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Asymmetric Addition of Diethylzinc to Ketones promoted by Tartaric Acid Derivatives

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Abstract: The preparation of new sulfonamide ligands derived from L-tartaric acid and camphor sulfonyl chloride are described. The employment in the titanium tetraisopropoxide-promoted enantioselective addition of diethylzinc to ketones has been studied. The best enantiomeric excess is up to 99% with 7 mol% catalyst loading at room temperature.

Keywords: Asymmetric addition; Diethylzinc; Ketone; Sulfonamide; Tartaric acid

INTRODUCTION

The synthesis of chiral building blocks containing a quaternary stereogenic carbon center[1] is a considerable challenge in organic synthesis, mainly because of steric factors. The enantioselective addition of organometallic reagents to ketones is probably the most straightforward and useful method for achieving this goal. Among these organometallics, dialkylzinc reagents are ideal alkyl nucleophile synthons because it is possible to prepare many different functionalized reagents, due to their low reactivity.[2] On the other hand, this low reactivity resulted in the difficulty for the adding dialkylzinc reagents to ketones. Therefore the new catalyst is crucial for this addition reaction. However, as far as we know, only a few chiral catalysts have been developed to promote

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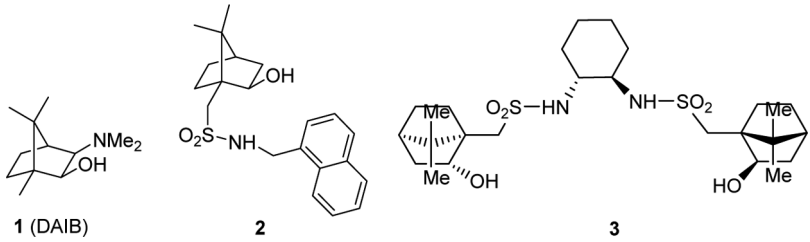
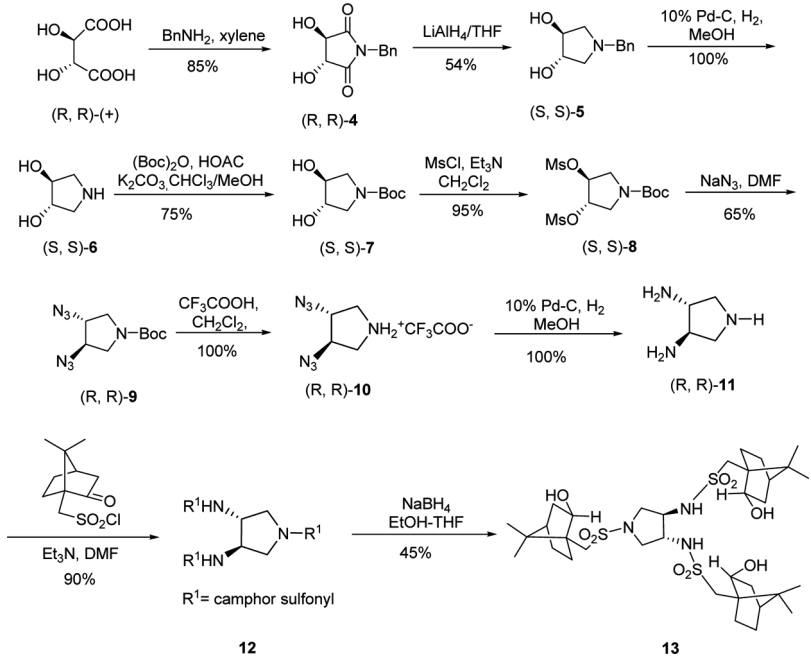


Figure 1. Typical chiral promoters for the asymmetric addition of alkyls or phenyl to ketones.

the asymmetric addition of diarylzinc or dialkylzinc reagents to ketones. In 1998, Dosa and Fu[3] reported the first catalytic asymmetric addition of phenyl groups to ketones. They employed 15 mol% of Noyori's amino alcohol ligand 3-exo-(dimethylamino)isoborneol (DAIB) (compound **1** in Fig. 1) as an effective catalyst, obtaining a new quarternary stereocenter in good to excellent enantioselectivity. In the same year, Ramón and Yus[4] reported the first example of enantioselective addition of alkyl groups to ketones. They employed hydroxysulfonamide ligand (compound **2** in Fig. 1) in combination with titanium tetraisopropoxide to perform the asymmetric addition and realized enantioselectivities from 16% to 89% with good yields. However, the catalyst reactivity was very low; 20 mol% of catalyst loading was required, and the reaction time was between 4 and 14 days for consumption of the substrate. Afterward, García et al.[5] and Yus et al.[6,7] independently synthesized trans-1, 2-bis-(hydroxyl-camphor-sulfonamide)-cyclohexane (compound **3** in Fig. 1), which was also successfully used in the addition of diphenylzinc to ketones.[8,9] Recent studies showed the ligands with C_2-symmetrical axes could catalyze this asymmetric addition to efficiently afford quaternary stereogenic carbon center.[5–15] Taking the advantage of the chirality of L-tartaric acid, we[15] designed and synthesized a sereies of ligands with C_2-symmetrical axes, as shown in Schemes 1 and 2. These ligands were employed as promoters in the addition of diethylzinc to ketones, and satisfactory yields and ee values were obtained.

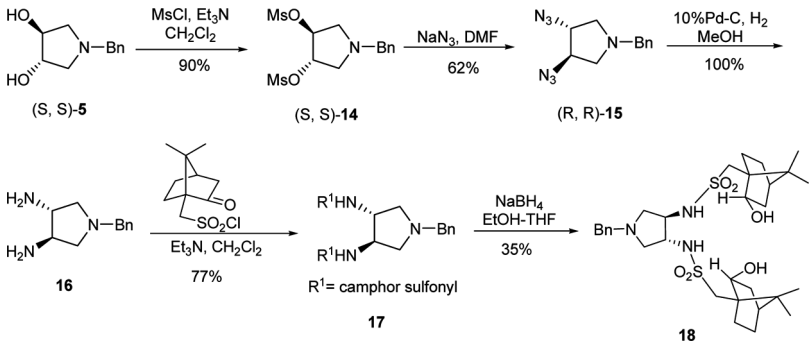
RESULTS AND DISCUSSION

The synthesis of these new catalysts is described here. Initially, L-tartaric acid was reacted with benzyl amine to generate amide **4**, which was reduced in the presence of lithium alumina hydride to obtain diol **5**. The benzyl group in compound **5** was replaced with tert-butoxycarbonyl



Scheme 1. Synthesis of chiral ligand **12** and ligand **13**.

group in compound **7** via hydrogenation and the protection. Then the diol **7** was mesylated with methanesulfonyl chloride in triethyl amine to furnish the bis(mesylates) **8**. Subsequently, double nucleophilic substitution with sodium azide in N, N-dimethyl formamide (DMF) yielded the bis(azides) **9**. After deprotection of the amino group with trifluoroacetic acid and hydrogenation under Pd/C, compound **9** was converted

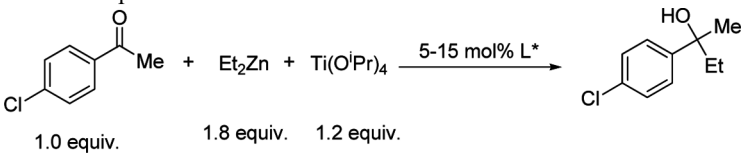


Scheme 2. Synthesis of chiral ligand **17** and ligand **18**.

into amine **11**.[16] Ligand **12**[17] was obtained when compound **11** reacted with camphor sulfonyl chloride. The same method was used for the synthesis of ligand **17**, as shown in Scheme 2.

Our initial experiments in the asymmetric addition of diethylzinc to *p*-chloro acetophenone involved the use of ligand **12** and ligand **17**. Under the condition, the reaction was carried out slowly, giving the desired tertiary alcohol with the enantioselectivity of less than 40% (entries 1 and 2 in Table 1). These results inspired us to modify the ligand further. It was assumed that catalytic reactivity could be enhanced by constraining the geometry of the ligand, which would result in a more open binding site. Therefore compounds **12** and **17** were reduced with $NaBH_4$ to generate diastereomers. The major products **13** and **18** were isolated by chromatography on silica gel.[5] By employing ligand **13** or **18** in the asymmetric addition of diethylzinc to p-chloro acetophenone, the enantioselectivity was obviously enhanced, giving 80% ee and 73% ee respectively (entries 3 and 4 in Table 1). These results indicated the importance of the hydroxyl group in the catalytic process. Next, the reaction was performed in hexane; the reaction yield and the enantiomeric excess decreased a little (entry 5 vs. entry 3, entry 6 vs. entry 4 in

Table 1. Optimization of the reaction condition



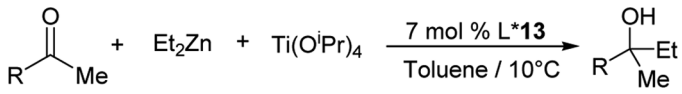
Entry	L* (mol%)	Solvent	T (°C)	Yield (%)[a]/Time (h)	Ee (%)[b]
1	**12** (5)	Toluene	10	60/48	38
2	**17** (5)	Toluene	10	46/50	30
3	**13** (5)	Toluene	10	72/48	80
4	**18** (5)	Toluene	10	50/60	73
5	**13** (5)	Hexane	10	63/48	75
6	**18** (5)	Hexane	10	48/60	63
7	**13** (10)	Toluene	10	76/48	85
8	**18** (10)	Toluene	10	51/60	72
9	**13** (15)	Toluene	10	75/48	84
10	**13** (7)	Toluene	10	75/48	85
11	**13** (7)	Toluene	35	76/48	82
12	**13** (7)	Toluene	60	65/48	74
13	**13** (7)	Toluene	0	67/60	80

[a]Isolated yields.
[b]The enantiomeric excess was determined by chiral HPLC using OJ-H column.

Table 1). Increasing the amount of the ligand **13** helped improve the enantiomeric excess, which was up to 85% (entry 7 vs. entry 3 in Table 1). However, the enantioselectivity decreased a little for ligand **18** (entry 8 vs. entry 4 in Table 1). So, ligand **13** was selected as the model catalyst (entries 9 and 10 in Table 1). Subsequently, the temperature effect was also studied. Elevating or reducing temperature was a disadvantage to the enantioselectivity (entries 11–13 in Table 1). At last, the condition of entry 10 was selected as the optimal option. To extend the scope of the reaction substrate, the effect of different ketones on the enantioselectivity was studied. All the experimental results are listed in Table 2.

As shown in Table 2, acetophenone was the best substrate for this catalyst, which gave excellent enantioselectivity (99% ee, entry 1 in Table 2). Electron-withdrawing substituents at the *para*-position of acetophenone favored both enantioselectivity and reaction yield, with the enantiomeric excess ranged from 75% to 85% (entries 2, 3, and 4 in Table 2), while electron-donating substituents at the *para*-position of acetophenone

Table 2. Asymmetric addition of ethyl groups to ketones



Entry	R	Yield (%)[a]/Time (h)	Ee (%) (config.)[b]
1	C_6H_5	75/50	99 (S)
2	4-FC_6H_4	81/40	83
3	4-ClC_6H_4	75/48	85
4	4-BrC_6H_4	65/64	75 (S)
5	4-MeC_6H_4	45/50	30
6	4-PhC_6H_4	65/30	54
7	4-$MeOC_6H_4$	48/60	20
8	2-ClC_6H_4	35/60	12
9[c]	2-MeC_6H_4	—	—
10[c]	3-MeC_6H_4	—	—
11	2-Furan	68/70	22
12	2-Thiophene	70/70	36
13	2-Naphthyl	83/40	86

[a]Isolated yields.

[b]The enantiomeric excess was determined by chiral HPLC using OD-H or OJ-H column and the configuration was determined by comparision of specific rotations with literature data.

[c]No desired product was detected.

did not favor either reaction yield or enantioselectivity (entries 5, 6, and 7 in Table 2). The substituents at the *ortho*-position or *meta*-position were negative to the yield and the enantioselectivity. 2-Chloro acetophenone gave a lower yield and poor enantioselectivity (entry 8 in Table 2). No desired product was detected when 2-methyl or 3-methyl acetophenone were introduced in the addition reaction (entries 9 and 10 in Table 2). This phenomena was ascribed to the steric repulsion of the substituent (Cl, Me) located in *ortho*-position or *meta*-position and the ethyl group. As a result, the ethyl nucleophile can hardly approach the carbon atom of carbonyl. In addition, we also investigated ketones containing heteroaromatic groups in the asymmetric addition reaction, such as 2-acetyl furan and 2-acetyl thiophene, which generated the corresponding products with low enantioselectivities and moderate yields under the condition (entries 11 and 12 in Table 2). This result may stem from the binding of the heteroatom (O, S) in the substrate with the Ti center. In fact, only the coordination of the oxygen atom in carbonyl and the center of titanium were positive to enantioselectivity. Therefore, the reactivity of the chiral ligand was weakened to a certain extend. Poor enantioselectivity was obtained in these substrates (entries 7, 11, and 12 in Table 2). It was noted that substrate 2-acetyl naphthalene, which has more steric hindrance than other ketones, gave excellent enantioselectivity in this addition reaction (entry 13 in Table 2).

CONCLUSIONS

In summary, a new ligand **13** derived from L-tartaric acid was designed and synthesized, which is efficient to catalyze the asymmetric addition of diethylzinc to ketones. Moreover, the reaction condition is mild and the catalyst loading is only 7 mol%. Further modification in the ligand is currently under investigation.

EXPERIMENTAL

Unless other indicated, all reactions using diethylzinc and titanium tetraisopropoxide were carried out in dry glassware under nitrogen. Hexane, tetrahydrofuran, and toluene were freshly distilled from sodium and benzophenone. Dichloromethane was freshly distilled from CaH_2. Titanium tetraisopropoxide was freshly distilled under reduced pressure. Triethylamine was distilled and stored in 4 Å MS. Diethylzinc solution was 1.5 M in hexane and used directly. Reactions were monitored by thin-layer chromatography (TLC) analysis. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker AC-300 FT (^{1}H: 300 MHz, ^{13}C: 75.5 MHz) or AC-400 FT

(^{1}H: 400 MHz, ^{13}C: 100 MHz) using TMS as internal reference. The chemical shifts (δ) and coupling constants (J) were expressed in (parts per million) and hertz respectively. IR spectra were recorded on a Perkin-Elmer 2000 Fourier-transform infrared (FTIR). High-resolution mass spectra (HRMS) were obtained on GCT-time of flight (TOF) spectrometer. The optical rotations were measured on WZZ-2 polarimeter. Chiral HPLC was performed in an Agilent 1100 series instrument equipped with a diode array detector. Chiralcel OD-H column and Chiralcel OJ-H column were purchased from Daicel Chemical Industries with 0.46 cm $\Phi \times 25$ cm. Rention times (t) for HPLC are given in minutes.

Preparation and Characterization of Chiral Ligands

The synthesis of chiral ligands was referred from the literature.[16,17]

Spectral and physical data for compound **12**: Yellow solid; mp 115–117 °C; $[\alpha]_D^{25}$ +32.0 (c 1.0, $CHCl_3$); IR (KBr): 3438, 3288, 2961, 1743, 1147 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (s, 3H), 0.92 (s, 6H), 1.03 (s, 6H), 1.07 (s, 3H), 1.43–1.46, 1.65–2.04, 2.12–2.42 (3 m, 3H, 12H, 6H respectively), 2.90 (d, $J = 14.9$ Hz, 1H), 3.00 (d, $J = 15.1$ Hz, 2H), 3.41–3.43 (m, 2H), 3.48 (d, $J = 14.9$ Hz, 1H), 3.56 (d, $J = 15.1$ Hz, 2H), 3.96–3.99 (m, 2H), 4.18–4.20 (m, 2H), 5.82 (d, $J = 5.0$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.52$, 19.70, 19.78, 19.83, 25.21, 25.95, 27.01, 42.72, 42.78, 42.83, 46.74, 48.56, 48.77, 50.11, 50.66, 58.13, 58.41, 58.94, 216.16, 216.44 ppm.

Spectral and physical data for compound **13**: White foam solid; mp 125–127°C; $[\alpha]_D^{25}$ −52.7 (c 0.5, $CHCl_3$); IR (KBr): 3534, 3280, 2957, 1142 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.85$ (s, 9H), 1.07 (s, 9H), 1.10–1.15 1.42–1.48, 1.74–1.80 (3 m, 3H, 3H, 15H respectively), 2.83 (d, $J = 12.3$ Hz, 1H), 2.97 (d, $J = 13.3$ Hz, 2H), 2.82–3.00 (br, 3H), 3.30 (br, 2H), 3.44 (d, $J = 12.3$ Hz, 1H), 3.59 (d, $J = 13.4$ Hz, 2H), 3.87 (m, 2H,), 4.03–4.08 (m, 5H), 5.75 (d, $J = 5.9$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.99$, 20.07, 20.62, 20.71, 27.42, 30.52, 39.56, 39.67, 44.49, 49.03, 49.07, 50.19, 50.42, 50.62, 53.83, 57.55, 76.28, 76.44 ppm; m/z (HPLC-ESI/MS) 748 $(M\text{-}H)^-$. Anal. calcd. for $C_{34}H_{59}N_3O_9S_3$: C, 54.45; H, 7.93; N, 5.60. Found: C, 54.53; H, 7.90; N, 5.53.

Spectral and physical data for compound **17**: colorless solid; mp 57–59°C; $[\alpha]_D^{28}$ +11.30 (c 0.5 $CHCl_3$); IR (KBr): 3448, 3299, 2960, 1742, 1329, 1147 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.86$ (s, 6H), 1.01 (s, 6H), 1.42–1.48, 1.88–2.39 (2 m, 2H and 12H respectively), 2.58 (m, 2H), 2.97 (d, $J = 15.2$ Hz, 2H), 3.10 (m, 2H), 3.49 (d, $J = 15.2$ Hz, 2H), 3.64–3.67 (m, 2H), 3.98 (m, 2H), 5.55 (br, 2H), 7.26–7.31 (m, 5H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 19.61$, 19.90, 26.38, 27.07, 42.89,

42.93, 48.68, 50.46, 58.52, 59.09, 59.72, 59.85, 127.30, 128.43, 128.81, 137.96, 216.31 ppm.

Spectral and physical data for compound **18**: yellow foam solid; $[\alpha]_D^{28}$ −44.0 (*c* 0.5 $CHCl_3$); IR (KBr): 3532, 3276, 2956, 1320, 1143 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.82$ (s, 6H), 1.05 (s, 6H), 1.10–1.13, 1.44–1.49, 1.71–1.80 (3 m, 2H, 2H, 10H respectively), 2.53 (dd, $J = 5.4$ Hz, 9.9 Hz, 2H), 2.92 (d, $J = 13.8$ Hz, 2H), 3.04 (dd, $J = 6.8$ Hz, 9.9 Hz, 2H), 3.23 (br, 2H), 3.53 (d, $J = 13.8$ Hz, 2H), 3.63 (m, 2H), 3.87 (m, 2H), 4.06 (m, 2H), 5.13 (d, $J = 3.2$ Hz, 2H), 7.26–7.34 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.96$, 20.59, 27.41, 30.55, 39.33, 44.48, 48.89, 50.53, 53.44, 58.89, 59.63, 59.79, 76.43, 127.56, 128.55, 128.90, 137.37 ppm. Anal. calcd for $C_{31}H_{49}N_3O_6S_2$: C, 59.68; H, 7.92; N, 6.74. Found: C, 59.74; H, 7.93; N, 6.70.

General Procedure for Enantioselective Addition of Diethylzinc to Ketones

Ligand **13** (27 mg, 0.035 mmol, 0.07 equiv.) and $Ti(O^iPr)_4$ (175 mg, 0.6 mmol, 1.2 equiv.) were dissolved in toluene (2.5 ml) under nitrogen. The resulting mixture was stirred for 2 min at room temperature (10°C). Diethylzinc solution (0.6 ml, 0.9 mmol, 1.8 equiv.) was added to the flask, and the color of solution became orange-green. After 2 min, the corresponding ketone (0.5 mmol, 1.0 equiv., dissolved in 0.5 ml of toluene or diluted with 0.5 ml of toluene) was added at this temperature. The reaction was stirred for the appointed time in Table 2 until it was quenched with diluted hydrochloric acid. The resulting mixture was filtered through silica gel and extracted with ethyl acetate (3×10 ml), and the organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash-chromatography column to afford the expected *tert*-alcohol. The enantiomeric excess was determined by chiral HPLC.

Data

All the spectral data of *tert*-alcohol were listed in the experiment section of another article.[15]

2-(2-Chloro-phenlyl)-butan-2-ol (entry 8 in Table 2): colorless oil, $[\alpha]_D^{25}$ −0.6 (*c* 2.0, acetone); IR (film): 3435, 2972, 1162 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.78$ (t, $J = 7.4$ Hz, 3H), 1.69 (s, 3H), 1.92–1.99 (m, 1H), 2.23–2.33 (m, 2H), 7.17–7.36 (m, 3H), 7.66–7.69 (m, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 8.49$, 27.61, 33.56, 75.85,

126.85, 128.22, 131.09, 131.39, 143.81 ppm; HRMS calcd. for $C_{10}H_{13}ClO$ 184.0655; found 184.0653. Chiral OD-H column: hexane/isopropanol = 98:2 (v/v), flow rate = 0.4 ml/min, 260 nm, 25°C, $t_1 = 18.2$ min, $t_2 = 20.3$ min.

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REFERENCES

1. Fuji, K. Asymmetric creation of quaternary carbon centers. *Chem. Rev.* **1993**, *93*, 2037–2066; (b) Corey, E. J.; Guzmán, A. The catalytic enantioselective construction of molecules with quaternary carbon stereocenters. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 388–401; (c) Pu, L. Asymmetric alkynylzinc additions to aldehydes and ketones. *Tetrahedron* **2003**, *59*, 9873–9886; (d) Ramón, D. J.; Yus, M. Chiral tertiary alcohols made by catalytic enantioselective addition of unreactive zinc reagents to poorly electrophilic ketones. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 284–287.
2. Knochel, P.; Perea, J. J. A.; Jones, P. Organozinc mediated reactions. *Tetrahedron* **1998**, *54*, 8275–8319; (b) Knochel, P. Stereoselective reactions mediated by functionalized diorganozincs. *Synlett* **1995**, 393–403; (c) Knochel, P.; Singer, R. D. Preparation and reactions of polyfunctional organozinc reagents in organic synthesis. *Chem. Rev.* **1993**, *93*, 2117–2188.
3. Dosa, P. I.; Fu, G. C. Catalytic asymmetric addition of $ZnPh_2$ to ketones: Enantioselective formation of quaternary stereocenters. *J. Am. Chem. Soc.* **1998**, *120*, 445–446.
4. Ramón, D. J.; Yus, M. First enantioselective addition of dialkylzinc to ketones promoted by titanium(IV) derivatives. *Tetrahedron Lett.* **1998**, *39*, 1239–1242; (b) Ramón, D. J.; Yus, M. First enantioselective addition of diethylzinc and dimethylzinc to prostereogenic ketones catalysed by camphorsulfonamide-titanium alkoxide derivatives. *Tetrahedron* **1998**, *54*, 5651–5666.
5. García, C.; LaRochelle, L. K.; Walsh, P. J. A practical catalytic asymmetric addition of alkyl groups to ketones. *J. Am. Chem. Soc.* **2002**, *124*, 10970–10971.
6. Yus, M.; Ramón, D. J.; Prieto, O. Highly enantioselective addition of dialkylzinc reagents to ketones promoted by titanium tetraisopropoxide. *Tetrahedron: Asymmetry* **2002**, *13*, 2291–2293.
7. Yus, M.; Ramón, D. J.; Prieto, O. (−)-Frontalin: Synthesis using the catalytic enantioselective addition of dimethylzinc to a ketone. *Eur. J. Org. Chem.* **2003**, 2745–2748.

8. García, C.; Walsh, P. J. Highly enantioselective catalytic phenylation of ketones with a constrained geometry titanium catalyst. *Org. Lett.* **2003**, *5*, 3641–3644.
9. Prieto, O.; Ramón, D. J.; Yus, M. Highly enantioselective arylation of ketones. *Tetrahedron: Asymmetry* **2003**, *14*, 1955–1957.
10. Yus, M.; Ramón, D. J.; Prieto, O. Synthesis of new C_2-symmetrical bis(hydroxycamphorsulfonamide) ligands and their application in the enantioselective addition of dialkylzinc reagents to aldehydes and ketones. *Tetrahedron: Asymmetry* **2003**, *14*, 1103–1114.
11. de Parrodi, C. A.; Walsh, P. J. Trans-1,2-diaminocyclopentane-based catalyst for the asymmetric addition of alkyl-, aryl-, and vinyl groups to ketones. *Synlett* **2004**, 2417–2420.
12. Forrat, V. J.; Ramón, D. J.; Yus, M. Chiral tertiary alcohols from a trans-1-arenesulfonyl-amino-2-isoborneolsulfonylaminocyclohexane-catalyzed addition of organozincs to ketones. *Tetrahedron: Asymmetry* **2005**, *16*, 3341–3344.
13. Jeon, S. J.; Li, H. M.; García, C.; LaRochelle, L. K.; Walsh, P. J. Catalytic asymmetric addition of alkylzinc and functionalized alkylzinc reagents to ketones. *J. Org. Chem.* **2005**, *70*, 448–455.
14. Jeon, S. J.; Li, H. M.; Walsh, P. J. A green chemistry approach to a more efficient asymmetric catalyst: Solvent-free and highly concentrated alkyl additions to ketones. *J. Am. Chem. Soc.* **2005**, *127*, 16416–16425.
15. Hui, A. L.; Zhang, J. T.; Fan, J. M.; Wang, Z. Y. A new chiral sulfonamide ligand based on tartaric acid: Synthesis and application in the enantioselective addition of diethylzinc to aldehydes and ketones. *Tetrahedron: Asymmetry* **2006**, *17*, 2101–2107.
16. For the synthesis of chiral amine **11** and **16** from L-tartaric acid, see (a) Nagel, U.; Kinzel, E.; Andrade, J.; Prescher, G. Enantioselective catalysis .4. synthesis of N-substituted (R, R)-3,4-bis (diphenylphosphino) pyrrolidines-the use of their rhodium complexes for the asymmetric hydrogenation of alpha-(acylamino) acrylic acid derivatives. *Chem. Ber.* **1986**, *119*, 3326–3343; (b) Caldwell, C. G.; Chen, P.; He, J. F.; Parmee, E. R.; Leiting, B.; Marsilio, F.; Patel, R. A.; Wu, J. K.; Eiermann, G. J.; Petrov, A.; He, H. B.; Lyons, K. A.; Thornberry, N. A.; Weber, A. E. Fluoropyrrolidine amides as dipeptidyl peptidase IV inhibitors. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1265–1268; (c) Nagel, U. Asymmetric hydrogenation of α-(acetylamino)cinnamic acid with a novel rhodium complex: The design of an optimal ligand. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 435–436; (d) Siedlecka, R.; Wojaczyńska, E.; Skarżewski, J. Chiral pyrrolidine thioethers: Effective nitrogen–sulfur donating ligands in palladium-catalyzed asymmetric allylic alkylations. *Tetrahedron: Asymmetry* **2004**, *15*, 1437–1444; (e) Ryan, K.; Gershell, L. J.; Still, W. C. A synthetic receptor motif designed for extended peptide conformations. *Tetrahedron* **2000**, *56*, 3309–3318; (f) Skarżewski, J.; Gupta, A. Synthesis of C_2-symmetric primary vicinal diamines: Double stereospecific mitsunobu reaction on the heterocyclic diols derived from tartaric acid. *Tetrahedron: Asymmetry* **1997**, *8*, 1861–1867; (g) Kuppert, D.; Sander, J.;

Roth, C.; Wörle, M.; Weyhermüller, T.; Reiss, G. J.; Schilde, U.; Müller, I.; Hegetschweiler, K. The coordination chemistry of cis-3,4-diaminopyrrolidine and related polyamines. *Eur. J. Inorg. Chem.* **2001**, 2525–2542.

17. Balsells, J.; Walsh, P. J. Design of diastereomeric self-inhibiting catalysts for control of turnover frequency and enantioselectivity. *J. Am. Chem. Soc.* **2000**, *122*, 3250–3251.