# Asymmetric Diethyl- and Diphenylzinc Additions to Aldehydes by Using a Fluorine-Containing Chiral Amino Alcohol: A Striking Temperature Effect on the Enantioselectivity, a Minimal Amino Alcohol Loading, and an Efficient Recycling of the Amino Alcohol

**Jin Kyoon Park,[a] Hong Geun Lee,[a] Carsten Bolm,*[b] and B. Moon Kim*[a]**

**Abstract:** A chiral pyrrolidinylmethanol derivative containing perfluoro-ponytails (**5**) was prepared from (*S*)-proline. The use of this perfluoro-substituted amino alcohol in catalytic asymmetric additions of organozinc reagents to aldehydes affords products with high enantioselectivities in both pure hexane and a mixture of hexane and FC-72 (perfluorohexane). Enantiomeric excesses up to 94 and 88% *ee* have been achieved in $Et_2Zn$ and $Ph_2Zn$ additions, respectively. For the reactions in the biphasic solvent system a striking temperature effect was observed. Thus, when the temperature was raised from 0 to 40°C the *ee* value of the product increased from 81 to 92%. Furthermore, the catalyst loading could be remarkably low, and with only 0.1 mol% of amino alcohol **5** a product with 90% *ee* was obtained in the $Et_2Zn$ addition to benzaldehyde in hexane. The perfluoro-ligand was easily recovered by simple phase separation, and until the ninth repetition its reuse proceeded without significant loss of enantioselectivity and reactivity.

**Keywords:** amino alcohols · asymmetric catalysis · biphasic catalysis · catalyst recycling

## Introduction

In asymmetric catalysis aimed at large-scale production of chiral compounds, the cost of the catalyst is often too high. To resolve this issue, recycling of catalysts has been recognized as one of the most practical approaches. For this purpose immobilization of a homogeneous catalyst onto a heterogeneous system has frequently been employed.[1] Even though various chiral ligands have efficiently been attached onto solid supports, heterogeneous applications of homogeneous chiral catalysts have often been associated with undesirable properties such as a reduced kinetic profile and a low enantioselectivity.

Recently, fluorous organic biphase systems (FBS) pioneered by Hovárth have been recognized as highly effective recycling methods for asymmetric reactions.[2] The FBS strategy allows one to separate fluorous ligands from the reaction mixture by simple phase separation at lower temperature after the reaction has been performed at elevated temperature, where the fluorous ligand becomes soluble to both phases.

Successful examples of FBS include asymmetric protonations,[3] epoxidations,[4] diethylzinc and triethylaluminum-mediated addition reactions,[5] and others.[6] Diorganozinc addition reactions to carbonyl compounds have extensively been studied and many excellent catalysts have been developed to give the resulting secondary alcohols with very high enantioselectivities.[7] The first application of a diethylzinc addition in FBS was reported by Kleijn et al.[5a] and since then several similar approaches have been detailed by Nakamura et al.[5b,d,f] and Tian et al.,[5c,e] who employed fluorous chiral binaphthol derivatives and fluorous chiral amino alcohols, respectively. Herein, we wish to present an effective perfluoro catalyst for diorganozinc addition reactions based on the modification of pyrrolidinylmethanol[8,9] derivatives. We chose the perfluoro-prolinol system **5** due to the high enantioselectivity described for reactions involving known prolinol derivatives.

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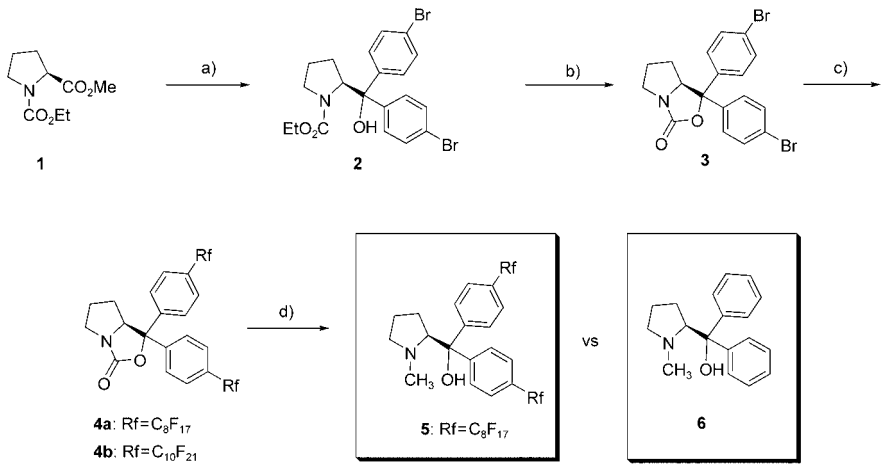
## Results and Discussion

Fluorous amino alcohol **5** was synthesized from known (*S*)-proline derivative **1** as shown in Scheme 1.[10] For the introduction of a perfluoro-ponytail at the 4-position of the aromatic ring, 4-bromophenylmagnesium bromide was prepared and coupled in situ with ester **1**, furnishing compound **2** in 70% yield. Treatment of **2** with NaOH in MeOH provided cyclic carbamate **3** quantitatively. Introduction of the fluoro-ponytail was accomplished by adding perfluoroalkyl iodide slowly to the DMSO solution of **3** in presence of copper powder.




Scheme 1. Preparation of amino alcohol **5**. a) 1,4-Dibromobenzene, Mg, $Et_2O$, 70%; b) MeOH, NaOH, quantitative; c) Cu, $C_8F_{17}I$, DMSO, 120°C, 70% or $C_{10}F_{21}I$, DMSO, 120°C, trace; d) DIBAL, toluene, 50°C, quantitative.

For this coupling reaction, it was critical to maintain the reaction temperature at 120°C and to add the perfluoroalkyl iodide slowly over a period of 30 min. In this manner, the desired product **4a** was obtained in 70% yield. Removal of the carbamate protecting group and introduction of N-methyl functionality was achieved through reduction of **4a** by using diisobutylaluminum hydride (DIBAL). The desired N-methylated derivative **5** was obtained in a quantitative yield. By using the same protocol, the synthesis of compound **4b** bearing a longer perfluoro-ponytail was also attempted, however, the reaction from **3** to **4b** was extremely sluggish and only a trace amount of the desired product was obtained. This result may be due to the lower solubility of $C_{10}F_{21}I$ in the reaction medium than $C_8F_{17}I$, which was sparingly soluble. For a control experiment, non-perfluoroponytail containing ligand **6**[10] was prepared.

Investigation of the asymmetric diethylzinc addition to benzaldehyde was carried out by using 3 mol% of the amino alcohol **5** or **6**, which was deprotonated with *n*-butyllithium (3.7 mol%) before starting the catalysis. Monophasic (hexane) and biphasic (hexane/FC-72) solvent systems were employed, and reactions at various temperatures were examined. The results are summarized in Table 1. Surprisingly in the case of fluorous amino alcohol **5** in the biphasic solvent system, the *ee* of the product increased from 81, 86 to 92% when the reactions were performed at 0, 20 and 40°C, respectively, as clearly indicated in the plot in Figure 1. At 60°C, the reaction proceeded very fast (in 10 min), however,

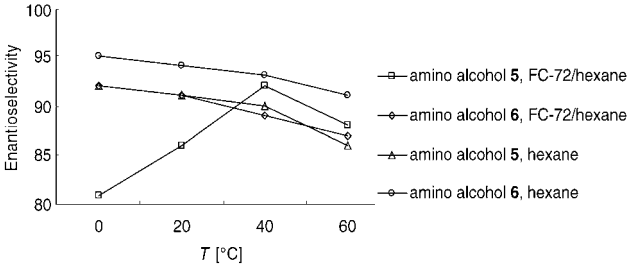



Figure 1. Temperature profile of the enantioselectivity in the diethylzinc addition reaction to benzaldehyde under monophasic and biphasic reaction conditions.

the enantioselectivity was somewhat reduced (88% *ee*). This increase in enantioselectivity is in sharp contrast to the reactions involving non-fluorous amino alcohol **6** (Figure 1), where the *ee* of the product gradually decreases from 92 to 89% in the fluorous biphasic system as the reaction temperature was increased from 0 to 60°C, respectively. Although the origin of this peculiar temperature effect is not clear, we reason that it could be partly due to an increased solubility of fluorous amino alcohol **5** at elevated temperature. Consequently, more catalysts are available at higher temperature, culminating in the unprecedented enantioselectivity improvement. When the reaction with amino alcohol **5** was run in hexane at 0°C, the product *ee* was 92% (Figure 1). In hexane, reactions with both amino alcohols **5** and **6** led to slightly reduced enantioselectivities when the temperature was increased. Amino alcohol **6** (Figure 1) gave products with somewhat higher enantioselectivities than **5**, but the trend of decreasing selectivity according to the temperature rise was the same. When *n*-butyllithium

**Abstract in Korean:**

(*S*)-프롤린으로부터 유도된 과불소 치환기를 갖는 피롤리딘메탄올 유도체를 합성하였다. 단일상인 헥산용매와 이중상인 헥산과 FC-72하에서 이 유도체를 이용하여 성공적으로 비대칭 다이에틸아연 첨가반응과 다이페닐아연 첨가반응을 수행하여 높은 입체선택성을 갖는 생성물을 얻었다. 94%와 88%에 이르는 거울상 초과량이 각각 다이에틸아연 첨가반응과 다이페닐아연 첨가반응에서 얻어졌다. 이중상 용매하의 반응에서는 현저한 온도 효과를 보였다. 온도가 0도에서 40도로 상승하면 생성물의 거울상 초과량이 81%에서 92%로 증가하였다. 또한 촉매의 사용량을 놀랄만큼 줄여 다이에틸아연 첨가반응에서 단지 0.1몰%의 아미노알코올 5를 사용하여 90%의 거울상 초과량을 갖는 생성물을 얻었다. 과불화 리간드를 단순 층분리로 쉽게 회수하였고 9번째 회수실험까지 입체선택성과 반응성의 의미있는 손실없이 재사용하였다.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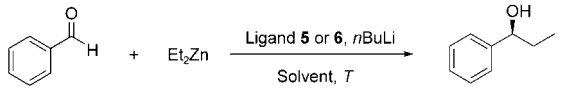
was omitted from the reaction employing **6** at 0 °C, the *ee* dropped to 72 %. Moreover, product of only 57 % *ee* was obtained by switching the solvent to toluene. The reaction was relatively fast compared with the previously reported ones.[7] Monitoring the aldehyde conversion in the reaction using amino alcohol **5** at 40 °C with a React-IR indicated that it was complete within 30 min. At 60 °C the reaction took only 10 min.

Table 1. Enantioselectivities of the diethylzinc addition reactions to benzaldehyde in monophasic and biphasic systems depending on the temperature.




| Solvent (ligand[a]) | *ee* [%][b] 0 °C | 20 °C | 40 °C | 60 °C |
|---|---|---|---|---|
| FC-72/hexane (**5**) | 81 | 86 | 92 (80[c]) | 88 (84[d]) |
| FC-72/hexane (**6**) | 92 | 91 | 89 | 87 |
| Hexane (**5**) | 92 (72[d], 57[e]) | 90 | 90 | 86 |
| Hexane (**6**) | 95 | 94 | 93 | 91 |

[a] Reactions were carried out at 0.15 M concentration by using 3 mol % of amino alcohol and 3.7 mol % of *n*BuLi. [b] Enantioselectivities and yields were determined by HPLC and/or GC analysis using a Chiralcel OD and/or a cyclodex β column. In all cases the yields were over 95 %, with 2–3 % of benzyl alcohol as a side product. [c] Results with 1 mol % of amino alcohol. [d] Result without *n*BuLi addition. [e] Toluene was used as a solvent.

In order to examine the scope of the fluorous ligand system, $Et_2Zn$ addition reactions to other aldehydes were carried out at 40 °C in fluorous biphasic solvents in the presence of the amino alcohol **5** (Table 2). While the reaction with *p*-chlorobenzaldehyde exhibited similar enantioselectivity (90 % *ee*) to that of benzaldehyde, reactions with *p*-methoxybenzaldehdye and cinamaldehyde showed somewhat decreased selectivities (83 and 78 % *ee*, respectively).

Table 2. Enantioselectivity of the diethylzinc addition to aldehydes at 40 °C in FC-72/hexanes (1/1).

| Entry | Aldehyde | Catalyst loading [mol %] | *n*BuLi [mol %] | Reaction *t* [h] | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|---|---|
| 1 | *p*-chlorobenzaldehyde | 3 | 3.6 | 1 | 90 | 90[c] |
| 2 | *p*-methoxybenzaldehyde | 3 | 3.6 | 1 | 80 | 83[d] |
| 3 | cinnamaldehyde | 3 | 3.6 | 1 | 85 | 78[e] |

[a] After column chromatography. [b] Determined by HPLC analysis by using chiral columns. [c] Chiralcel OD-H 99:1 heptane/2-propanol, 1.0 mL min$^{-1}$. [d] Chiralcel AD 98:2 heptane/2-propanol, 1.0 mL min$^{-1}$. [e] Chiralcel OD-H 98:2 heptane/2-propanol, 1.0 mL min$^{-1}$.

The approximate partition coefficients of the fluorous amino alcohol **5** between representative organic solvents and FC-72 were determined experimentally, and the results are summarized in Table 3. Hexane and FC-72 turned into a homogeneous phase by addition of fluorous amino alcohol **5** at room temperature. After cooling to 0 °C, however, two phases separated. When the reaction was carried out at 40 °C with the fluorous amino alcohol **5**, the reaction medium still remained separated in two phases. The mixture was cooled to 0 °C before phase separation. It was found by $^1$H NMR spectroscopy that the peaks of fluorous amino alcohol **5** were not detected from the organic phase, and the amino alcohol was recovered from the fluorous phase almost quantitatively, although the partition coefficient of the free amino alcohol **5** in FC-72 over hexane is only 2.3. This effect could be explained by the formation of aggregates of the ligand **5**-Li·$Et_2Zn$ complex,[11] which should enforce the catalyst system to stay in the fluorous phase.

Table 3. Partition coefficients of amino alcohol **5** between representative organic solvents and FC-72.

| Solvent | Partition coefficient[a] ($P = C_{\text{fluorous phase}}/C_{\text{organic phase}}$) |
|---|---|
| $CH_3CN$ | 47 |
| $CHCl_3$ | 1.6 |
| hexane | 2.3 |
| THF | 1.2 |
| toluene | 2.5 |

[a] Determined as follows: A mixture of 50 mg of amino alcohol **5** in FC-72 (1 mL) and an organic solvent (1 mL) was stirred at rt for 10 min. Then the two phases were separated at 0 °C and solvents in each phase were evaporated in vacuo. The contents of the fluorous amino alcohol **5** in each phase were determined by measuring the weights of the residue.

Repetition experiments by using **5** were carried out in FC-72/hexane, and it was found that the fluorous amino alcohol could be recovered by simple phase separation and used at least nine times without significant loss of enantioselectivity and reactivity. The results of these experiments are summarized in Table 4. After the ninth reaction a product of 81 % *ee* was obtained, which is about the value (80 % *ee*) obtained from the reaction with 1 mol % of catalyst at the same temperature. This result indicates that after nine runs the remaining catalyst in the reaction mixture may be approximately 1 mol %.

Recently, Katagiri et al. reported that fluorinated amino alcohol promoted unexpectedly higher aggregation of diethylzinc species, which showed an interesting concentration effect on the enantioselectivity. Compared to the non-fluorous ligand a higher concentration of the fluorous ligand was required to give better enantioselectivities.[12] Gratifyingly, in our case a small quantity of **5** was sufficient to ensure high enantioselectivity (Table 5). To our surprise, we observed almost constant *ee* values irrespective of the catalyst loading until 0.1 mol %, which may indicate to the amount of the dissolved catalyst available in this reaction mixture. This is in sharp contrast to the result obtained with amino alcohol **6**, where a gradual decrease of the enantioselectivity upon decreasing amount of the amino alcohol was observed. The most noticeable difference in that respect was observed in reactions involving 0.05 mol % of amino alco-

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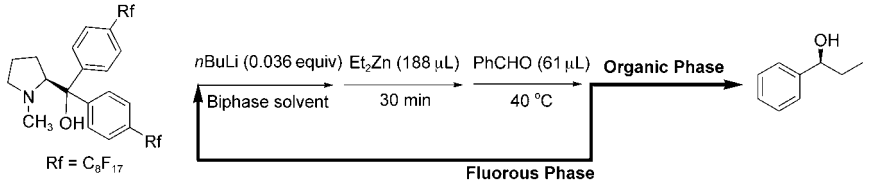
Table 4. Enantioselectivities of diethylzinc addition reactions to benzaldehyde and recycling of amino alcohol **5** by simple phase separation.

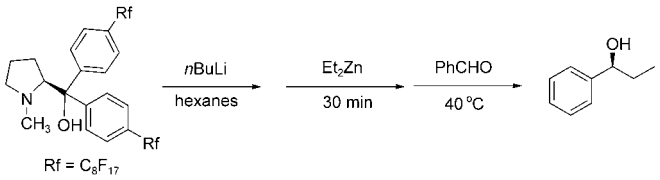



0.018 mmol in FC-72 (1.5 mL) and hexane (1.5 mL)

| Run | 1st | 2nd | 3rd | 4th | 5th | 6th | 7th | 8th | 9th |
|---|---|---|---|---|---|---|---|---|---|
| *ee* (%) of the product | 92 | 92 | 91 | 92 | 91 | 91 | 86 | 86 | 82 |

hols **5** and **6**, which gave 71 and 30% *ee*, respectively. The results are summarized in Table 5.

Table 5. Enantioselectivity in the diethylzinc addition reaction to benzaldehyde in hexanes depending on the catalyst loading.



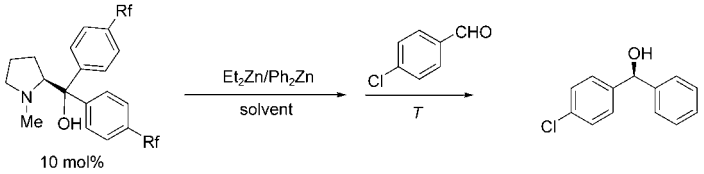

| Entry | Amino alcohol [mol%] | Reaction time [h] | *ee* [%][a] Amino alcohol **5** | **6** |
|---|---|---|---|---|
| 1[b] | 10 | 0.5 | 90 | 90 |
| 2[b] | 3 | 1 | 91 | 93 |
| 3[c] | 1 | 1 | 94 | 90 |
| 4[c] | 0.5 | 2 | 90 | 87 |
| 5[c] | 0.1 | 4 | 90 | 83 |
| 6[d] | 0.05 | 20 | 71 | 30 |

[a] Enantioselectivities and yields were determined by HPLC and GC analysis by using a Chiralcel OD and a cyclodex-β column, respectively. In all cases the yields were over 95% and benzyl alcohol was formed in 2–5%. (The production of benzyl alcohol increased when the catalyst loading was lowered). [b] Reaction concentrations were 0.15 M. [c] Reaction concentrations were 0.3 M. [d] Reaction concentration was 1 M.

Next, we examined the performance of the fluorous amino alcohol **5** in phenyl transfer reactions to an aromatic aldehyde.[13] Recently, Zhao et al. reported enantioselective phenylations using pyrrolidinylmethanol derivatives.[9] Various (*S*)-proline-derived amino alcohols were examined and the best enantioselectivity (92.6% *ee*, at −30°C) was achieved with 15 mol% of **6**, pure $Ph_2Zn$ and a slow addition of the substrate (*p*-chlorobenzaldehyde). By using only 10 mol% of **6** at −30°C, a product with 89.1% *ee* was obtained. In our study we followed the method developed by one of the authors employing mixtures of $Ph_2Zn$ and $Et_2Zn$ as aryl source.[13] With 10 mol% of amino alcohol **5** at 40°C the desired diarylmethanol having an ee of 88% was obtained almost quantitatively. No ethylation product was observed. Thus, the enantioselectivity was close to the one obtained with **6** at much lower temperature. After the catalysis amino alcohol **5** was recovered almost quantitatively by simple phase separation. When *n*BuLi was employed as additive, a decrease in the enantioselectivity was observed, which is in contrast to the results obtained in the previously discussed diethylzinc additions (Table 6).

In summary, we prepared a pyrrolidinylmethanol derivative from (*S*)-proline containing perfluoro-ponytails. It was successfully applied in catalyzed asymmetric additions of organozinc reagents to aldehydes in monophasic and biphasic solvent systems. At 40°C enantiomeric excesses of up to 94 and 88% were achieved in $Et_2Zn$ and $Ph_2Zn$ additions, respectively. Both reactions were complete within one hour. Reactions employing the fluorous amino alcohol **5** exhibited a striking temperature effect in the biphasic solvent system. Thus, the *ee* of the product increased from 81 to 92% when the temperature was raised from 0 to 40°C. Under optimal conditions, use of only 0.1 mol% of the catalyst in hexane provided the ethylated product of 90% *ee*. The perfluoro ligand was easily recovered by simple phase separation, and its reuse in nine sequential runs proceeded without significant loss of enantioselectivity and reactivity.

Table 6. Enantioselectivity in the phenyl transfer reaction to *p*-chlorobenzaldehyde catalyzed by amino alcohol **5**.




**5**: Rf = $C_8F_{17}$

| Entry | Solvent | *T* [°C] | Reaction time [h] | *ee* [%] | Config. |
|---|---|---|---|---|---|
| 1 | FC-72/hexane | rt | 1 | 77 | *S* |
| 2 | FC-72/hexane | 40 | 0.5 | 87 | *S* |
| 3[a] | FC-72/toluene | 40 | 0.5 | 78 | *S* |
| 4 | FC-72/toluene | 40 | 0.5 | 88 | *S* |

[a] *n*BuLi was added as additive.

## Experimental Section

**Compound 2**: Magnesium turnings (484 mg, 19.9 mmol) were added to a two-necked flask charged with $Et_2O$ (5 mL). The mixture was sonicated for 1 h. A solution of 1,4-dibromobenzene (4.69 g, 19.9 mmol) in $Et_2O$ (15 mL) was slowly transferred into the reaction mixture, and stirring was continued for 2 h. Compound **1** was then added at 0°C and the mixture stirred for additional 2 h. After the addition of a saturated aqueous solution of $NH_4Cl$ (100 mL) at 0°C, the reaction mixture was extracted with ethyl acetate (3×100 mL). Combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give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the crude product. Column chromatography (hexane/ethyl acetate 5:1) gave the product (6.72 g, 13.9 mmol, 70%). $^1$H NMR (300 MHz, $CDCl_3$, 25°C, TMS): $\delta$ =7.48–7.42 (m, 4H), 7.28–7.26 (m, 4H), 4.85 (dd, $^2J$(H,H)=8.9, 4.0 Hz, 1H), 4.20–4.11 (m, 2H), 3.47–3.41 (m, 1H), 3.00–2.98 (m, 1H), 2.14–2.07 (m, 1H), 1.89–1.86 (m, 1H), 1.59–1.52 (m, 1H), 1.27 (t, $^3J$(H,H)=7.1 Hz, 3H), 0.92–0.88 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25°C, TMS): $\delta$ =160.0, 142.0, 139.0, 132.1, 131.9, 127.9, 127.5, 85.3, 69.2, 46.5, 29.4, 25.2; HRMS (FAB+): *m/z*: calcd for $C_{35}H_{30}N_2O_4$: 481.9961; found: 481.9989 $[M+H]^+$.

**Compound 3**: Compound **2** (2.42 g, 5.00 mmol) was dissolved in MeOH (15 mL), and after the addition of NaOH (400 mg, 10 mmol) the mixture was stirred for 4 h at rt. Solvent was evaporated under reduced pressure, and then water (30 mL) was added. The reaction mixture was extracted with dichloromethane (3×50 mL). Combined organic extracts were dried over anhydrous $MgSO_4$, and the solvent was evaporated to afford the product (2.19 g, 5.00 mmol) in a quantitative yield. $^1$H NMR (300 MHz, $CDCl_3$, 25°C, TMS): $\delta$ = 7.51–7.47 (m, 4H), 7.35 (d, $^2J$=8.3 Hz, 2H), 7.23 (d, $^2J$=8.0 Hz, 2H), 4.45 (dd, $^2J$=10.5, 5.4 Hz, 1H), 3.77–3.68 (m, 1H), 3.29–3.21 (m, 1H), 2.03–1.86 (m, 2H), 1.75–1.68 (m, 1H), 1.14–1.06 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25°C, TMS): $\delta$ =159.0, 145.3, 142.8, 131.5, 131.1, 130.3, 129.7, 122.1, 122.0, 81.4, 77.6, 66.4, 62.6, 48.2, 30.1, 23.5, 15.0; HRMS (FAB+): *m/z*: calcd for $C_{35}H_{30}N_2O_4$: 435.9543; found: 435.9547 $[M+H]^+$.

**Compound 4**: Freshly activated copper (2.75 mmol, 200 mg) and compound **3** (200 mg, 0.46 mmol) were added into a two-neck flask charged with anhydrous DMSO (1.15 mL). The mixture was heated to 120°C and perfluorooctyl iodide (291 μL, 1.10 mmol) was slowly added to the reaction mixture over 30 min. Stirring was continued for 24 h at 120°C and then the mixture was poured into ethyl acetate (10 mL). The precipitated brownish solid was removed by filtration. The filtrate was concentrated under reduced pressure to afford a yellowish solid. Recrystallization of this crude solid from pentane gave the desired product (357 mg, 70%, 0.32 mmol). $[\alpha]_D^{20}$ =−56.2 (*c*=0.01 in EtOAc); $^1$H NMR (300 MHz, $CDCl_3$, 25°C, TMS): $\delta$ =7.69–7.54 (m, 8H), 4.55 (dd, $^2J$=10.6, 5.4 Hz, 1H), 3.78–3.72 (m, 1H), 3.32–3.24 (m, 1H), 2.07–1.90 (m, 2H), 1.79–1.75 (m, 1H), 1.14–1.07 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25°C, TMS): $\delta$ =159.8. 146.7, 143.7, 127.7, 127.4, 126.4, 126.0, 85.0, 69.4, 46.4, 29.3, 25.1; elemental analysis calcd (%) for $C_{34}H_{15}F_{34}NO_2$: C 36.61, H 1.36, N 1.26; found C 36.71, H 1.40, N 1.21.

**Compound 5**: DIBAL (0.915 mmol, 763 μL, 1.2 M in toluene) was added to the suspension of compound **4** (204 mg, 0.183 mmol) in toluene (1 mL). The mixture was heated to 50°C for 18 h and then water (5 mL) was added. The mixture was extracted with ethyl acetate (3×5 mL). Combined organic extracts were dried over anhydrous $MgSO_4$, and solvents were removed under reduced pressure to afford the resulting product (202 mg, 0.183 mmol) in a quantitative yield. $[\alpha]_D^{20}$ =+3.25 (*c*=0.02 in EtOAc); $^1$H NMR (300 MHz, $CDCl_3$, 25°C, TMS): $\delta$ =7.80 (d, $^2J$=8.2 Hz, 2H), 7.68 (d, $^2J$=8.2 Hz, 2H), 7.51 (d, $^2J$=8.2 Hz, 4H), 5.2–4.8 (broad, 1H; OH), 3.8–3.5 (m, 1H), 3.2–3.0 (m, 1H), 2.6–2.4 (m, 1H), 2.0–1.5 (m, 7H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25°C, TMS): $\delta$ =126.9 (2C), 125.9, 125.8, 77.3, 59.0, 42.8, 29.9, 23.9, 1.1; elemental analysis calcd (%) for $C_{34}H_{19}F_{34}NO$: C 37.01, H 1.74, N 1.27; found C 37.45, H 1.80, N 1.26.

**Typical procedure for the repetition reactions**: *n*BuLi (14 μL, 0.022 mmol, 1.6 M solution in hexanes) was added to a solution of amino alcohol **5** (20 mg, 0.018 mmol) in FC-72 (1.5 mL) and hexane (1.5 mL). After stirring for 30 min, $Et_2Zn$ (188 μL, 1.83 mmol) was added. Stirring was continued for additional 30 min at 40°C, and benzaldehyde (61 μL, 0.60 mmol) was injected at 40°C. After the reaction was complete, the mixture was cooled to 0°C and the upper organic phase was decanted carefully under an Ar atmosphere. The organic solution was diluted with hexanes (5 mL) and quenched with a saturated aqueous solution of $NH_4Cl$ (5 mL). The mixture was extracted with hexanes (2×5 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered. Enantioselectivities and yields were determined through HPLC and GC analyses. In the repetition reactions, additional *n*BuLi (14 μL, 0.022 mmol, 1.6 M solution in hexanes) and hexane (1.5 mL) were added to the remaining fluorous phase. After stirring for 30 min, $Et_2Zn$ (188 μL, 1.8 mmol) was added again. Stirring was continued for additional 30 min at 40°C, and benzaldehyde (61 μL, 0.60 mmol) was injected at 40°C. The reactions were repeated 9×. The monophasic reaction conditions are the same as those of the biphasic one except for the addition of FC-72.

**Typical reaction procedure for the diphenylzinc addition**: In a glove box a dried Schlenk flask was charged with diphenylzinc (20 mg, 0.09 mmol). The flask was sealed and removed from the glove box. Freshly distilled toluene (500 μL) and FC-72 (500 μL) were added followed by diethylzinc (24 μL, 0.225 mmol). After stirring the mixture for 30 min at room temperature, compound **5** (10 mg, 0.009 mmol) was added. Stirring was continued for additional 10 min at 40°C, and *p*-chlorobenzaldehyde (13 mg, 0.09 mmol) was then added directly in one portion. The Schlenk flask was sealed, and the reaction mixture was stirred at 40°C for 30 min. The mixture was diluted with toluene (2 mL) and FC-72 (2 mL). The upper toluene phase was decanted carefully under an Ar atmosphere. The organic phase was washed with water (2 mL). Drying with anhydrous $MgSO_4$ and evaporation of the solvent from the filtrate under reduced pressure gave the product in almost quantitative yields. The purity of product was checked by $^1$H NMR spectroscopy, and the enantiomeric excess of the product determined through HPLC analysis.

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