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.9, 128.8, 128.4, 127.4, 124.9 (q, J_{C-F}=281.2 Hz), 68.2 (q, J_{C-F}=29.7 Hz), 62.6, 58.1, 53.6, 23.9, 23.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.4 (d, J=6.8 Hz, 3F); MS (ESI) m/z 260.2 $(M+H)^+$; IR (thin film) 2970, 2808, 1741, 1456, 1274, 1138, 836, 701 cm^{-1}. Anal. Calcd for $C_{13}H_{16}F_3NO$: C, 60.22; H, 6.22; N, 5.40. Found: C, 60.22; H, 6.35; N, 5.23. Compound **8′**: $[\alpha]_D^{27}$ −10.8 (*c* 0.91, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.23 (s, 1H), 4.04 (d, J=13.2 Hz, 1H), 3.60 (dq, J=7.8, 2.7 Hz, 1H), 3.59 (d, J=12.6 Hz, 1H), 3.29 (dt, J=13.5, 3.0 Hz, 1H), 2.93 (m, 1H), 2.52 (m, 1H), 2.15 (m, 1H), 1.77 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.5, 128.6, 128.4, 127.3, 125.2 (q, J_{C-F}=285.5 Hz), 72.0 (q, J_{C-F}=29.1 Hz), 61.3 (q, J_{C-F}=2.9 Hz), 60.4, 54.1, 32.5, 24.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −78.2 (d, J=6.5 Hz, 3F); MS (ESI) m/z 260.1 $(M+H)^+$; IR (thin film) 2970, 2822, 1455, 1280, 1164, 1139, 875, 704 cm^{-1}. Anal. Calcd for $C_{13}H_{16}F_3NO$: C, 60.22; H, 6.22; N, 5.40. Found: C, 60.33; H, 6.20; N, 5.24.

4.2.9. (S)-2-[(S)-2-Pyrrolidinyl]-1,1,1-trifluoro-2-ethanol (**9**)

$Pd(OH)_2$/C (20%, 600 mg) was added in one portion to a solution of the appropriate compound **8** (1.036 g, 4.00 mmol) in methanol (32 mL). The mixture was stirred under hydrogen and the reaction was monitored by TLC. After completion of the reaction, the catalyst was removed by filtration, washed with methanol, and then concentrated in vacuo. The residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH=8:1) to give compound **9** (578 mg, 86%) as a white solid: mp 106–108 °C; $[\alpha]_D^{25}$ −22.2 (*c* 0.93, MeOH); ^{1}H NMR (300 MHz, MeOH-d_4) δ 4.03 (dq, J=7.5, 4.5 Hz, 1H), 3.28 (m, 1H), 3.05 (m, 1H), 2.86 (m, 1H), 1.84 (m, 4H); ^{13}C NMR (75.5 MHz, MeOH-d_4) δ 126.6 (q, J_{C-F}=282.0 Hz), 71.6 (q, J_{C-F}=31.0 Hz), 59.1, 47.3, 26.9, 26.1; ^{19}F NMR (282 MHz, MeOH-d_4) δ −78.5 (d, J=7.9 Hz, 3F); MS (ESI) m/z 170.1 $(M+H)^+$; IR (thin film) 3311, 2878, 2567, 1357, 1256, 1169, 1082, 847 cm^{-1}; HRMS calcd for $C_6H_9F_3NO$ $(M-H)^+$: 168.0636. Found: 168.0644.

4.2.10. (S)-2-[(S)-1-Methyl-2-pyrrolidinyl]-1,1,1-trifluoro-2-ethanol (**3a**)

A mixture of compound **9** (338 mg, 2.00 mmol), formic acid (2.00 mL), and 37% aqueous formaldehyde (2.00 mL) was heated at reflux overnight. The reaction was then cooled to room temperature rendered alkaline with 20% aqueous NaOH until Dragendorff test was negative, then extracted with ethyl ether. The combined organic phase was washed with brine, dried over $NaSO_4$, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH=10:1) to give compound **3a** (246 mg, 67%) as a clear oil: $[\alpha]_D^{23}$ −19.6 (*c* 1.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.38 (s, 1H), 4.01 (dq, J=7.8, 2.1 Hz, 1H), 3.12 (m, 1H), 2.56 (m, 1H), 2.39 (s, 3H), 2.29 (m, 1H), 2.10 (m, 1H), 1.75 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 125.0 (q, J_{C-F}=282.5 Hz), 68.0 (q, J_{C-F}=29.6 Hz), 65.2, 56.7, 40.8, 23.7, 23.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.0 (d, J=7.6 Hz, 3F); MS (ESI) m/z 184.1 $(M+H)^+$; IR (thin film) 3102, 2955, 1459, 1276, 1137, 1035, 835, 684 cm^{-1}; HRMS calcd for $C_7H_{10}F_3N$ $(M-H_2O)^+$: 165.0765. Found: 165.0769.

4.2.11. (R)-2-[(S)-2-Pyrrolidinyl]-1,1,1-trifluoro-2-ethanol (**9′**)

$Pd(OH)_2$/C (20%, 600 mg) was added in one portion to a solution of the appropriate compound **8′** (1.036 g, 4.00 mmol) in methanol (32 mL). The mixture was stirred under hydrogen and the reaction was monitored by TLC. After completion of the reaction, the catalyst was removed by filtration, washed with methanol, and then concentrated in vacuo. The residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH=8:1) to give compound **9′** (541 mg, 80%) as a white solid: mp 86–88 °C; $[\alpha]_D^{24}$ −5.7 (*c* 1.04, MeOH); ^{1}H NMR (300 MHz, MeOH-d_4) δ 3.82 (dq, J=7.5, 5.1 Hz, 1H), 3.26 (m, 1H), 2.97 (m, 1H), 2.85 (m, 1H), 1.94 (m, 1H), 1.82 (m, 2H), 1.66 (m, 1H); ^{13}C NMR (75.5 MHz, MeOH-d_4) δ 126.7 (q, J_{C-F}=282.3 Hz), 72.2 (q, J_{C-F}=30.6 Hz), 58.3, 47.1, 29.6, 26.1; ^{19}F NMR (282 MHz, MeOH-d_4) δ −78.9 (d, J=8.7 Hz, 3F); MS (ESI) m/z 170.0 $(M+H)^+$; IR (thin film) 3273, 2891, 2530, 1368, 1256, 1163, 1083, 849 cm^{-1}. Anal. Calcd for $C_{13}H_{16}F_3NO$: C, 42.61; H, 5.96; N, 8.28. Found: C, 42.46; H, 5.94; N, 8.20.

4.2.12. (R)-2-[(S)-1-Benzyl-2-pyrrolidinyl]-1,1,1-trifluoro-2-ethanol (**3b**)

A mixture of compound **9′** (338 mg, 2.00 mmol), formic acid (2.00 mL), and 37% aqueous formaldehyde (2.00 mL) was heated at reflux overnight. The reaction was then cooled to room temperature rendered alkaline with 20% aqueous NaOH until Dragendorff test was negative, then extracted with ethyl ether. The combined organic phase was washed with brine, dried over $NaSO_4$, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH=10:1) to give compound **3b** (217 mg, 59%) as a white solid: mp 44–46 °C; $[\alpha]_D^{23}$ +16.4 (*c* 1.09, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70 (s, 1H), 3.53 (dq, J=7.5, 3.0 Hz, 1H), 3.16 (m, 1H), 2.92 (m, 1H), 2.51 (m, 4H), 2.14 (m, 1H), 1.75 (m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 125.1 (q, J_{C-F}=282.4 Hz), 72.1 (q, J_{C-F}=30.5 Hz), 62.6, 57.3, 43.0, 32.4, 24.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ −78.0 (d, J=7.6 Hz, 3F); MS (ESI) m/z 184.1 $(M+H)^+$; IR (thin film) 2855, 1466, 1274, 1165, 1118, 1033, 846, 697 cm^{-1}; HRMS calcd for $C_7H_{10}F_3N$ $(M-H_2O)^+$: 165.0765. Found: 165.0764.

4.3. General procedure for asymmetric Reformatsky reactions

4.3.1. Preparation of Reformatsky reagent

A flame dried three-necked flask fitted with a reflux condenser and septum was charged with zinc dust (1.260 g, 19.27 mmol), TMSCl (0.30 mL, 2.40 mmol), and THF (7.70 mL), then heated to reflux with stirring under nitrogen for 15 min. The flask was then removed from the heat and ethyl bromoacetate (1.97 mL, 17.70 mmol) in dry THF (7.70 mL) was added via syringe at such a rate as to maintain gentle reflux. Stirring was resumed for 5 min then stopped and the suspension allowed to settle leaving a green solution of the Reformatsky reagent.

4.3.2. Reformatsky reaction, representative procedure

The ligand (0.48 mmol) was dissolved in THF (1.00 mL) and stirred under nitrogen at 40 °C. A solution of the Reformatsky reagent (1.44 mL, 1.44 mmol) was added by syringe and stirred for

10 min. Benzaldehyde (424 mg, 0.40 mmol) in dry THF (2.40 mL) was then added in one portion and the reaction was stirred for 24 h. The reaction was quenched by the addition of saturated, aqueous NH_4Cl (2 mL) and extracted three times with ethyl acetate; the combined organic layers were then washed with saturated sodium bicarbonate solution and brine, dried over $NaSO_4$, then concentrated in vacuo. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate=10:1) to give ethyl (*S*)-3-hydroxy-3-phenylpropanoate **10** as a colorless oil. The ee was determined HPLC analysis (Chiralpak OD column, hexane/propan-2-ol=90:10; flow rate 0.7 mL min^{-1}; rt, UV detection at 214 nm).

4.4. Synthesis of chiral ligands for the enantioselective addition of diethylzinc to *N*-(diphenylphosphinoyl)imine

*4.4.1. (2S,3S)-3-Benzylamino-1,1,1-trifluoro-2-butanol (**12a**)*

Benzyl bromide (0.24 mL, 2.00 mmol), potassium carbonate (305 mg, 2.20 mmol), and **1d** (286 mg, 2.00 mmol) were added to acetonitrile (6 mL) and stirred overnight. The reaction was then filtered and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate=3:1) to give compound **12a** (354 mg, 76%) as a white solid: mp 67–69 °C; $[\alpha]_D^{23}$ +42.0 (*c* 1.12, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5H), 3.91 (dq, *J*=8.1, 4.5 Hz, 1H), 3.90 (d, *J*=12.9 Hz, 1H), 3.73 (d, *J*=13.2 Hz, 1H), 3.04 (m, 1H), 2.79 (s, 2H), 1.23 (dq, *J*=6.9, 1.5 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 139.0, 128.6, 128.1, 127.4, 125.1 (q, J_{C-F}=282.1 Hz), 69.9 (q, J_{C-F}=29.1 Hz), 52.4, 51.3, 14.5 (q, J_{C-F}=2.9 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.1 (d, *J*=7.6 Hz, 3F); MS (ESI) *m*/*z* 234.1 $(M+H)^+$; IR (thin film) 3288, 2947, 1463, 1274, 1157, 1035, 897, 700 cm^{-1}. Anal. Calcd for $C_{11}H_{14}F_3NO$: C, 56.65; H, 6.05; N, 6.01. Found: C, 56.52; H, 5.75; N, 5.90.

*4.4.2. (2S,3S)-3-Benzylamino-1,1,1-trifluoro-4-methyl-2-pentanol (**12b**)*

Benzyl bromide (0.24 mL, 2.00 mmol), potassium carbonate (305 mg, 2.20 mmol), and **4** (342 mg, 2.00 mmol) were added to acetonitrile (6 mL) and stirred overnight. The reaction was then filtered and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate=10:1) to give compound **12b** (386 mg, 74%) as a clear oil: $[\alpha]_D^{23}$ +23.3 (*c* 1.14, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.25 (s, 1H), 4.00 (m, 2H), 3.76 (d, *J*=12.9 Hz, 1H), 2.66 (t, *J*=6.0 Hz, 1H), 2.04 (m, 1H), 1.49 (s, 1H), 1.11 (d, *J*=6.9 Hz, 3H), 1.01 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 139.0, 128.6, 128.1, 127.4, 125.6 (q, J_{C-F}=284.1 Hz), 69.0 (q, J_{C-F}=28.2 Hz), 63.9, 54.1, 29.7, 20.7, 18.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.1 (d, *J*=7.9 Hz, 3F); MS (ESI) *m*/*z* 262.1 $(M+H)^+$, 284.1 $(M+Na)^+$; IR (thin film) 3386, 2966, 1455, 1276, 1163, 1103, 861, 700 cm^{-1}; HRMS calcd for $C_{13}H_{19}F_3NO$ $(M+H)^+$: 262.1414. Found: 262.1413.

*4.4.3. (2S,3S)-3-Benzylamino-1,1,1-trifluoro-3-phenyl-2-propanol (**12e**)*

Benzyl bromide (0.24 mL, 2.00 mmol), potassium carbonate (305 mg, 2.20 mmol), and **13** (410 mg, 2.00 mmol) were added to acetonitrile (6 mL) and stirred overnight. The reaction was then filtered and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate=6:1) to give compound **12e** (460 mg, 78%) as a white solid: mp 63–65 °C; $[\alpha]_D^{26}$ +73.6 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 10H), 4.23 (dq, *J*=6.9, 4.8 Hz, 1H), 4.06 (d, *J*=5.1 Hz, 1H), 3.82 (d, *J*=12.8 Hz, 1H), 3.59 (d, *J*=12.8 Hz, 1H), 3.05 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.9, 136.8, 128.6, 128.5, 128.3, 128.2, 128.0, 127.4, 124.7 (q, J_{C-F}=283.5 Hz), 72.2 (q, J_{C-F}=28.9 Hz), 61.4, 51.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.5 (d, *J*=7.6 Hz, 3F); MS (ESI) *m*/*z* 296.1 $(M+H)^+$, 318.1 $(M+Na)^+$; IR (thin film) 3322, 3071, 2717, 1455, 1268, 1162, 927, 699 cm^{-1}. Anal. Calcd for $C_{16}H_{16}F_3NO$: C, 65.08; H, 5.46; N, 4.74. Found: C, 65.10; H, 5.51; N, 4.82.

*4.4.4. N,N-Dibenzyl-L-isoleucine benzyl ester (**15**)*

To a refluxing suspension of L-isoleucine **5** (3.933 g, 30.00 mmol) was added a solution of K_2CO_3 (6.996 g, 50.40 mmol) and NaOH (2.016 g, 50.40 mmol) in H_2O/MeOH (36 mL, 1:1) followed by BnBr (10.68 mL, 90.00 mmol). Stirring under reflux was continued for 1 h. The cooled mixture was extracted with Et_2O. The combined Et_2O extracts were washed with brine, dried over $NaSO_4$, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate=50:1) to give compound **15** (8.184 g, 68%) as a clear oil: $[\alpha]_D^{27}$ −93.1 (*c* 1.10, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 15H), 5.30 (d, *J*=12.0 Hz, 1H), 5.17 (d, *J*=12.0 Hz, 1H), 3.97 (d, *J*=13.8 Hz, 2H), 3.28 (d, *J*=13.8 Hz, 2H), 3.02 (d, *J*=10.8 Hz, 1H), 1.96 (m, 2H), 1.08 (m, 1H), 0.74 (m, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.7, 139.4, 136.1, 128.8, 128.6, 128.4, 128.2, 128.1, 126.8, 66.3, 65.6, 54.6, 33.0, 24.6, 15.4, 10.0; MS (ESI) *m*/*z* 402.2 $(M+H)^+$, 424.2 $(M+Na)^+$; IR (thin film) 3065, 2965, 1729, 1455, 1139, 968, 746, 697 cm^{-1}; HRMS calcd for $C_{27}H_{32}NO_2$ $(M+H)^+$: 402.2419. Found: 402.2428.

*4.4.5. (2S,3S)-3-(Dibenzylamino)-1,1,1-trifluoro-4-methyl-2-hexanol (**17**) and (2R,3S)-3-(dibenzylamino)-1,1,1-trifluoro-4-methyl-2-hexanol (**17′**)*

By use of the same procedures as that described for **2b** and **2b′**, compound **15** (5.080 g, 12.66 mmol) was converted to compounds **17** (2.264 g, 49% for four steps) and **17′** (360 mg, 8% for four steps) as clear oils. Compound **17**: $[\alpha]_D^{26}$ +12.5 (*c* 0.97, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 10H), 4.11 (s, 1H), 3.74 (m, 4H), 3.02 (s, 1H), 2.85 (m, 1H), 2.08 (m, 1H), 1.95 (m, 1H), 1.28 (m, 1H), 0.96 (m, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 139.1, 129.2, 128.4, 127.3, 125.5 (q, J_{C-F}=284.0 Hz), 67.9 (q, J_{C-F}=29.3 Hz), 62.6, 55.2, 33.5, 27.8, 16.2, 11.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.9 (d, *J*=8.2 Hz, 3F); MS (ESI) *m*/*z* 366.3 $(M+H)^+$, 388.1 $(M+Na)^+$; IR (thin film) 3449, 2968, 1455, 1274, 1157, 1070, 865, 699 cm^{-1}; HRMS calcd for $C_{21}H_{27}F_3NO$ $(M+H)^+$: 366.2039. Found: 366.2043. Compound **17′**: $[\alpha]_D^{26}$ +33.4 (*c* 1.98, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 10H), 5.56 (s, 1H), 4.09 (m, 1H), 3.91 (d, *J*=11.4 Hz, 2H), 3.53 (d, *J*=13.2 Hz, 2H), 2.94 (d, *J*=8.4 Hz, 1H), 1.99 (m, 1H), 1.38 (m, 2H), 1.10 (d, *J*=6.6 Hz, 3H), 0.95 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.8, 129.2, 128.6, 127.6, 125.3 (q, J_{C-F}=282.5 Hz), 66.0 (q, J_{C-F}=30.5 Hz), 60.2, 54.2, 33.2, 28.8, 16.3, 12.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.6 (d, *J*=7.3 Hz, 3F); MS (ESI) *m*/*z* 366.3 $(M+H)^+$, 388.1 $(M+Na)^+$; IR (thin film) 3066, 2968, 1455, 1274, 1164, 1073, 873, 699 cm^{-1}; HRMS calcd for $C_{21}H_{27}F_3NO$ $(M+H)^+$: 366.2039. Found: 366.2036.

*4.4.6. (2S,3S)-3-Benzylamino-1,1,1-trifluoro-4-methyl-2-hexanol (**12c**)*

$Pd(OH)_2$/C (20%, 650 mg) was added in one portion to a solution of the appropriate compound **17** (1.360 g, 3.72 mmol) in methanol (30 mL). The mixture was stirred under hydrogen and the reaction was monitored by TLC. After completion of the reaction, the catalyst was removed by filtration, washed with methanol, and then concentrated in vacuo to give the crude reduction product (602 mg, 87%). The crude product was subjected to the next step without purification. Benzyl bromide (0.39 mL, 3.25 mmol), potassium carbonate (541 mg, 3.90 mmol), and the above product (602 mg, 3.25 mmol) were added to acetonitrile (6 mL) and stirred overnight. The reaction was then filtered and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate=10:1) to give compound **12c** (590 mg, 58% for two steps) as a clear oil: $[\alpha]_D^{26}$ +19.0 (*c* 0.83, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.28 (s, 1H), 4.00 (m, 2H), 3.74 (d, *J*=13.2 Hz, 1H), 2.74 (t, *J*=5.7 Hz, 1H), 1.81 (m, 2H), 1.47 (s, 1H), 1.24 (m, 1H), 0.96 (m, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$)

δ 139.7, 128.6, 128.1, 127.4, 125.6 (q, J_{C-F}=284.3 Hz), 68.9 (q, J_{C-F}=28.5 Hz), 63.7, 54.1, 36.3, 25.3, 16.4, 11.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.0 (d, J=7.1 Hz, 3F); MS (ESI) m/z 276.1 $(M+H)^+$; IR (thin film) 3362, 2967, 1456, 1269, 1163, 1103, 851, 701 cm^{-1}; HRMS calcd for $C_{14}H_{21}F_3NO$ $(M+H)^+$: 276.1570. Found: 276.1579.

4.4.7. (2S,3S)-3-(Dibenzylamino)-1,1,1-trifluoro-4,4-dimethyl-2-pentanol (**18**) and (2R,3S)-3-(dibenzylamino)-1,1,1-trifluoro-4,4-dimethyl-2-pentanol (**18′**)

By use of the same procedures as that described for **2b** and **2b′**, compound **16** (5.468 g, 13.63 mmol) was converted to compounds **18** (2.628 g, 53% for four steps) and **18′** (286 mg, 6% for four steps) as clear oils. Compound **18**: $[\alpha]_D^{26}$ −13.5 (*c* 1.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 10H), 4.53 (m, 1H), 3.77 (m, 4H), 2.75 (s, 1H), 2.34 (d, J=6.3 Hz, 1H), 0.96 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 139.3, 129.3, 128.2, 127.2, 125.5 (q, J_{C-F}=283.3 Hz), 70.5 (q, J_{C-F}=30.9 Hz), 63.0, 56.9, 36.6, 29.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ −74.3 (d, J=9.3 Hz, 3F); MS (ESI) m/z 366.2 $(M+H)^+$, 388.1 $(M+Na)^+$; IR (thin film) 3554, 2962, 1455, 1283, 1141, 1028, 852, 699 cm^{-1}; HRMS calcd for $C_{21}H_{27}F_3NO$ $(M+H)^+$: 366.2039. Found: 366.2044. Compound **18′**: $[\alpha]_D^{27}$ −12.8 (*c* 0.80, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 10H), 4.56 (s, 1H), 4.42 (m, 1H), 3.95 (m, 4H), 3.04 (d, J=3.0 Hz, 1H), 1.12 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.8, 129.3, 128.4, 127.3, 125.7 (q, J_{C-F}=283.7 Hz), 68.7 (q, J_{C-F}=29.8 Hz), 63.2, 56.6, 37.8, 29.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −75.0 (d, J=9.9 Hz, 3F); MS (ESI) m/z 366.2 $(M+H)^+$, 388.2 $(M+Na)^+$; IR (thin film) 3444, 2960, 1455, 1282, 1163, 1029, 863, 699 cm^{-1}; HRMS calcd for $C_{21}H_{27}F_3NO$ $(M+H)^+$: 366.2039. Found: 366.2038.

4.4.8. (2S,3S)-3-Benzylamino-1,1,1-trifluoro-4,4-dimethyl-2-pentanol (**12d**)

By use of the same procedures as that described for **12c**, compound **18** (1.480 g, 4.05 mmol) was converted to compound **12d** (580 mg, 52% for two steps) as a clear oil: $[\alpha]_D^{27}$ +24.5 (*c* 1.11, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5H), 4.01 (d, J=13.2 Hz, 1H), 3.92 (m, 1H), 3.74 (d, J=13.2 Hz, 1H), 3.65 (s, 1H), 2.66 (d, J=5.1 Hz, 1H), 1.32 (s, 1H), 1.01 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 140.3, 128.6, 128.1, 127.3, 125.6 (q, J_{C-F}=283.3 Hz), 70.4 (q, J_{C-F}=28.5 Hz), 68.9, 55.6, 35.6, 27.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.6 (d, J=6.8 Hz, 3F); MS (ESI) m/z 276.1 $(M+H)^+$, 298.1 $(M+Na)^+$; IR (thin film) 3429, 2962, 1455, 1262, 1164, 1074, 846, 700 cm^{-1}; HRMS calcd for $C_{14}H_{21}F_3NO$ $(M+H)^+$: 276.1570. Found: 276.1567.

4.5. General procedure for the enantioselective addition of diethylzinc to *N*-(diphenylphosphinoyl)imine

Phosphinoylimine **19** (46 mg, 0.15 mmol) and the ligand (0.15 mmol) were dissolved in dry toluene (0.9 mL) under nitrogen, and the mixture was stirred for 10 min at room temperature. To the mixture was added Et_2Zn in hexane (0.45 mL, 0.45 mmol) at room temperature. After the mixture was stirred for 24 h, the reaction was quenched with saturated aqueous ammonium chloride and the aqueous layer was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over $NaSO_4$, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate=2:3) to give *N*-(1-phenylpropyl)-*P*,*P*-diphenylphosphinoylamide **20** as a white solid. The ee was determined HPLC analysis (Chiralpak OD column, hexane/propan-2-ol=90:10; flow rate 0.8 mL min^{-1}; rt, UV detection at 214 nm).

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