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Highly enantioselective addition of dimethylzinc to arylaldehydes catalyzed by (2*S*)-1-ferrocenyl-methylaziridin-2-yl(diphenyl)methanol

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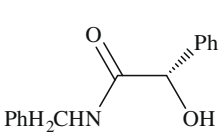
ABSTRACT

Asymmetric addition of dimethylzinc to a wide variety of aromatic aldehydes is described in the presence of a catalytic amount of chiral β-amino alcohol [(2*S*)-1-ferrocenyl- methylaziridin-2-yl(diphenyl)methanol], and a reaction enantioselectivity of up to 97.5% ee was achieved in this transformation in the absence of additional metals such as Ti or Ni. The results showed that this particular addition reaction, characterized by the lower reactivity of dimethylzinc with aldehydes, was more sensitive to structural variations in substrate aldehydes than the corresponding diethylzinc addition. A possible transition state for the catalytic asymmetric addition has been proposed on the basis of previous studies.

1. Introduction

Since chiral secondary alcohols containing a 1-hydroxyethyl unit are versatile and important chiral building blocks for the synthesis of natural products and drug compounds[1] as well as for preparation of chiral ligands in enantioselective synthesis,[2] the efficient and highly enantioselective synthesis of a chiral 1-hydroxyethyl moiety is of primary importance not only to academia but also to industrial scientists. One of the most efficient approaches to these chiral secondary alcohols is the catalytic asymmetric addition of a methyl group to aldehydes. Because of the high reactivity of methyllithium and methyl Grignard reagents, at least 1 equiv of a generally expensive and difficult-to-prepare chiral ligand is compulsory to guarantee high enantioselectivity in all cases. To reduce the amount of chiral ligand required, a dimethylzinc reagent with lower nucleophilic character is usually considered. However, due to the decreased reactivity of dimethylzinc relative to diethylzinc,[3] there are sparse reports regarding the asymmetric addition of dimethylzinc to aldehydes in the presence of β-amino alcohols.[4] In addition, the substrate scope was limited to benzaldehyde or to only a few other aldehydes. This is in great contrast to the chiral amino alcohol-catalyzed asymmetric addition of diethylzinc to aldehydes, which is a very effective and general method.[5]

Because of the lack of reactivity of dimethylzinc combined with the importance of the addition products in synthesis, asymmetric addition of dimethylzinc to aldehydes has become very challenging in catalytic asymmetric synthesis. In recent years, the enantioselective addition of dimethylzinc to aldehydes has received a special attention in the presence of catalytic amounts of chiral ligands.[6–12] In 2005, α-hydroxy amide **1** was synthesized and used as a chiral ligand for asymmetric addition of Me_2Zn to aromatic aldehydes with good enantioselectivity by means of titanium isopropoxide.[6] In 2006, Cozzi and Kotrusz developed a highly enantioselective addition of Me_2Zn to aldehydes, including aromatic and hindered aliphatic aldehydes or α,β-unsaturated aldehydes, in the presence of the commercially available ClCr(Salen) **2**.[7] Later, Ando et al. synthesized a new fluorous ligand **3** that



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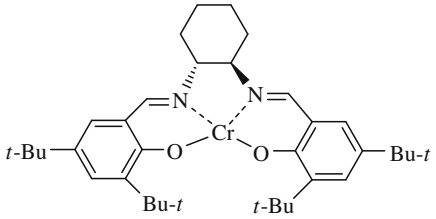

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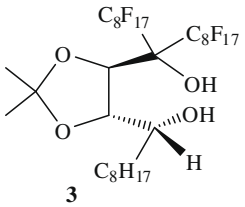

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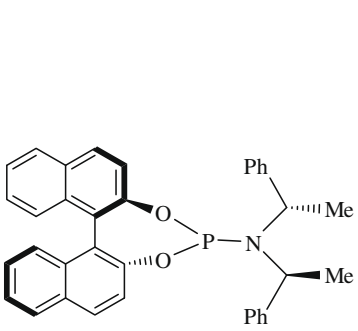

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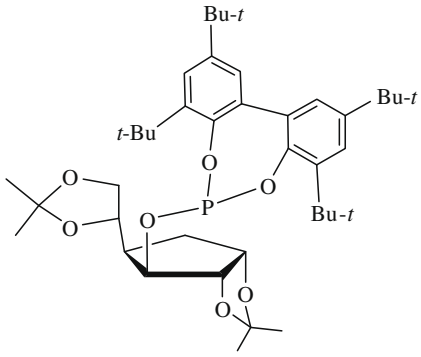

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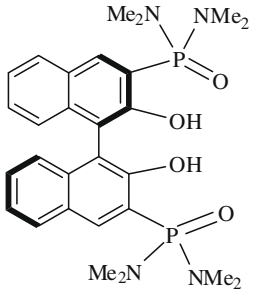

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showed excellent asymmetric induction for the addition of Me_2Zn to aldehydes.[8]

At the same time, alternative methylation reagents for a highly enantioselective addition of Me_3Al to aldehydes have been also reported. Woodward et al. first reported the asymmetric addition of Me_3Al to arylaldehydes with high enantioselectivities by employing a nickel catalyst in the presence of a phosphoroamidite **4**.[9] Later, the same group found that the monophosphite chiral ligand **5** provided high enantioselectivities for the Ni-catalyzed asymmetric addition of Me_3Al to several arylaldehydes.[10]

However, these impressive methods depended on additional metals (other than simple alkylmetals zinc and aluminum) complexes of specific chiral ligands, and therefore may complicate the extension to other zinc or aluminum species or to the use of other ligands. In 2006, Ishihara et al. described a highly enantioselective dialkylzinc (R_2Zn), including Me_2Zn, Et_2Zn, Bu_2Zn, and Ph_2Zn, addition to a series of aromatic, aliphatic, and heteroaromatic aldehydes based on conjugate Lewis acid–Lewis base catalysis by means of chiral ligand **6**.[11] More recently Wang et al. also reported a general and highly enantioselective ligand **7** for asymmetric methylation, ethylation, arylation, and alkynylation of a wide variety of aldehydes.[12] Almost at the same time, Pericàs et al. synthesized a series of chiral β-amino alcohols with a common 2-amino-2-aryl-1,1-diphenylethanol skeleton such as **8**, and used them as catalysts for asymmetric ethylation, methylation, and phenylation of aldehydes with high enantioselectivities.[13a] The asymmetric addition of simple alkylmetals to a variety of aldehydes with high enantioselectivities and yields is rare in the presence of a catalytic amount of chiral ligands. Therefore, the asymmetric methylation of aldehydes employing only a catalytic amount of chiral ligands and no additional central metals, which gives high catalytic performance in enantioselectivity and chemical yield, is still challenging.

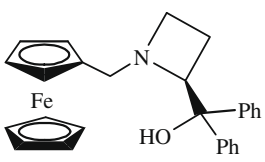
In our previous work, (2*S*)-1-(ferrocenylmethyl)aziridin-2-yl(diphenyl)methanol **9** was synthesized and applied to the catalytic asymmetric addition of diethylzinc to aldehydes, and in the best case, enantioselectivities of up to 99% ee were obtained.[14] This chiral ligand **9** was also used in asymmetric aryl transfer to aldehydes to obtain diarylmethanols with up to 98% ee.[15] In order to examine the effect of the rigidity of three-membered aziridine ring (relative to the four-membered azetidine ring) on chiral induction for the methylation of aldehydes, and extend further the scope of our chiral ferrocenyl aziridino alcohol **9**, herein, we report our results on the highly enantioselective addition of dimethylzinc to aldehydes in the presence of a catalytic amount of chiral ferrocenyl aziridino alcohol **9**.

2. Results and discussion

The chiral ferrocenyl aziridino alcohol **9** was easily synthesized from commercially available L-serine according to our previously reported procedure (Scheme 1).[14]

At the outset of our study, we examined a reaction of dimethylzinc with benzaldehyde at 0 °C in the presence of 3 mol % **9**. Unfortunately, there was almost no reaction even after 72 h (Table 1, entry 1). This further suggested that the reactivity of dimethylzinc with benzaldehyde is lower than that of diethylzinc because the reaction of diethylzinc with benzaldehyde performed well under the same reaction conditions.[14] When the reaction was carried out at 30 °C, a dramatic improvement in catalytic activity and enantioselectivity was realized. The reaction of benzaldehyde with 2 equiv of dimethylzinc (hexane solution) was conducted in toluene in the presence of 3 mol % **9** for 48 h to give the corresponding addition product in 96% yield and 89.9% ee (Table 1, entry 2). Increasing the amount of ligand **9** from 3 to 5 mol % did not lead to a further improvement in catalytic activity and reaction enantioselectivity (Table 1, entry 3).

In order to examine the generality of substrates for this transformation, 3 mol % chiral ligand **9** and 30 °C were selected as the reaction conditions for the asymmetric addition of dimethylzinc to a wide variety of arylaldehydes, and the results are summarized in Table 1 (entries 4–19). As can be seen from Table 1, good to excellent enantioselectivities could be achieved for various aromatic aldehydes, including *ortho*-, *para*-, and *meta*-substituted benzaldehydes (Table 1, entries 4–16), heliotropin (Table 1, entry 17), ferrocenecarboxaldehyde (Table 1, entry 18), and α-naphthaldehyde (Table 1, entry 19). However, a strong substrate dependence was observed in this catalytic system, that is, the electronic effects and different positions of substituents on the benzene ring highly



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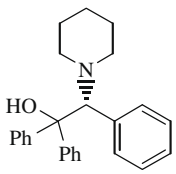

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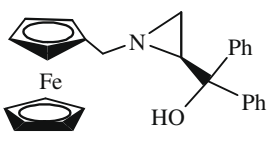

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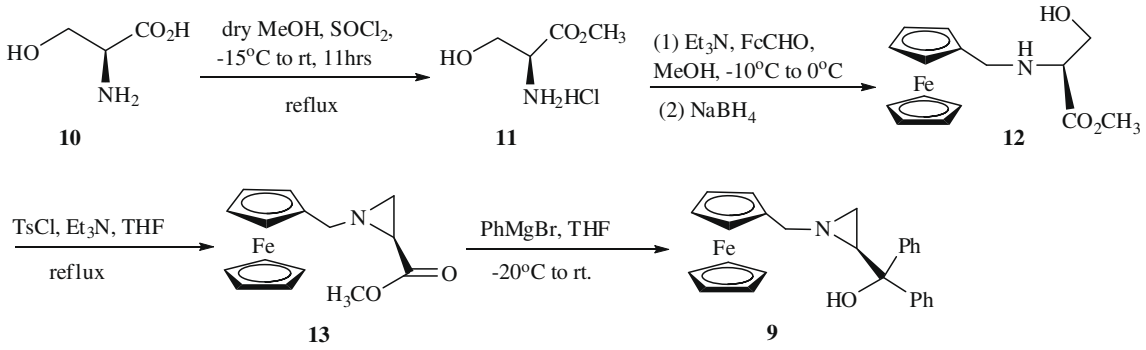
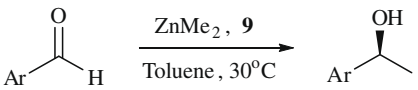
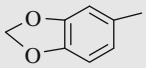


Scheme 1. Synthesis of the aziridino alcohol **9**.

Table 1
Asymmetric addition of dimethylzinc to aldehyde catalyzed by **9**[a]



Entry	Ar	**9** (mol %)	Temperature (°C)	Time (h)	Yield[b] (%)	ee[c] (%)	Configuration[d]
1	C_6H_5	3	0	72	Trace	ND	
2	C_6H_5	3	30	48	96	89.9	(*S*)
3	C_6H_5	5	30	48	95	89.7	(*S*)
4	*p*-MeC_6H_4	3	30	48	99	94.5	(*S*)
5	*p*-$MeOC_6H_4$	3	30	48	98	89.1	(*S*)
6	*p*-$Me_2NC_6H_4$	3	30	48	70	71.7	(*S*)
7	*p*-ClC_6H_4	3	30	48	85	74.1	(*S*)
8	*p*-BrC_6H_4	3	30	48	97	93.4	(*S*)
9	*o*-MeC_6H_4	3	30	48	96	74.5	(*S*)
10	*o*-$MeOC_6H_4$	3	30	48	98	90.2	(*S*)
11	*o*-ClC_6H_4	3	30	48	98	86.2	(*S*)
12	*m*-MeC_6H_4	3	30	48	94	90.6	(*S*)
13	*m*-$MeOC_6H_4$	3	30	48	93	90.8	(*S*)
14	*m*-$PhOC_6H_4$	3	30	48	99	92.0	(*S*)
15	*m*-ClC_6H_4	3	30	48	97	92.3	(*S*)
16	*m*-BrC_6H_4	3	30	48	95	94.3	(*S*)
17		3	30	48	96	90.3	(*S*)
18	Ferrocenyl	3	30	48	73	97.5	(*S*)
19	1-Naphthyl	3	30	48	82	71.0	(*S*)

[a] The mol ratio of Me_2Zn:aldehyde was 2:1.
[b] Isolated yields.
[c] Determined by HPLC using chiral columns: Chiralcel OD or OB, respectively. In all cases, the product chromatograms were compared against a known racemic mixture.
[d] Absolute configuration assigned by comparison with the known elution order from Chiralcel OD or OB columns according to the literature and considering the similarity in the stereochemical reaction pathway (Fig. 1).

affected the reaction enantioselectivity. For example, when aromatic aldehydes with electron-donating group at the *para*-positions on the phenyl ring were methylated, the enantioselectivities of the reaction decreased with the increase in the electron-donating effects of substituents (Table 1, entries 4–6). Similar phenomena were also observed in the catalytic asymmetric addition of dimethylzinc to arylaldehydes in the presence of β-amino alcohol [(2*S*)-3-*exo*-(dimethylamino)isoborneol].[3b] When aromatic aldehydes with electron-withdrawing group at *para*-positions on the phenyl ring were methylated, *p*-chlorobenzaldehyde with a stronger electron-withdrawing group resulted in a large decrease in enantioselectivity relative to *p*-bromobenzaldehyde (Table 1, entries 7 vs 8). When *ortho*-substituted benzaldehydes were methylated (Table 1, entries 9–11), *o*-methoxybenzaldehyde with a strong electron-donating group gave excellent enantioselectivity of up to 90.2% ee (Table 1, entry 10). Both electron-donating (Table 1, entries 12–14) and electron-withdrawing groups (Table 1, entries 15 and 16) at *meta*-positions on the benzene ring afforded excellent enantioselectivities of over 90% ee. The best asymmetric induction (as high as 97.5% ee) was found by using a ferrocenyl aldehyde as the substrate (Table 1, entry 18). The level of enantioselectivities achieved is comparable to that of other methods hitherto reported for the asymmetric addition of dimethylzinc to arylaldehydes.[6–10] Note that, unlike the previously reported catalytic systems for the addition of dimethylzinc to a wide range of substrates with high enantioselectivities, this catalytic system does not require the use of additional metal complexes such as Ti or Ni.[6–10]

It was worth mentioning that, in previous reports,[4,13a] when chiral β-amino alcohols were used as catalysts for the asymmetric addition of dimethylzinc to aldehydes, the reaction had to be performed in the presence of chiral ligand at a higher temperature than diethylzinc in order to obtain good yields and good enantioselectivities because of the decreased reactivity of dimethylzinc. Even so, a dramatic decrease in enantioselectivities for the methyl-

ation of aldehydes was usually observed compared to ethylation of the corresponding aldehydes in the presence of the same chiral ligand. For example, ethylation of benzaldehyde, *p*-methoxybenzaldehyde, *o*-methylbenzaldehyde, *m*-methylbenzaldehyde with 6 mol % of the chiral β-amino alcohol **8** afforded the corresponding addition products with 98% ee, 98% ee, 97% ee, and 98% ee,[13a] respectively, while methylation of the corresponding aldehydes with 10 mol % of **8** gave 90% ee, 84% ee, 88% ee, and 91% ee,[13a] respectively. However, the chiral β-amino alcohol **9** for asymmetric methylation does not result in a big decrease in enantioselectivities (relative to ethylation) in the presence of the same loading (3 mol %) of the catalyst. For example, ethylation of benzaldehyde, *p*-methoxybenzaldehyde, *o*-methoxybenzaldehyde, *m*-chlorobenzaldehyde, *m*-bromobenzaldehyde with 3 mol % of **9** afforded the corresponding ethylation products with 92.7% ee, 92.8% ee, 93.5% ee, 98.8% ee, and 96.4% ee,[14] respectively, while methylation of the corresponding aldehydes with 3 mol % of **9** gave 89.9% ee, 89.1% ee, 90.2% ee, 92.3% ee, and 94.3% ee (Table 1, entries 2, 5, 10, 15, and 16), respectively.

Compared with the four-membered azetidine with slightly less rigid ring backbone,[12] the rigid three-membered aziridine ring ligand **9** did not give an obvious improvement in reaction enantioselectivities for the asymmetric addition of dimethylzinc to aldehydes.

The (*S*)-absolute configuration for the addition products, the same for the addition of diethylzinc to arylaldehydes catalyzed by **9**,[14] was noted in all the cases studied (Table 1, entries 2–19). Comparison of the absolute configuration of the addition products for the methylation of arylaldehydes with the ethylation of arylaldehydes enabled us to ascertain that the present methylation process was mechanistically similar to the ethylation process.[14b] That is, the *si* face of arylaldehydes was attacked by a methyl group (Fig. 1), giving the corresponding addition products with the (*S*)-absolute configuration.

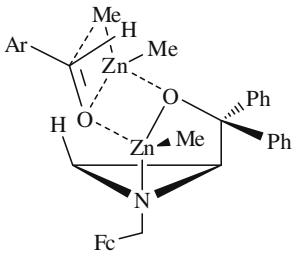


Figure 1. A possible transition state for the methylation of arylaldehydes.

3. Conclusion

In conclusion, we have demonstrated that the chiral ligand **9** is a good enantioselective catalyst for the asymmetric addition of dimethylzinc to a wide variety of arylaldehydes in the absence of additional metal complexes such as Ti or Ni. The results showed that the electronic effects and different positions of substituents on the benzene ring highly affected the reaction enantioselectivities. Further application of chiral ligands **9** for asymmetric synthesis is under investigation in our laboratory.

4. Experimental

4.1. General

Melting points were determined using YRT-3 melting point apparatus, and were uncorrected. Optical rotations were measured with Perkin Elmer, model 341 Polarimeter at 20 °C in $CHCl_3$. The ee value was determined by HPLC using a chiral column with hexane/2-propanol (ratio as indicated) as the eluent. The chiral HPLC methods were calibrated with the corresponding racemic mixtures. The chromatographic system consisted of a JASCO model PU-1580 intelligent HPLC pump and a JASCO model UV-1575 intelligent UV–vis detector (216 nm). The injection loop had a 20 μL capacity. The column used was a Chiralcel OD, and OB (250 × 4.6 mm) from Daicel Chemical Ind., LTD (Japan). The column was operated at ambient temperature. TLC was performed on dry silica gel plates developed with hexane/ethyl acetate. NMR Spectra (^1H and ^{13}C) were performed on a Bruker DPX 400 (400 MHz) spectrometer using solutions in $CDCl_3$ (referenced internally to Me_4Si); *J* values are given in Hertz. IR spectra were determined on a Therme Nicolet IR 200 spectrophotometer. Mass spectra were obtained using a Waters a-Tof micro™ instrument with an electrospray ionization source (ESIMS). All the ESIMS spectra were performed using MeOH as the solvent.

4.2. Reagents and solvents

Except for dimethylzinc purchased from Aldrich, all other reagents were purchased in China. Toluene was pre-dried over calcium chloride, and then distilled from sodium before use. Ether was distilled from sodium benzophenone ketyl. All other reagents are commercially available and were used as received.

4.3. General procedure for the asymmetric addition of diethylzinc to arylaldehydes catalyzed by 9

A solution of dimethylzinc (1.66 mL, 200 mol %, 1.2 mol/L in toluene) was added to a dried Schlenk tube containing toluene (2 mL) and chiral ligand **9** (6.4 mg, 3 mol %) under a nitrogen atmosphere. The mixture was stirred for 0.5 h at 40 °C, followed by cooling to 0 °C, and aldehyde (0.5 mmol) was added. The resulting mixture was warmed to 30 °C, and kept stirring for another 48 h at the same temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl (4 mL).The mixture was extracted with Et_2O (3 × 8 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. Purification of the residue by the preparative silica gel TLC plate (hexane/EtOAc) afforded the (*S*)-1-aryl-1-ethanol. The ee was determined by HPLC analyses using a chiral column: OB, and OD, respectively. In all cases, the product chromatograms were compared against a known racemic mixture.

4.3.1. (*S*)-1-Phenyl-1-ethanol (entry 2 in Table 1)[6–10]

Enantiomeric excess: 89.9%, Chiralcel OD, 216 nm, *i*-PrOH/hexane = 5/95, 0.5 mL/min, t_R = 15.2 min, t_S = 17.8 min.

4.3.2. (*S*)-1-*p*-Methylphenyl-1-ethanol (entry 4 in Table 1)[8–10]

Enantiomeric excess: 94.5%, Chiralcel OB, 216 nm, *i*-PrOH/hexane = 1/100, 0.4 mL/min, t_R = 39.77 min, t_S = 34.03 min.

4.3.3. (*S*)-1-*p*-Methoxyphenyl-1-ethanol (entry 5 in Table 1)[7–10]

Enantiomeric excess: 89.1%, Chiralcel OD, 216 nm, *i*-PrOH/hexane = 3/97, 0.7 mL/min, t_R = 21.41 min, t_S = 24.06 min.

4.3.4. (*S*)-1-*p*-Dimethylaminophenyl-1-ethanol (entry 6 in Table 1)[16]

^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, *J* = 6.4 Hz, 3H, CH_3), 2.96 [s, 6H, $N(CH_3)_2$] 4.17 (q, *J* = 6.4 Hz, 1H, CH_3CH); 6.73 (d, *J* = 8.8 Hz, 2H, Ph*H*), 7.16 (q, *J* = 8.8 Hz, 2H, Ph*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.6, 40.7, 73.5, 112.4, 127.3, 132.0, 145.0. Enantiomeric excess: 71.7%, Chiralcel OD, 216 nm, *i*-PrOH/hexane = 2/98, 0.7 mL/min, t_R = 38.66 min, t_S = 42.36 min.

4.3.5. (*S*)-1-*p*-Chlorophenyl-1-ethanol (entry 7 in Table 1)[6–10]

Enantiomeric excess: 74.1%, Chiralcel OD, 216 nm, *i*-PrOH/hexane = 2/98, 0.5 mL/min, t_R = 29.57 min, t_S = 27.31 min.

4.3.6. (*S*)-1-*p*-Bromophenyl-1-ethanol (entry 8 in Table 1)[7,10]

Enantiomeric excess: 93.4%, Chiralcel OD, 216 nm, *i*-PrOH/hexane = 2/98, 0.5 mL/min, t_R = 34.81 min, t_S = 31.80 min.

4.3.7. (*S*)-1-*o*-Methylphenyl-1-ethanol (entry 9 in Table 1)[6,9]

Enantiomeric excess: 74.5%, Chiralcel OB, 216 nm, *i*-PrOH/hexane = 10/150, 0.5 mL/min, t_R = 15.87 min, t_S = 11.78 min.

4.3.8. (*S*)-1-*o*-Methoxyphenyl-1-ethanol (entry 10 in Table 1)[6]

Enantiomeric excess: 90.2%, Chiralcel OB, 216 nm, *i*-PrOH/hexane = 3/100, 0.5 mL/min, t_R = 26.50 min, t_S = 16.39 min.

4.3.9. (*S*)-1-*o*-Chlorophenyl-1-ethanol (entry 11 in Table 1)[6,10]

Enantiomeric excess: 86.2%, Chiralcel OB, 216 nm, *i*-PrOH/hexane = 1/150, 0.5 mL/min, t_R = 13.62 min, t_S = 10.56 min.

4.3.10. (*S*)-1-*m*-Methylphenyl-1-ethanol (entry 12 in Table 1)[6,9]

Enantiomeric excess: 90.6%, Chiralcel OD, 216 nm, *i*-PrOH/hexane = 2/98, 0.5 mL/min, t_R = 24.82 min, t_S = 33.31 min.

4.3.11. (*S*)-1-*m*-Methoxyphenyl-1-ethanol (entry 13 in Table 1)[6]

Enantiomeric excess: 90.8%, Chiralcel OB, 216 nm, *i*-PrOH/hexane = 1/150, 0.5 mL/min, t_R = 21.12 min, t_S = 25.47 min.

4.3.12. (*S*)-1-*m*-Phenoxyphenyl-1-ethanol (entry 14 in Table 1)

$[\alpha]_D^{20} = -28.0$ (*c* 0.26, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (d, *J* = 6.4 Hz, 3H, CH_3); 4.83 (q, *J* = 6.4 Hz, 1H, CH_3CH); 6.87–7.34 (m, 8H, Ph*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1, 69.9, 115.8, 117.6, 118.87, 118.90, 120.1, 123.3, 129.71, 129.74, 147.9, 157.0, 157.4. IR (KBr pellets): 3397 cm^{-1}. MS: *m*/*z* (ESI) 237 (M^++Na). Enantiomeric excess: 92.0%, Chiralcel OB, 216 nm, *i*-PrOH/hexane = 1/150, 0.5 mL/min, t_R = 22.38 min, t_S = 17.58 min.

4.3.13. (*S*)-1-*m*-Chlorophenyl-1-ethanol (entry 15 in Table 1)[8,10]

Enantiomeric excess: 92.3%, Chiralcel OB, 216 nm, *i*-PrOH/hexane = 1/150, 0.5 mL/min, t_R = 17.27 min, t_S = 13.42 min.

4.3.14. (*S*)-1-*m*-Bromophenyl-1-ethanol (entry 16 in Table 1)[7]

Enantiomeric excess: 94.3%, Chiralcel OD, 216 nm, *i*-PrOH/hexane = 2/98, 0.5 mL/min, t_R = 34.17 min, t_S = 31.03 min.

4.3.15. (*S*)-1-[3,4-(Methylenedioxy)phenyl]-1-ethanol (entry 17 in Table 1)

$[\alpha]_D^{20} = -42.0$ (*c* 0.61, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (d, *J* = 6.4 Hz, 3H, CH_3); 4.76 (q, *J* = 6.4 Hz, 1H, CH_3CH); 5.91 (s, 2H, OCH_2O), 6.72–6.85 (m, 3H, Ph*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1, 70.1, 100.9, 106.0, 108.0, 118.6, 139.9, 146.7, 147.7. IR (KBr pellets): 3395 cm^{-1}. MS: *m*/*z* (ESI) 189 (M^++Na). Enantiomeric excess: 90.3%, Chiralcel OD, 216 nm, *i*-PrOH/hexane = 2/98, 0.5 mL/min, t_R = 52.68 min, t_S = 56.63 min.

4.3.16. (*S*)-1-Ferrocenyl-1-ethanol (entry 18 in Table 1)[17]

Enantiomeric excess: 97.5%, Chiralcel OD, 216 nm, *i*-PrOH/hexane = 1/300, 1 mL/min, t_R = 56.37 min, t_S = 48.27 min.

4.3.17. (*S*)-1-α-Naphthyl-1-ethanol (entry 19 in Table 1)[18]

Enantiomeric excess: 71.0%, Chiralcel OD, 216 nm, *i*-PrOH/hexane = 1/150, 0.5 mL/min, t_R = 41.94 min, t_S = 26.58 min.

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