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Enantioselective ethylation of aldehydes using a regenerable polymer-supported *N*-picolylvalinol tridentate ligand

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Abstract—A supported pyridine-based tridentate chiral ligand has been prepared and evaluated for enantioselective addition of diethylzinc to aldehydes. The catalyst allowed the preparation of various chiral alcohols with the *R* configuration in good yields and enantiomeric excesses (up to 93%) and was found reusable.

1. Introduction

The pioneering works by Oguni have revealed that the reaction of diethylzinc with benzaldehyde could be made moderately enantioselective using (*S*)-leucinol as catalyst.[1] This discovery was the starting point for numerous enantioselectivity improvements of this very important reaction for the preparation of optically active alcohols. Many chiral ligands have been synthesized and involved with success in the enantioselective catalytic process. β-amino alcohols are among the best catalysts allowing the preparation of chiral alcohols in good yields and high enantiomeric excesses.[2]

The safe recovery and recycling of catalysts is an important challenge for modern chemistry in the aim to develop sustainable processes. Especially in the field of asymmetric synthesis, the attachment of chiral catalysts to an insoluble support is an attractive way for simplifying the purification of optically enriched products and reduction of expensive materials waste. In addition, the immobilization can allow running reactions in continuous flow processes.[3]

The strategy of anchoring ligands to a polymeric support such as a Merrifield resin has been adopted by several groups. The first synthetic approach was the direct reaction of the chiral aminoalcohol with the chloromethyl moieties of the resin through its nucleophilic nitrogen atom (Fig. 1, e.g., ligands **A** and **B**).[4] This approach, which implies the vicinity of the amino group and polymer matrix can induce some perturbation of the enantioselective pathway since the nitrogen is known to be strongly involved in the formation of the intermediate chiral zinc complex.[5] Consequently, other routes have been investigated in which aminoalcohols have been attached via functionalities remote from the coordinating nitrogen and oxygen resulting in good retention of the performances of the soluble counterpart (Fig. 1, e.g., ligands **C**, **D**, and **E**).[6]

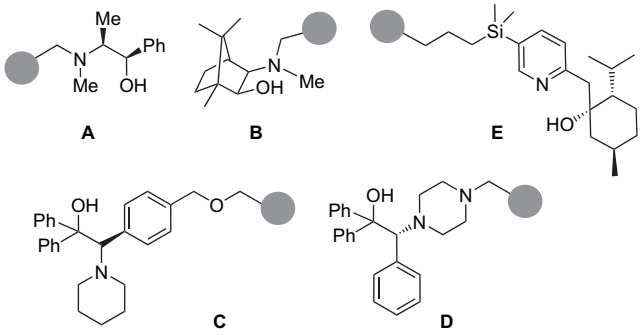

Figure 1. Relevant supported catalysts of the literature.

Pyridine-based tridentate ligands are also valuable platforms for such purpose for two main reasons. At first, several methodologies are now available to selectively functionalize the pyridine ring making possible the anchoring of the polystyrene backbone far from the chelating actors of the enantioselective process. Secondly, in addition to dual activation,[7] the tridentate chelation is an additional way to create a robust chiral environment around the zinc metal center expecting minimized perturbation by the polymer backbone.

To our knowledge no ligand of this type has been immobilized on a polystyrene support and obviously no data is

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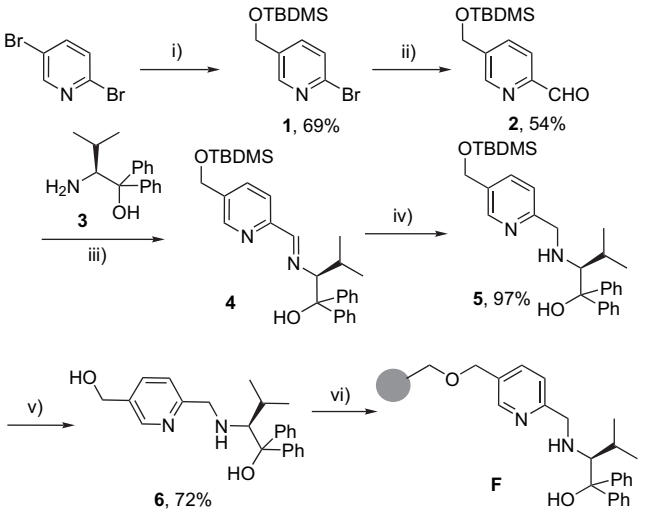
available about its use as supported catalyst in enantioselective addition. After examination of potential candidates we focused our attention on ligand **F** (Scheme 1). Herein we report the preparation of this new supported catalyst and its efficiency in enantioselective addition of diethylzinc to aldehydes.



Scheme 1. Preparation of catalyst **F**. (i) (1) *n*-BuLi (1.05 equiv), Et_2O, −90 °C, 1 h; (2) DMF (1.1 equiv), 1 h, −78 °C then $NaBH_4$ (0.5 equiv), MeOH, 15 min; (3) TBDMSCl (1.05 equiv), Et_3N (2 equiv), DMF, 15 min. (ii) (1) *n*-BuLi (1.2 equiv), THF, −78 °C, 1 h; (2) DMF (1.2 equiv), −78 °C, 1 h. (iii) Compound **3** (1 equiv), toluene, reflux, overnight. (iv) $NaBH(OAc)_3$ (2 equiv), 1,2-dichloroethane, rt, 120 h. (v) TBAF (1 equiv), THF, rt, 1 h. (vi) (1) NaH (1 equiv), DMF, 0 °C, 1.5 h; (2) chloromethylated Merrifield resin (0.5 equiv), KI (0.5 equiv), DMF, 80 °C, 48 h.

2. Results and discussion

2.1. Preparation of the supported catalyst F

The first step was the installation of a hydroxymethyl sidearm on the pyridine ring for subsequent grafting to the polymer. The synthetic strategy was based on the regioselective lithiation of 2,5-dibromopyridine. The bromine at C-5 was first exchanged selectively with *n*-BuLi in diethylether at −90 °C[8] followed by quenching with DMF and reduction with $NaBH_4$. The obtained alcohol was then silylated using TBDMSCl giving **1**, which was metallated with *n*-BuLi at −78 °C in THF and reacted with DMF giving pyridyl carboxaldehyde **2** in 54% yield (Scheme 1).[9]

With the appropriate functional pyridine in hand, the chiral part was brought by reaction with the diphenyl valinol derivative **3** prepared from (L)-valine methylester hydrochloride and an excess of PhMgBr.[10] The corresponding imino alcohol **4** was then reduced quantitatively into the aminoalcohol **5**. After fluoride-assisted deprotection of the hydroxymethyl arm, the monomer **6** was obtained in 72% yield.

Compound **6** was finally reacted with a 2% DVB crosslinked Merrifield resin yielding the expected ligand **F** with a 0.99 mmol/g loading based on nitrogen content (elemental analysis). The selectivity of the reaction has been verified in homogeneous conditions by reacting benzyl chloride instead of the Merrifield resin, the benzylation occurred exclusively on the pyridine hydroxymethyl group and the aminoalcohol part was not affected.

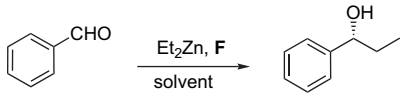
2.2. Evaluation of F in asymmetric ethylation

Then we turned to the evaluation of **F** in asymmetric addition of diethylzinc to aldehydes (Table 1). Various reaction conditions were screened such as the solvent effect, the temperature, the catalyst and diethylzinc amount versus benzaldehyde.

The first experiments were realized in 1/2.2 toluene–hexane solvent mixtures. Excellent conversions were obtained whatever the catalyst amount and the enantioselectivity (87% ee) remained constant (runs 1–3). An increase of hexane proportion in the mixture did not affect the conversion that was complete but the enantioselectivity dropped to 80% ee in pure hexane (runs 4 and 5). So it appeared that the solvent polarity more affected the enantiocontrol than the catalyst activity indicating that the accessibility to the immobilized chiral ligand was not impeded by swellability parameters. In contrast the chiral induction process was found more solvent-dependent.

When hexane was banished from the solvent, the experiments performed in pure toluene gave the chiral alcohol in good 93% ee after 4 h at room temperature (runs 9 and 11). This result was identical to those obtained with the parent homogeneous ligand in tol/hex (4/1).[11] The amount of the organozinc was also critical since 1.1 equiv allowed to decrease the catalyst content to 5 mol % while 8 mol % were required for the same result using 2.2 equiv of Et_2Zn. There was an optimal catalyst amount since 2 or 8 mol % of the catalyst gave similar lower conversions and enantioselectivities (runs 13 and 14). At 0 °C, the catalyst gave poor conversion and lower ee.

Table 1. Parameters screening for ethylation catalysis with **F**[a]



Run	F (mol %)	Et_2Zn (equiv)	Solvent	T (°C)	t (h)	Conv.[d] (%)	ee[e] (%)
1	5	2.2	Tol/hex (1/2.2)[b]	rt	3	>99	87
2	3	2.2	Tol/hex (1/2.2)[b]	rt	7	>99	87
3	1	2.2	Tol/hex (1/2.2)[b]	rt	7	>99	87
4	5	2.2	Tol/hex (1/4.4)[b]	rt	4	>99	85
5	5	2.2	Hexane[b]	rt	4.5	>99	80
6	5	2.2	Tol/hex (4/1)[b]	rt	4	>99	86
7	5	2.2	Toluene[c]	rt	4	>99	90
8	10	2.2	Toluene[c]	rt	4	>99	91
9	8	2.2	Toluene[c]	rt	4	>99	93
10	8	2.2	Toluene[c]	0	5.5	78	86
11	5	1.1	Toluene[c]	rt	4	>99	93
12	5	1.1	Toluene[c]	0	6	51	79
13	2	1.1	Toluene[c]	rt	7.5	88	87
14	8	1.1	Toluene[e]	rt	4	91	87

[a] Reaction performed on 1 mmol of benzaldehyde.
[b] Et_2Zn (1 M in hexane).
[c] Et_2Zn (1.1 M in toluene).
[d] Determined by GC and ^1H NMR of the crude product.
[e] Determined by GC on a chiral Supelco Betadex 120 (30 m) column. Average value from 3 injections.

Then, we examined the synthetic interest of the catalytic process by reacting a set of aldehydes under the best conditions above determined (Table 2).

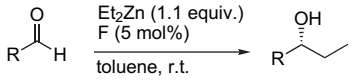
As shown, aldehydes were generally efficiently reacted giving the expected chiral alcohols with the *R* configuration[12] in good yields (58–97%) and enantiomeric excesses (83–93%). 2-Methoxybenzaldehyde gave a good ee despite the presence of coordinating substituents expected to favor side racemic processes. Piperonal led to (*R*)-marginatumol, an antifungal natural product in 58% yield and 86% ee.[13] The nitrogen of pyridine carboxaldehyde was too chelating and while efficiently produced, the corresponding pyridyl alcohol was obtained with poor optical activity.[14] In contrast, we were pleased to obtain an excellent enantioselectivity (93% ee) with *n*-octanal for which loss of enantiocontrol is often observed due to side enolizations.[15]

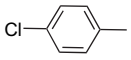
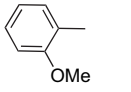
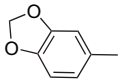
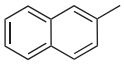
The catalyst was easily recovered from the product mixture via simple filtration and we finally checked its reusability by repeating the reaction five times with the same sample (Table 3).

(*R*)-Phenylpropanol was obtained in similar yields (95–97%) and ees (92–93%) in each run and elemental analysis of the catalyst sample after each run did not reveal any loss of the nitrogen content.

In conclusion, we have prepared an efficient supported tridentate chiral catalyst for enantioselective addition of diethylzinc to aldehydes. The catalyst is reusable and gives chiral alcohols in good yields and enantiomeric excesses (up to 93%) with variously substituted aldehydes. Work is now in progress to extend the scope of the new catalyst to other asymmetric transformations.

Table 2. Enantioselective ethylation of aldehydes[a]



R	t (h)	Conv.[b] (%)	Yield[c] (%)	ee[d] (%)
	4	>99	97	93
	5.5	95	80	88
	4	>99	88	90
	5	66	58	86
	4	96	82	86
	4	70	65	4
	6	98	78	85
n-Heptyl	4	84	82	93

[a] Reaction performed on 1 mmol of aldehyde in toluene with a Et_2Zn/RCHO/**F** ratio=1.1:1:0.05.
[b] Determined by GC and ^1H NMR on the crude product.
[c] Isolated yield after column chromatography.
[d] Determined by GC on a chiral Supelco Betadex 120 (30 m) column. Average value from 3 injections.

Table 3. Recycling of catalyst **F**[a]

Cycle	Conv.[b] (%)	ee[c] (%)
1	95	93
2	94	92
3	97	92
4	95	93
5	95	93

[a] Reaction performed on 1 mmol of PhCHO in toluene with a Et_2Zn/PhCHO/**F** ratio=1.1:1:0.05.
[b] Determined by GC and ^1H NMR on the crude product.
[c] Determined by GC on a chiral Supelco Betadex 120 (30 m) column. Average value from 3 injections.

3. Experimental

3.1. General

All reactions were performed under an argon atmosphere using anhydrous solvents distilled and stored over sodium wires before use. Commercially available solutions of diethylzinc in hexane (1 M) and toluene (1.1 M)were used as received. Aldehydes were used as such or distilled when necessary to remove acidic traces. The Merrifield resin (2% DVB crosslinked) was commercially available and contained 2.18 mmol Cl/g (elemental analysis).

^1H and ^{13}C (200 and 50 MHz, respectively) were obtained on a Brucker AM 200 spectrometer in $CDCl_3$ with TMS as internal standard. The specific rotations were measured on a Perkin–Elmer 141 polarimeter using a 1 dm cell. The configurations were determined by comparison of the specific rotation with those of the known compounds. Chiral GC experiments were performed on a Shimadzu chromatograph equipped with an FID detector (H_2) fitted with a 30 m Supelco Betadex 120 column (det. 250 °C, inj. 250 °C) using N_2 as carrier. Column chromatographies on silica gel were performed using AcOEt–hexane mixtures as eluents.

3.2. Preparation of catalyst F

3.2.1. 5-[[[*tert*-Butyl(dimethyl)silyl]oxy]methyl]-2-pyridine carbaldehyde (2).[9] Prepared in 37% yield (from 2,5-dibromopyridine) according to Ref. 9. ^1H NMR (200 MHz, $CDCl_3$): δ=0.14 (s, 6H), 0.93 (m, 9H), 4.87 (s, 2H), 7.86 (d, J=8.1 Hz, 1H), 7.95 (d, J=8.1 Hz, 1H), 8.75 (s, 1H), 10.07 (s, 1H). ^{13}C NMR (200 MHz, $CDCl_3$): δ=−5.2, 18.5, 26.1, 62.7, 121.7, 134.7, 142.0, 148.3, 152.0, 193.3.

3.2.2. (*S*)-2-Amino-3-methyl-1,1-diphenylbutan-1-ol (3).[10] PhMgBr (48 mmol) was prepared under a nitrogen atmosphere in 25 mL of anhydrous THF (addition of PhBr to a suspension of Mg° pellets in THF). The temperature was cooled to 0 °C (ice bath) and L-valine methylester hydrochloride (1 g, 6 mmol) was added portionwise while controlling the temperature below 10 °C. After 3 h at room temperature, the mixture was hydrolyzed carefully with satd aqueous NH_4Cl. The organic phase was extracted

with diethylether and ethyl acetate. The aqueous phase was extracted with MTBE. The organic phases were then mixed and acidified at 0 °C (concd HCl). The precipitate was filtered, washed with MTBE, dissolved in dichloromethane, and made basic at 0 °C (NaOH 35%). After phase separation the aqueous phase was extracted twice with dichloromethane. The organic phases were washed with brine, dried over $MgSO_4$, and evaporated. The crude was finally recrystallized from MTBE yielding **3** (1.02 g, 67%) as a white solid. Mp 96 °C (lit.[10] mp 97–98 °C), $[\alpha]_D^{23}$ −127.1 (*c* 0.7, $CHCl_3$) (lit.[10] $[\alpha]_D^{25}$ −127.7 (*c* 0.6, $CHCl_3$)); ^1H NMR (200 MHz, $CDCl_3$): δ=0.90 (d, *J*=7.2 Hz, 3H), 0.94 (d, *J*=7.2 Hz, 3H), 1.16 (s, 2H), 1.77 (m, 1H), 3.88 (d, *J*=1.6 Hz, 1H), 7.15–7.21 (m, 2H), 7.26–7.34 (m, 4H), 7.48 (d, *J*=7.6 Hz, 2H), 7.60 (d, *J*=8.0 Hz, 2H).

3.2.3. (2*S*)-2-({[5-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)pyridin-2-yl]methyl}amino)-3-methyl-1,1-diphenylbutan-1-ol (5). Compounds **3** (1.89 g, 7.43 mmol) and **2** (1.91 g, 7.43 mmol) were placed in a flask equipped with a Dean–Stark and dissolved in toluene (150 mL). The mixture was then refluxed under nitrogen overnight. After cooling at room temperature, the solvent was evaporated yielding **4** as an orange viscous oil. ^1H NMR (200 MHz, $CDCl_3$): δ=0.10 (m, 6H), 0.58 (d, *J*=7 Hz, 3H), 0.94 (m, 9H), 1.08 (d, *J*=7 Hz, 2H), 1.86 (m, 1H), 3.47 (m, 1H), 3.95 (d, *J*=6 Hz, 1H), 4.82 (s, 2H), 5.49 (s, 1H), 7.18–7.71 (m, 12H), 8.71 (s, 1H). Compound **4** was used as such in the next step. To a solution of **4** in 1,2-dichlorethane (30 mL) was added portionwise sodium triacetoxyborohydride (3.40 g, 15.83 mmol). The suspension was stirred for five days at room temperature. The medium was hydrolyzed with satd Na_2CO_3 and the organic phase extracted with dichloromethane, dried over $MgSO_4$, and evaporated yielding **5** quantitatively (1.84 g, 97%) as a red viscous oil, for which purification was not necessary. ^1H NMR (200 MHz, $CDCl_3$): δ=0.10 (s, 6H), 0.93 (m, 15H), 2.00 (m, 1H), 3.41 (m, 2H), 3.60 (s, 1H), 4.71 (s, 2H), 6.85 (d, *J*=8 Hz, 1H), 7.13–7.75 (m, 11H), 8.46 (s, 1H). ^{13}C NMR (200 MHz, $CDCl_3$): δ=−5.0, 16.3, 18.6, 22.8, 26.2, 29.2, 55.6, 62.9, 69.0, 78.9, 122.3, 126.4, 127.4, 128.1, 128.5, 134.7, 135.3, 145.8, 147.6, 149.5, 162.2.

3.2.4. (2*S*)-2-({[5-(Hydroxymethyl)pyridin-2yl]methyl}-amino-3-methyl-1,1-diphenylbutan-1-ol (6). A solution of **5** (2.937 g, 6 mmol) in anhydrous THF (15 mL) was placed under a nitrogen atmosphere and was treated by a THF solution of tetrabutylammonium fluoride (6 mL, 6 mmol). After 1 h the mixture was evaporated. The residue was purified by column chromatography using a 20:80 hexane–ethyl acetate mixture yielding **6** (1.63 g, 72%) as a gummy solid. $[\alpha]_D^{19}$ −43 (*c* 2.14, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ=0.84 (d, *J*=7.1 Hz, 3H), 0.91 (d, *J*=7.1 Hz, 3H), 1.99 (m, 1H), 3.45 (m, 2H), 3.60 (s, 1H), 4.50 (s, 2H), 6.81 (d, *J*=8 Hz, 1H), 7.11–7.73 (m, 11H), 8.29 (s, 1H). ^{13}C NMR (200 MHz, $CDCl_3$): δ=15.73, 22.33, 28.53, 54.70, 61.23, 68.22, 78.64, 122.02, 125.37, 125.44, 125.78, 126.13, 127.57, 127.70, 135.07, 145.00, 148.53, 157.66.

3.3. Grafting of 6 on the Merrifield resin

To a suspension of sodium hydride (139.2 mg, 3.5 mmol) in DMF (9.5 mL) cooled at 0 °C under a nitrogen atmosphere was added a solution of **6** (1.32 g, 3.5 mmol) in DMF (10 mL). After 1.5 h, the orange solution was transferred via cannula into a second flask containing the Merrifield resin (0.80 g, 1.75 mmol) priorly swelled for 1 h in DMF (5 mL) and KI (146 mg, 0.88 mmol). The suspension was then heated to 80 °C and stirred gently for 60 h. After cooling, the resin was filtered and washed subsequently with DMF, water, THF, and finally diethylether. After drying under vacuum, **F** was obtained as a pale orange solid (0.94 g). The average nitrogen content (elemental analysis from 3 aliquots) was 2.77% indicating a loading of 0.99 mmol/g (70% yield from initial resin Cl content).

3.4. General procedure for ethylation of aldehydes

A suspension of **F** (50 mg, 5 mol %) in toluene (1 mL) was stirred under argon at room temperature for 30 min. A solution of diethylzinc in toluene (1.1 mL, 1.1 mmol) was then added. After 20 min, the aldehyde (1 mmol) was added and the suspension was stirred for 4–6 h. the mixture was then cooled at 0 °C and hydrolyzed with satd NH_4Cl (5 mL). The resin was then recovered by filtration. The aqueous phase was extracted with dichloromethane (3×5 mL) and the collected organic phases dried over $MgSO_4$ and evaporated yielding the crude product, which was analyzed by chiral GC. Purification by column chromatography yielded the chiral alcohols in yields reported in Table 2 with spectroscopic data identical to those of the known products. Catalyst **F** was washed with NH_4OH (5 mL), water (5 mL), THF (5 mL), and diethylether (5 mL) and dried under vacuum after which it can be used. The same sample of **F** was reused five times in the ethylation of benzaldehyde. After each experiment, the above work-up was repeated and the nitrogen content measured (elemental analysis) giving 2.68, 2.67, 2.66, 2.65, 2.67% for runs 1, 2, 3, 4, 5, respectively.

3.4.1. 1-Phenylpropanol. Yield: 97%, ee: 93%. ^1H NMR (200 MHz, $CDCl_3$): δ=0.89 (t, *J*=8 Hz, 3H), 1.76 (m, 2H), 2.15 (m, 1H), 4.55 (t, *J*=6 Hz, 1H), 7.28 (m, 5H). Chiral GC conditions: (60–150 °C, 5 °C/min): t_R (*R*)=33.92, t_R (*S*)=35.21.

3.4.2. 1-(2-Methoxy-phenyl)propanol. Yield: 88%, ee: 90% ^1H NMR (200 MHz, $CDCl_3$): δ=0.94 (t, *J*=8 Hz, 3H), 1.73–1.87 (m, 2H), 2.66 (s, 1H), 3.83 (s, 3H), 4.77 (t, *J*=8 Hz, 1H), 6.85–6.98 (m, 2H), 7.19–7.31 (m, 2H). Chiral GC conditions (60–180 °C, 5 °C/min): t_R (*S*)=37.34, t_R (*R*)=38.02.

3.4.3. 1-(4-Chloro-phenyl)propanol. Yield: 80%, ee: 88%. ^1H NMR (200 MHz, $CDCl_3$): δ=0.85 (t, *J*=8 Hz, 3H), 1.64–1.78 (m, 2H), 2.70 (s, 1H), 4.48 (t, *J*=8 Hz, 1H), 7.17–7.33 (m, 4H). Chiral GC conditions (80–180 °C, 5 °C/min): t_R (*R*)=35.36, t_R (*S*)=36.37.

3.4.4. 1-(1,3-Benzodioxol-5-yl)propan-1-ol. Yield: 58%, ee: 86%. ^1H NMR (200 MHz, $CDCl_3$): δ=0.87 (t, *J*=8 Hz, 3H), 1.64–1.77 (m, 2H), 2.35 (s, 1H), 4.45 (t, *J*=7 Hz, 1H), 5.92 (s, 2H), 6.75–6.77 (m, 2H), 6.83 (s, 1H). Chiral GC conditions (80–180 °C, 5 °C/min): t_R (*R*)=55.55, t_R (*S*)=56.45.

3.4.5. 1-Naphtalen-2-yl-propanol. Yield: 82%, ee: 86%. ^1H NMR (200 MHz, $CDCl_3$): δ=0.86 (t, *J*=8 Hz, 3H), 1.71–

1.86 (m, 2H), 2.59 (s, 1H), 4.61 (t, J=7 Hz, 1H), 7.29–7.43 (m, 3H), 7.57–7.75 (m, 4H). Chiral GC conditions (80–180 °C, 5 °C/min): t_R (R)=106.28, t_R (S)=108.45.

3.4.6. 1-Pyridin-4-yl-propan-1-ol. Yield: 64%, ee: 4%. ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.93 (t, J=6 Hz, 3H), 1.71–1.78 (m, 2H), 4.63 (t, J=6 Hz, 1H), 5.10 (s, 1H), 7.32 (d, J=5 Hz, 2H), 8.43 (d, J=5 Hz, 2H). Chiral GC conditions (60–150 °C, 5 °C/min): t_R (R)=64.75, t_R (S)=66.27.

3.4.7. 2-Methyl-1-phenyl-pent-1-en-3-ol. Yield: 78%, ee: 85%. The ee was determined by ^{19}F NMR of the (R)-Mosher ester. ^{19}F NMR (188 MHz, C_6F_6, $CDCl_3$): δ=−74.62 (S) −74.36 (R). ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.93 (t, J=8 Hz, 3H), 1.59–1.73 (m, 2H), 1.84 (s, 3H), 2.11 (s, 1H), 4.07 (t, J=7 Hz, 1H), 6.47 (s, 1H), 7.19–7.36 (m, 5H).

3.4.8. Decan-3-ol. Yield: 82%, ee: 93%. ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.85–0.96 (m, 6H), 1.15–1.47 (m, 12H), 2.31 (m, 2H), 3.50 (m, 1H), 5.28 (s, 1H). Chiral GC conditions: (60–150 °C, 5 °C/min): t_R (R)=26.79, t_R (S)=27.85.

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