Tetrahedron: *Asymmetry* 19 (2008) 2563–2567

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Divergent enantioselective pathways in the catalytic asymmetric addition of diethylzinc to aldehydes in the presence and absence of titanium tetraisopropoxide

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ARTICLE INFO

Article history:
Received 24 August 2008
Accepted 21 October 2008

ABSTRACT

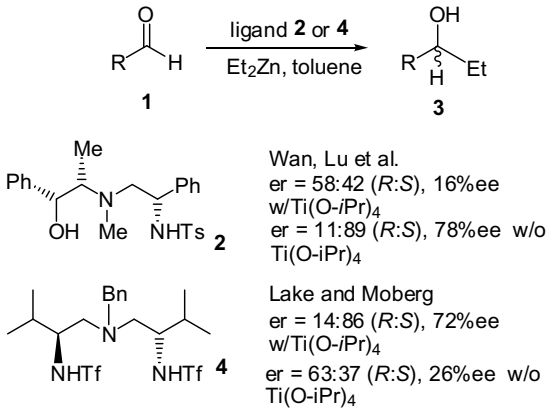
The stereochemical outcome of the asymmetric addition of diethylzinc to aldehydes catalyzed by (*R,R*)-hydrobenzoin can be influenced by the absence or presence of Ti(O-*i*Pr)$_4$. The enantiomeric ratios obtained in the absence of Ti(O-*i*Pr)$_4$ favor the (*S*)-enantiomer, whereas the ratios obtained from the use of Ti(O-*i*Pr)$_4$ favor the formation of the (*R*)-enantiomer. The formation of the opposite enantiomers is attributed to the different transition states mediated by either zinc or titanium.

1. Introduction

The catalytic asymmetric addition of diorganozinc reagents to carbonyl compounds, which was first reported by Oguni et al. in 1984, has experienced tremendous growth.[1] The process has been well studied and reviewed by Pu[2] and Walsh.[3] A common additive that is employed to help facilitate the asymmetric addition of diorganozinc reagents to carbonyl substrates, is titanium tetraisopropoxide [Ti(O-*i*Pr)$_4$]. This reagent has become nearly ubiquitous in its application in this process, as it has been demonstrated to be a powerful promoter of the addition process.[3–6] In this regard, Walsh et al. demonstrated that there is a reaction between the Ti(O-*i*Pr)$_4$ and diethylzinc to give a reactive intermediate EtTi(O-*i*Pr)$_3$ that is the likely alkylating agent.[3]

An interesting aspect of the use of Ti(O-*i*Pr)$_4$ in the diorganozinc addition reaction is the impact on the stereochemical outcome of the enantioselective addition. It has been reported that varying the stoichiometric amount of Ti(O-*i*Pr)$_4$ from zero equivalents to multiple equivalents can cause significant changes in the observed ratio of enantiomers from the addition reaction. The change in the enantiomeric ratio of the addition product by the addition of Ti(O-*i*Pr)$_4$ and Et$_2$Zn to aldehydes was previously observed by Wan, Lu et al. using a tridentate ephedrine-based ligand (Scheme 1).[7] The reversal of enantioselectivity was significant but not practical in its scope. It was suggested that the reversal was the result of the differences in the 'coordination forms', wherein zinc is the central coordinating atom in one case and titanium in the other.[7a] There have been reports on the successful and practical reversal of the enantioselectivity of the catalytic asymmetric addition, which have been attributed to structural changes of the catalyst systems that have been used.[8] However, to our knowledge a reaction mediator, such as Ti(O-*i*Pr)$_4$, has only been employed with the discrete purpose of achieving practical divergent enantioselective reactions with diethylzinc.[7,9]

Lake and Moberg[9] conducted a study in which they employed a tridentate catalyst derived from L-valine in conjunction with varying amounts of Ti(O-*i*Pr)$_4$ in the asymmetric addition of diethylzinc to aromatic aldehydes. The enantioselectivities that were obtained using this catalyst system, ranged from 63:37 favoring the (*R*)-enantiomer to 14:86 favoring the (*S*)-enantiomer with increasing amounts of Ti(O-*i*Pr)$_4$. Zhang[10] and Seebach[11] have independently observed that the use of sub-stoichiometric amounts of Ti(O-*i*Pr)$_4$ with varying chiral catalysts in the asymmetric addition of



Scheme 1. Enantioselective addition of diethylzinc to aldehydes.

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doi:10.1016/j.tetasy.2008.10.033

diorganozinc reagents to carbonyl compounds afforded decreased enantioselectivities.

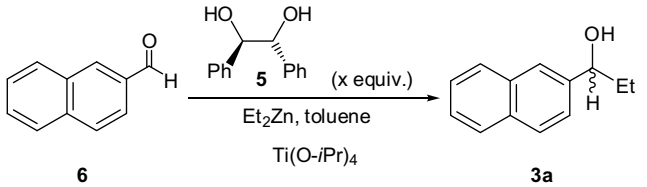
A central theme in these literature examples is that it is difficult to predict if changing the amount of the Ti(O-*i*Pr)$_4$ will cause a significant reversal of enantioselectivity, or if the enantioselectivity will simply be compromised. We became interested in determining if there might be an optimal ligand system that would be useful in terms of achieving high enantioselectivity for one enantiomer in the absence of Ti(O-*i*Pr)$_4$ and high selectivity for the opposite enantiomer in the presence of Ti(O*i*Pr)$_4$. Numerous research groups have pursued and, in some cases, have achieved excellent enantioselectivities for the Ti(O-*i*Pr)$_4$ mediated addition of diorganozinc reagents to carbonyl compounds.[1,2] However, there are few examples of exploiting the presence and absence of Ti(O-*i*Pr)$_4$ as a means of obtaining either enantiomer of the addition product.[7a,b] The optimal ligand for such an application would allow for the opposing 'coordination forms' and was proposed by Mao et al. to be 'symmetrical' from the standpoint of the interaction of the metal center. This appeared to be a feature that previous studies either did not pursue or did not optimize. One ligand system that was explored early in the development of the catalytic asymmetric addition of diethylzinc to aldehydes was 1,2-diphenyl-1,2-ethanediol **5** (hydrobenzoin).[12] Salvadori et al. employed this ligand system in the enantioselective addition of diethylzinc to a variety of aromatic aldehydes and generated enantiomeric ratios that were as high as 89:11.[12] The use of Ti(O-*i*Pr)$_4$ with binaphthol-based systems and bis(sulfonamides) has been well documented.[2,3] In contrast, to the best of our knowledge, there are no reports describing the use of Ti(O-*i*Pr)$_4$ with enantiomerically enriched hydrobenzoin. Herein, we report our efforts to evaluate hydrobenzoin in the catalytic asymmetric addition of diethylzinc to aldehydes in the absence and the presence of Ti(O-*i*Pr)$_4$. We also report on the divergent pathways that occur for these two systems and contrast them with previous observations of the reversal of enantioselectivity of the diethylzinc reactions with carbonyl compounds involving Ti(O-*i*Pr)$_4$. The reversal of enantioselectivities observed herein represents some of the best changes in magnitude reported in the literature to date.

2. Results and discussion

We began this study by first examining the impact of the number of equivalents of the (*R*,*R*)-hydrobenzoin ligand **5** on the asymmetric addition of diethylzinc to 2-naphthaldehyde in the absence or presence of Ti(O-*i*Pr)$_4$ (Table 1). All reactions were run for 18 h at ambient temperature. Attempts to run the reactions at lower temperatures (0 °C, −10 °C, and −78 °C) gave incomplete reactions and lower enantioselectivities. It was determined that the enantiomeric ratios underwent a slight improvement as the amount of **5** was increased (entries 1–4) but decreased at a point of 0.5 equiv (entry 5). Mechanistically, this might suggest that that an excess of **5** may lead to multiple reactive intermediates that are structurally dissimilar and have different capacities for enantioselection. The results collected suggest that the use of 0.3 equiv of **5** would be ideal for further experimentation. It is worth noting that the use of 0.4 equiv gave comparable or better enantioselectivities (entries 4 and 9); however, the amount of catalytic ligand was considered to be too excessive for practical consideration.

Furthermore, there was a change in the absolute configuration of the product of the asymmetric addition in the presence of Ti(O-*i*Pr)$_4$ from the (*R*)-configuration to the (*S*)-configuration (entries 1–5 vs entries 6–10). We became interested in determining if varying the relative amount of the Ti(O-*i*Pr)$_4$ relative to the (*R*,*R*)-hydrobenzoin in the asymmetric addition would have a similar effect as observed in other research programs[7,9] (Table 2).

Table 1
Catalytic asymmetric synthesis with (*R*,*R*)-hydrobenzoin **5**

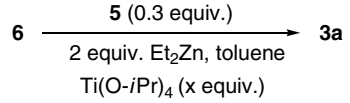


6 **3a**

Entry	Cat. 5 (equiv)	Ti(O-*i*Pr)$_4$ (equiv)	Yield[a]	er [*R*:*S*, (|*R*−*S*|)][b]	Config.[c]
1	0.10	0	74[d]	11.5:88.5 (77)	(*S*)
2	0.20	0	95	8.0:92.0 (84)	(*S*)
3	0.30	0	93	7.5:92.5 (85)	(*S*)
4	0.40	0	93	8.5:91.5 (83)	(*S*)
5	0.50	0	70[d]	13.5:86.5 (73)	(*S*)
6	0.10	1	85	79.1:20.9 (58)	(*R*)
7	0.20	1	84	81.5:18.5 (63)	(*R*)
8	0.30	1	87	82.0:18.0 (64)	(*R*)
9	0.40	1	83	86.5:13.5 (73)	(*R*)
10	0.50	1	70[d]	82.0:18.0 (64)	(*R*)

[a] Isolated yield after flash chromatography.
[b] Enantiomeric ratios were determined by CSP HPLC with a Chiralcel OD column.
[c] The absolute configuration of the product was determined by correlation of HPLC data with literature values for HPLC and specific rotations.[8a,14]
[d] There was a significant amount of remaining aldehyde and the corresponding reduction product.[13]

Table 2
Variation of Ti(O-*i*Pr)$_4$ in the asymmetric catalysis with (*R*,*R*)-hydrobenzoin



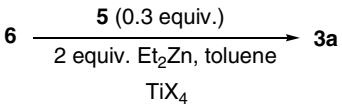
Entry	Ti(O-*i*Pr)$_4$	Yield[a]	er [*R*:*S*, (|*R*−*S*|)][b]	Config.[c]
1	0.30	92	78.5:21.5 (57)	(*R*)
2	0.50	70[d]	86.0:14.0 (72)	(*R*)
3	0.70	70[d]	85.0:15.0 (70)	(*R*)
4	1.00	87	82.0:18.0 (64)	(*R*)
5	1.25	70[d]	78.0:22.0 (56)	(*R*)

[a] Isolated yield after flash chromatography.
[b] Enantiomeric ratios were determined by CSP HPLC with a Chiralcel OD column.
[c] The absolute configuration of the product was determined by correlation of HPLC data with literature values for HPLC and specific rotations.
[d] There was a significant amount of the direct reduction product, 2-naphthylmethanol.[13]

With the exception of one instance (entry 2), the enantioselectivities were fairly consistent and ranged between 78:22 and 87:13 favoring the (*R*)-enantiomer. However, some of the addition reactions were compromised in terms of the isolated yield due to the presence of unreacted aldehyde and 2-naphthylmethyl alcohol, the product of reduction by diethylzinc.[13] The use of 25% excess of Ti(O-*i*Pr)$_4$ caused the enantiomeric ratio to decrease. As was postulated for the results in Table 1, we propose that an excess of the reagent, Ti(O-*i*Pr)$_4$ in this case, was responsible for the evolution of multiple catalytic species that afford different enantioselectivities. Ultimately, the combination that was determined to be optimal in terms of the enantiomeric ratio and isolated yield involved the use of 0.30 equiv of **5** and 1.0 equiv of the Ti(O-*i*Pr)$_4$.

The use of an alternate titanium alkoxide was also considered as a means of improving the enantioselectivity of the process. Recently, Tanski and co-workers disclosed that the identity of the alkoxy group of the titanium mediator could have an influence over the course of the asymmetric addition of diethylzinc to

Table 3
Catalysis with different titanium reagents



Entry	TiX_4, X=	Yield[a]	er, [*R*:*S*, (|*R*−*S*|)][b]	Config.[c]
1	$-OCH_3$	61	52.0:48.0 (4)	(*R*)
2	–O-*n*-Bu	92	69.0:31.0 (38)	(*R*)
3	–O-*i*-Pr	87	82.0:18.0 (64)	(*R*)
4	–Cl	37	47.0:53.0 (6)	(*S*)

[a] Isolated yield after flash chromatography.
[b] Enantiomeric ratios were determined by CSP HPLC with a Chiralcel OD column.
[c] The absolute configuration of the product was determined by correlation of HPLC data with literature values for HPLC and specific rotations.

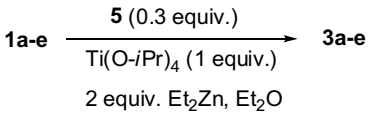
aldehydes.[15] Although Tanski et al. employed enantiomerically enriched titanium *tetra*-2-butoxide as the mediator, we only sought to make simple adjustments in the nature of the alkoxy group (Table 3).

We were disappointed to learn that the use of either titanium *tetra*-methoxide [$Ti(OMe)_4$] or titanium *tetra*-*n*-butoxide [$Ti(O\text{-}n\text{-}Bu)_4$] led to significantly lower enantioselectivities. This may have been a result of a faster background reaction with the smaller alkoxides. As expected, the more Lewis acidic titanium tetrachloride generated the desired product as well as numerous by-products and was not pursued further. Interestingly, there was no reversal of the enantiomeric ratio as compared to the example of hydrobenzoin without a titanium mediator. The use of $Ti(O\text{-}t\text{-}Bu)_4$ was not pursued as an earlier study suggested that this compound had provided limited success. Thus, it was determined that $Ti(O\text{-}i\text{Pr})_4$ was the best stoichiometric reagent for the transformation.

The last variable that was explored was the use of the solvent. Using the optimized conditions of 0.3 equiv of the catalyst and one equivalent of $Ti(O\text{-}i\text{Pr})_4$, the use of dichloromethane and diethyl ether was explored. It was determined that the use of dichloromethane led to the formation of the product 1-(2-naphthyl)-1-propanol in an enantiomeric ratio of 83.5 (*R*) to 16.5 (*S*) versus that of the reaction conducted in toluene, which afforded a diastereomeric ratio of 82.0 (*R*) to 18.0 (*S*). The use of diethyl ether gave a slight improvement in the enantiomeric ratio of 85.0 (*R*):15.0 (*S*). Based on this information, we conducted a series of reactions with different aromatic aldehydes (Table 4).

In general, the aldehyde substrates underwent a smooth transformation to form either enantiomer depending on the conditions that were applied. This suggested that the difference in the free energies of zinc-mediated pathway and the titanium-mediated pathway was not as good as in related literature examples (cf. Mao et al.[7] and Lake and Moberg[9]). In contrast, the use of *trans*-cinnamaldehyde gave inferior results, presumably due to the

Table 4
Optimized conditions diethylzinc addition catalyzed by hydrobenzoin



Entry	RCHO	$Ti(O\text{-}i\text{Pr})_4$ (equiv)	Yield[a]	er [*R*:*S*, (|*R*−*S*|)][b]	$[\alpha]_D^{24}$ in $CHCl_3$	Config.[c]
1	$2\text{-}C_{10}H_7-$	1	87	82.0:18.0 (64)	+22.4 (*c* 1.11)	(*R*)-**3a**
2	$2\text{-}C_{10}H_7-$	0	93	7.5:92.5 (85)	−32.3 (*c* 1.11)	(*S*)-**3a**
3	$1\text{-}C_{10}H_7-$	1	71	83.7:16.3 (68)	+34.9 (*c* 0.54)	(*R*)-**3b**
4	$1\text{-}C_{10}H_7-$	0	81	11.0:89.0 (78)	−41.7 (*c* 0.57)	(*S*)-**3b**
5	$4\text{-}MeOC_6H_5-$	1	64	71.9:28.1 (44)	+21.6 (*c* 0.40)	(*R*)-**3c**
6	$4\text{-}MeOC_6H_5-$	0	65	17.4:82.6 (65)	−23.4 (*c* 0.30)	(*S*)-**3c**
7	$C_6H_5CH{=}CH-$	1	66	61.6:38.4 (23)	+0.90 (*c* 0.44)	(*R*)-**3d**
8	$C_6H_5CH{=}CH-$	0	71	22.7:77.3 (55)	−5.25 (*c* 0.45)	(*S*)-**3d**
9	C_6H_5-	1	85	80.9:19.1 (62)	+29.6 (*c* 0.31)	(*R*)-**3e**
10	C_6H_5-	0	89	7.3:92.7 (85)	−36.1 (*c* 0.30)	(*S*)-**3e**

[a] Isolated yield after flash chromatography.
[b] Enantiomeric ratios were determined by CSP HPLC with a Chiralcel OD column.
[c] The absolute configuration of the product was determined by correlation of HPLC data with literature values for HPLC and specific rotations.

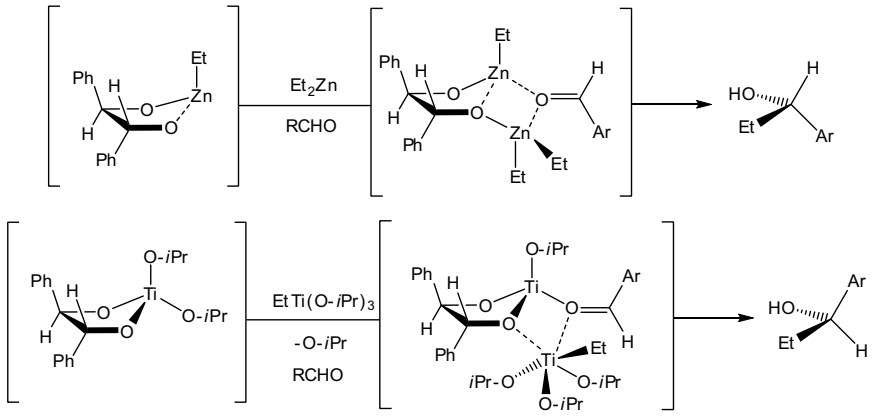
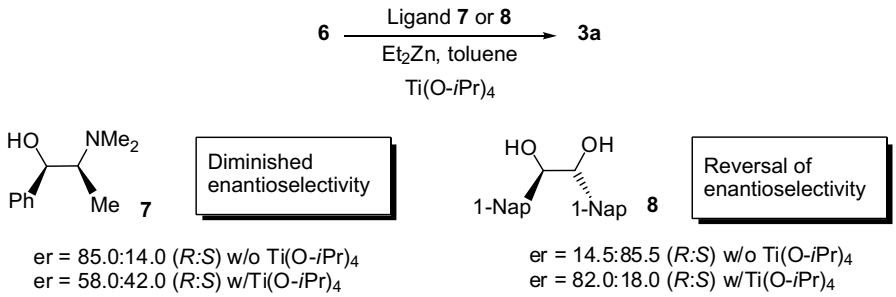


Figure 1. Proposed mechanism for enantiodivergent pathways.



Scheme 2. Ligand comparison.

stereoelectronic differences as compared to the aromatic aldehydes employed. Aliphatic aldehydes also proved to be problematic due to poor enantioselectivities and so were not pursued in this work.

The results listed in Table 4 strongly suggest that the development of enantiodivergent pathways in the asymmetric addition of diethylzinc to aldehydes via the use of Ti(O-*i*Pr)$_4$ might be optimal under the constraints of employing an ideal C_2-symmetric vicinal diol. This argument was developed based on the literature precedent that other ligand families that were not C_2-symmetric did not offer practical reversal of enantioselectivities.

Based on the literature precedents established Noyori et al.[16] and Walsh et al.,[3] a tentative mechanism has been proposed for these enantiodivergent pathways (Fig. 1). There are other mechanistic pathways that may be viable but these pathways most likely involve similar features, that is, the opposing coordinating forms as proposed by Mao et al..[7] More data should be collected before a more defined mechanism can be proposed as the results that have been obtained only suggest that C_2-symmetry is superior to C_1-systems and does not suggest any particular intermediates.

In order to further support this mechanistic proposal, two ligands, a C_1 β-amino alcohol **7** (*N*-methylephedrine) and a C_2-symmetric diol **8** (1,2-bis(1-naphthyl)ethane-1,2-diol), were employed in the asymmetric addition of diethylzinc with and without Ti(O-*i*Pr)$_4$ (Scheme 2). Ligand **7** afforded only a decrease in the enantioselection of the addition process. In contrast, the C_2-symmetric ligand **8** gave the opposite enantiomers in good to moderate enantioselectivity in the absence or presence of Ti(O-*i*Pr)$_4$. Although this evidence is limited in its scope, it still supports the use of C_2-symmetric vicinal diols in order to achieve practical levels of the reversal of enantioselectivity. A reaction mechanism detailing the key difference between the zinc-mediated and titanium-mediated pathways remains to be developed. It is postulated that whatever the key intermediates of the two pathways, C_2-symmetrical vicinal diols would allow them to have nearly opposite enantiofacial discrimination with aromatic aldehydes.

3. Conclusion

(*R*,*R*)-Hydrobenzoin has been employed as a ligand for the catalytic asymmetric addition of diethylzinc to aromatic and aldehydes in the absence or presence of Ti(O-*i*Pr)$_4$. The enantioselectivities of the process involving no Ti(O-*i*Pr)$_4$ were as high as 7.5:92.5, favoring the (*S*)-enantiomer (Table 4, entry 2). The enantioselectivities of the process where Ti(O-*i*Pr)$_4$ was used were as high as 83.7:16.3 favoring the (*R*)-enantiomer. A reversal in enantioselectivity was not observed when using *N*-methylephedrine, only diminished levels of selectivity. The results of this study suggest that it may be possible to design an optimal C_2-symmetric vicinal diol that would be able to afford very high enantioselectivities for either enantiomer when employed in the catalytic asymmetric addition of diorganozinc reagents with carbonyl compounds with and without Ti(O-*i*Pr)$_4$.

4. Experimental

4.1. General remarks

All reactions were run under a nitrogen atmosphere. Anhydrous toluene was purchased and stored under a nitrogen atmosphere. Diethylzinc was purchased as a 1 M solution in hexanes. All ^{1}H NMR spectra were recorded at 25 °C in $CDCl_3$ operating at 400 MHz. Chemical shifts are reported in parts per million (δ scale), and coupling constants (J values) are listed in Hertz (Hz). Optical activities were measured using at 589 nm using a Jasco digital polarimeter purchased with NSF grant #CHE 644950.

4.2. General procedure for the catalytic asymmetric addition of diethylzinc to aldehydes

In a flame-dried, nitrogen-purged round-bottomed flask were placed (*R*,*R*)-hydrobenzoin (0.10 g, 0.48 mmol, 0.3 equiv) and anhydrous ether (5 mL, ~0.3 M based on aldehyde). To this mixture, which was maintained at ambient temperature, was added diethylzinc (3.2 mL, 3.2 mmol, 2 equiv). This mixture was stirred for 15 min before the addition of the aldehyde (0.25 g, 1.6 mmol, 1 equiv). The reaction mixture was stirred overnight and then quenched by the slow addition of 1 M HCl, and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure to afford the crude products **3a**–**e**.

4.3. General procedure for the catalytic asymmetric addition of diethylzinc to aldehydes in the presence of Ti(O-*i*Pr)$_4$

In a flame-dried, nitrogen-purged round-bottomed flask were placed (*R*,*R*)-hydrobenzoin (0.10 g, 0.48 mmol, 0.3 equiv) and anhydrous diethyl ether (5 mL, ~0.3 M based on aldehyde). To this mixture, which was maintained at ambient temperature, was added titanium tetraisopropoxide (0.48 mL, 1.6 mmol, 1 equiv). This mixture was stirred for 25 min before the addition of the diethylzinc (3.2 mL, 3.2 mmol, 2 equiv). After 15 min, the aldehyde (0.25 g, 1.6 mmol, 1 equiv) was added and the reaction mixture was stirred overnight, and was quenched by the slow addition of 1 M HCl and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure to afford the crude products **3a**–**e**. In all cases, the enantiomeric ratio was determined by chiral stationary phase HPLC.

4.4. 1-(2′-Naphthyl)-1-propanol 3a[16]

Purified by flash chromatography (95:5, hexanes/EtOAc). 0.95 (t, J = 7.4 Hz, 3H), 1.80–1.95 (m, 2H), 4.78 (t, J = 6.3 Hz, 1H), 7.45–7.49 (m, 4H), 7.78–7.85 (m, 3H). (*S*)-**3a**: $[\alpha]_D^{24} = -32.3$ (*c* 1.11, $CHCl_3$); (*R*)-**3a**: $[\alpha]_D^{24} = +22.4$ (*c* 1.11, $CHCl_3$). CSP HPLC: OD, 98:2 (hex/IPA); t_R (*R*)-enantiomer (min) = 29.8. t_R (*S*)-enantiomer (min) = 25.4.

4.5. 1-(1′-Naphthyl)-1-propanol 3b[16]

Purified by flash chromatography (95:5, hexanes/EtOAc). 1.04 (t, J = 7.4 Hz, 3H), 1.91 (d, J = 3.6 Hz, 1H), 1.94–2.07 (m, 2H), 5.42 (dt, J = 4.3, 3.6 Hz, 1H), 7.46–7.54 (m, 3H), 7.64 (d, J = 6.8 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.86–7.88 (m, 1H), 8.12 (d, J = 7.6 Hz, 1H). (*S*)-**3b**: $[\alpha]_D^{24} = -41.7$ (*c* 0.57, $CHCl_3$); (*R*)-**3b**: $[\alpha]_D^{24} = +34.9$ (*c* 0.54, $CHCl_3$). CSP HPLC: OD, 90:10 (hex:IPA); t_R (*R*)-enantiomer (min) = 12.1. t_R (*S*)-enantiomer (min) = 7.08.

4.6. 1-(4-Methoxyphenyl)-1-propanol 3c[17]

Purified by flash chromatography (80:20, hexanes/EtOAc). 0.90 (t, J = 7.4 Hz, 3H), 1.67–1.88 (m, 2H), 3.81 (s, 3H), 4.56 (m, 1H), 6.88 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H). (*S*)-**3c**: $[\alpha]_D^{24} = -23.4$ (*c* 0.30, $CHCl_3$); (*R*)-**3a**: $[\alpha]_D^{24} = +21.6$ (*c* 0.40, $CHCl_3$). CSP HPLC: OD, 98:2 (hex:IPA); t_R (*R*)-enantiomer (min) = 16.6. t_R (*S*)-enantiomer (min) = 18.5.

4.7. 1-Phenyl-1-penten-3-ol 3d[17]

Purified by flash chromatography (95:5, hexanes/EtOAc). 0.98 (t, J = 7.4 Hz, 3H), 1.61–1.73 (m, 2H), 4.22 (dt, J = 12.4, 7.0 Hz, 1H), 6.22 (dd, J = 16.0, 7.0 Hz, 1H), 6.58 (d, J = 16.0 Hz, 1H), 7.24–7.40 (m, 5H). (*S*)-**3d**: $[\alpha]_D^{24} = -5.25$ (*c* 0.45, $CHCl_3$); (*R*)-**3d**: $[\alpha]_D^{24} = +0.9$ (*c* 0.44, $CHCl_3$). CSP HPLC: OD, 98:2 (hex/IPA); t_R (*R*)-enantiomer (min) = 21.1. t_R (*S*)-enantiomer (min) = 39.2.

4.8. 1-Phenyl-1-propanol 3e[17]

Purified by flash chromatography (80:20 hexanes/EtOAc). 0.92 (t, J = 7.4 Hz, 3H), 1.70–1.88 (m, 2H), 4.60 (t, J = 6.6 Hz, 1H), 7.26–7.29 (m, 2H), 7.34–7.36 (m, 3H). (*S*)-**3e**: $[\alpha]_D^{24} = -36.1$ (*c* 0.30, $CHCl_3$); (*R*)-**3e**: $[\alpha]_D^{24} = +29.6$ (*c* 0.31, $CHCl_3$). CSP HPLC: OD, 98:2 (hex/IPA); t_R (*R*)-enantiomer (min) = 11.5. t_R (*S*)-enantiomer (min) = 15.0.

Acknowlegment

The authors acknowledge support for this work by the National Science Foundation (NSF CHE #644950).

References

1. Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823–2824.
2. (a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824; (b) Pu, L. *Tetrahedron* **2003**, *59*, 9873–9886.
3. Walsh, P. J. *Acc. Chem. Res.* **2003**, *36*, 739–749.
4. (a) Degni, S.; Strandman, S.; Laari, P.; Nuopponen, M.; Wilen, C.-E.; Tenhu, H.; Rosling, A. *React. Funct. Polym.* **2005**, *62*, 231–240; (b) Rheiner, P. B.; Seebach, D. *Chem. Eur. J.* **1999**, *5*, 3221–3236; (c) Ito, Y. N.; Ariza, X.; Beck, A. K.; Bohac, A.; Ganter, C.; Gawley, R. E.; Kuehnle, F. N. M.; Tuleja, J.; Wang, Y. M.; Seebach, D. *Helv. Chim. Acta* **1994**, *77*, 2071–2110.
5. (a) Jiang, F.-Y.; Liu, B.; Dong, Z.-B.; Li, J.-S. *J. Organomet. Chem.* **2007**, *692*, 4377–4380; (b) Kang, S.-W.; Ko, D.-H.; Kim, K. H.; Ha, D.-C. *Org. Lett.* **2003**, *5*, 4517–4519; (c) Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233–6236; (d) Zhang, F.-Y.; Yip, C.-W.; Cao, R.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 585–589.
6. (a) Kozakiewicz, A.; Ullrich, M.; Welniak, M.; Wojtczak, A. *J. Mol. Catal. A* **2008**, *286*, 106–113; (b) Jeon, S.-J.; Li, H.; García, C.; Larochelle, L. K.; Walsh, P. J. *J. Org. Chem.* **2005**, *70*, 448–455; (c) Wu, K.-H.; Gau, H.-M. *Organometallics* **2004**, *23*, 580–588; (d) Balsells, J.; Walsh, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 1802–1803; (e) Prieto, O.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2000**, *11*, 1629–1644; (f) Prichett, S.; Woodmansee, D. H.; Gantzel, P.; Walsh, P. J. *J. Am. Chem. Soc.* **1998**, *120*, 6423–6424.
7. (a) Mao, J.; Wan, B.; Zhang, Z.; Wang, R.; Wu, F.; Lu, S. *J. Mol. Catal. A* **2005**, *225*, 33–37; (b) Mao, J.; Wan, B.; Wang, R.; Wu, F.; Lu, S. *J. Mol. Catal. A* **2005**, *232*, 9–12.
8. (a) Burguete, M. I.; Collado, M.; Escorihuela, J.; Luis, S. V. *Angew. Chem., Int. Ed.* **2007**, *46*, 9002–9005; (b) Huang, H.; Zheng, Z.; Chen, H.; Bai, C.; Wang, J. *Tetrahedron: Asymmetry* **2003**, *14*, 1285–1289; (c) Huang, H.; Chen, H.; Hu, X.; Bai, C.; Zheng, Z. *Tetrahedron: Asymmetry* **2003**, *14*, 297–304; (d) Cobb, A. J. A.; Marson, C. M. *Tetrahedron: Asymmetry* **2001**, *12*, 1547–1550; (e) Goldfuss, B.; Steigelmann, M.; Rominger, F. *Eur. J. Org. Chem.* **2000**, *9*, 1785–1792; (f) Sibi, M. P.; Chen, J.-X.; Cook, G. R. *Tetrahedron Lett.* **1999**, *40*, 3301–3304; (g) Kimura, K.; Sugiyama, E.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1992**, *33*, 3147–3150.
9. Lake, F.; Moberg, C. *Tetrahedron: Asymmetry* **2001**, *12*, 755–760.
10. Zhang, X.; Guo, C. *Tetrahedron Lett.* **1995**, *36*, 4947–4950.
11. Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 99–101.
12. Rosini, C.; Franzini, L.; Pini, D.; Salvadori, P. *Tetrahedron: Asymmetry* **1990**, *1*, 587–588.
13. The presence of the alcohol suggests the slow reduction of aldehyde by an ethylzincate intermediate wherein the b-hydrogen of the ethyl was reactive. See: (a) Sung, D. W. L.; Hodge, P.; Stratford, P. W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1463–1472; (b) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028–4036; (c) Itsuno, S.; Fréchet, J. M. J. *J. Org. Chem.* **1987**, *52*, 4140–4142.
14. Liu, S.; Wolf, C. *Org. Lett.* **2007**, *9*, 2965–2968.
15. MacMillan, S. N.; Ludford, K. T.; Tanski, J. M. *Tetrahedron: Asymmetry* **2008**, *19*, 543–548.
16. Ko, D.-H.; Kim, K. H.; Ha, D.-C. *Org. Lett.* **2002**, *4*, 3759–3762.
17. Burguete, M. I.; Collado, M.; Escorihuela, J.; Luis, S. V. *Angew. Chem., Int. Ed.* **2007**, *46*, 9002–9005.