Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 1521–1526

Syntheses of chiral hybrid *O*,*N*-donor ligands for the investigation of lanthanide complex reactivities in direct aldol condensations

Jacek Mlynarski,* Joanna Jankowska† and Bartosz Rakiel†

Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

Received 21 January 2005; accepted 18 February 2005
Available online 18 March 2005

Abstract—A method for the synthesis of new chiral α/β-dimethylamino esters and β-amino ethers from (*S*,*S*)-hydrobenzoin is described. These new *O*,*N*-donor ligands are expected to prove a useful platform for exploring the relationship between the ligand structure and stereoselective direct aldol condensation catalyzed by their lanthanide complexes. The initial survey of the catalytic utility of newly synthesized complexes in the unique aldol-Tishchenko reaction of aldehydes and aliphatic ketones is also presented.

1. Introduction

Lewis acid catalyzed reactions belong to one of the most powerful methods in modern synthetic chemistry.[1] Among the many Lewis acids developed so far, lanthanide triflates have received growing attention because of the unique combinations of their strong Lewis acidity mixed with mildness and usually high selectivity.[2] Therefore, not only $Ln(OTf)_3$ but also $Sc(OTf)_3$ and $Y(OTf)_3$ (rare earth metal triflates $RE(OTf)_3$) have been used for numerous processes including carbon–carbon bond forming reactions and other transformations.[3] An enantioselective version of all of these catalytic reactions would be of great value.[4] Despite the enormous development in lanthanide elements chemistry the knowledge about their interaction with a chiral ligands remains narrow, and a number of tested structures is still restricted.[5]

On the other hand, metal-catalyzed asymmetric direct aldol reactions of aldehydes with unmodified ketones still remain a challenge for synthetic chemists.[6] Remarkable success in this area is a result of Shibasaki's work on homo- and heterobimetallic catalysts.[7] Despite some promising reports on other metals (e.g., zinc,[7b,8] barium,[9] and calcium[10]) heterobimetallic catalyst containing lanthanides as the catalyst core turned out to be the most versatile.[11] In this case two parts of catalyst: Lewis acid and Brønsted base are necessary for the aldehyde acceptor activation and the enolization of the ketone substrate. To date, the scope of possible substrates and the selection of applicable catalytic systems remains still limited. In general, the elaborated methodology offers a versatile access to aldol-type products from methyl ketones[8–11] and the development of catalytic systems applicable to their methylene analogues[12] is more challenging and restricted mainly to α-hydroxymethyl ketones.[6,8b,11c]

This problem has been solved recently by Shibasaki et al., who presented an application of the bifunctional catalyst to the unique stereo- and enantioselective aldol-Tishchenko reaction.[13] In a one-step process, aldehydes were reacted with methylene ketones to give 1,3-diol monoesters, which were formed with a simultaneous creation of three adjacent stereogenic centers[14] as a result of bond reorganization in the cyclic Evans intermediate.[15] This methodology requires activated aromatic ketones, hence its application to aliphatic substrates needs further exploration.

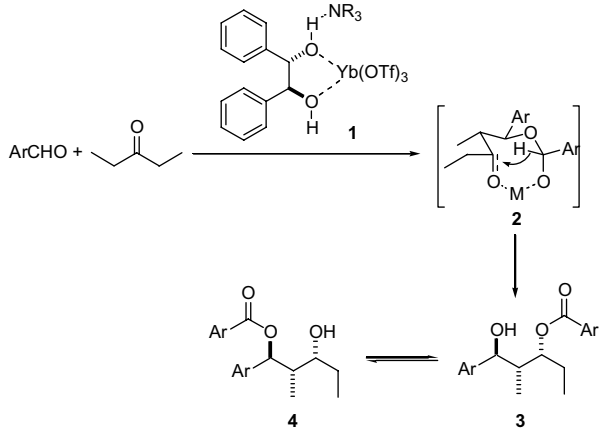
At around the same time, we reported the first example of the aldol-Tishchenko reaction of aliphatic ketone, for example, 3-pentanone (Scheme 1).[16] Although not yet selective enough, this catalytic system is applicable to aliphatic substrates, which makes this methodology interesting in terms of natural product synthesis. This premise encouraged us to carry on with our research.

* Corresponding author. Tel.: +48 223432130; fax: +48 226326681; e-mail: mlynar@icho.edu.pl
† Student of Warsaw University of Technology.

0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.02.023

2. Results and discussion

Previously, we revealed that a hydrobenzoin, ytterbium(III) triflate, and tertiary amine combination provided the highest level of asymmetric induction (up to 75% ee) observed to date in the addition of 3-pentanone to aldehydes (Scheme 1).[16] As we supposed, binding of the amine to the hydroxyl group (type-**1** structure) is essential for catalytic activity of this species.[17] We assumed that the existence of two active centers in this structure making possible simultaneous donor and acceptor activation toward direct aldol condensation is a condition sine qua non of the reaction. We presumed that the amino group fixed to molecule would exhibit catalytic activity as well, and that such a defined architecture would form a more efficient catalyst. To realize this concept and make use of the general principle of the two-center ligand, we herein report the synthesis of new compounds as promising ligands for stereoselective direct aldol condensation.



Scheme 1. Aldol-Tishchenko reaction of 3-pentanone with aldehydes.

While many structurally diverse architectures have been introduced in recent years to enantioselective reactions catalyzed by lanthanide elements,[4] there exists a paucity of reported variation in complexes containing $Ln(OTf)_3$ combined with mixed *O*,*N*-donor neutral ligands.[5] Moreover, the presented examples have been applied to another type of C–C bond forming reactions[18] and to the best of our knowledge such neutral ligands have never been applied to direct aldol condensation. In this regard, tuning of chiral hybrid ligands is necessary for reaction optimization. We addressed this deficiency by preparing a family of (*S*,*S*)-hydrobenzoin-based ligands possessing both *O*- and *N*-heteroatoms located along the catalyst arms. To enable a comprehensive study of the ligand effect we designed syntheses of diether **5** and diesters **6** and **7** equipped with dimethylamino groups (Fig. 1).

We decided to test two types of ligands, that is, having *N*-centers by two and one carbon atoms removed from oxygen atoms. Syntheses of the target ligands require a routine preparation of hindered ethers/esters in high yields from optically active precursors.[19,20] Our first aim was to synthesize the catalyst, which possess two

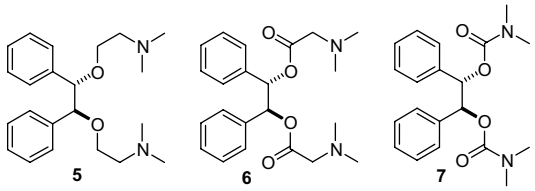
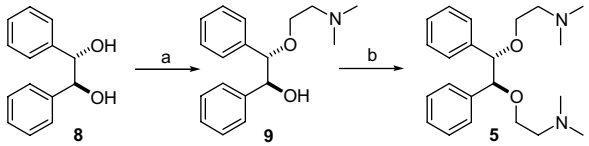


Figure 1.

amino ether moieties from commercially available hydrobenzoin. Our strategy for hindered chiral amino ether **5** required an optimized Williamson procedure at the etherification stage (Scheme 2). We applied double coupling of diol **8** with dimethylamino ethanol transformed previously into appropriate tosyl derivative. Considering the fact that the synthesis of the required tosylate is delicate and not suitably described in the literature,[21] probably because of high instability of the structure with leaving group in the β-position to amino function, we decided, nevertheless, to chance it this way.

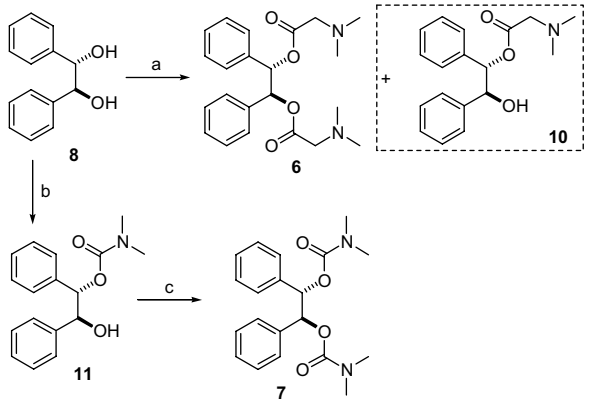


Scheme 2. Reagents and conditions: (a) KH, 18-crown-6, THF, then $Me_2N(CH_2)_2OTs$, rt; (b) reflux, 89%.

Despite the instability of the tosylate toward all isolation methods tested, it survived the substitution reaction conditions. Thus freshly prepared tosylate was cannulated into hydrobenzoin dianion solution at rt. To generate the dianion, potassium, and sodium hydride were tested. In both cases, after combining with the tosylate, only monosubstituted ether **9** was detected in the reaction mixture. Much better results were obtained when an improved Aspinall et al.[20] methodology was applied. The nucleophilicity of the hydrobenzoin anion was increased by solvation of the ion pair with 15-crown-5 (for Na^+) or 18-crown-6 (for K^+). In our hands, the application of potassium hydride was very promising. Under optimized conditions the desired diether **5** was isolated in 89% yield after 1-h reflux of the reaction mixture.

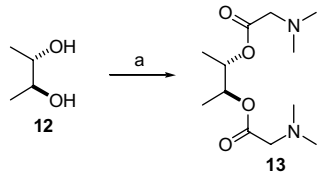
A similar protocol was applied for the acylation of **8** with dimethylcarbamoyl chloride. While all standard conditions (Hünig's base, DMAP, reflux in pyridine) failed in the case of such a hindered ester, application of crown ether/NaH resulted in the formation of monoester **11** transformed after short reflux in THF into diester **7** with 71% yield (Scheme 3).

DCC-promoted esterification was applied for obtaining diester **6**. When hydrobenzoin were treated with dimethylaminoglycine, DCC, and DMAP **6** was formed as the main product accompanied with some amount of **10**. After procedure optimization, when only a catalytic amount of DMAP was loaded, **6** was isolated with 97% yield.



Scheme 3. Reagents and conditions: (a) dimethylaminoglycine, DCC, DMAP, DCM, rt, 97%; (b) NaH, 15-crown-5, dimethylcarbamoyl chloride, THF, rt; (c) reflux, 71%.

To test a broad range of ligands we decided to apply an elaborated methodology to the esterification of the chiral 2,3-butanediol **12**. In this case, diester **13** was isolated in 63% yield (Scheme 4).



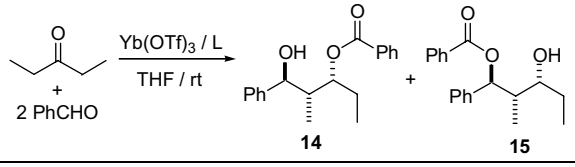
Scheme 4. Reagents and conditions: (a) dimethylaminoglycine, DCC, DMAP, DCM, rt, 63%.

Having the new ligands in hand, we tested their catalytic activity with ytterbium triflate, which was found as the most promising metal salt during previous screenings.[16] Preliminary results are summarized in Table 1. It is important to stress that homogeneous solutions were obtained from all ligands–$Yb(OTf)_3$ combinations in THF. When 20 mol % of ligand **5** was used, desired esters **14** and **15** were formed in 75% overall yield, albeit in racemate forms.

Unsymmetrical ligand **9** failed to react. In contrast, unsymmetrical monoester **10** delivered Tishchenko products in good yield, but in small enantiomeric excess (5% ee). Its acetyl derivative **Ac-10** showed similar reactivity and selectivity. When diester **6** was added as a chiral ligand, the reactivity and stereoselectivity increased, and both products were isolated in 96% yield after 2 h with 24 ee. Next we tried to reduce the catalyst loading, with the reaction carried out with 10% of **6**/$Yb(OTf)_3$ combination (entry 8). The yield, as well as stereoselectivity, remained at the same level. Interestingly, the stereoselectivity dropped when the reaction was run at −20 °C, and remained untouched at 40 °C. To check the role of the ligand arms structure we tested acetylated hydrobenzoin, which gave only unpromising results (entry 10) even with amine as additive. This observation shows that both the structural part of the ligand (ester moiety and amino group) is necessary for this reaction. Ligands with longer amino acid chains were tested (from hippuric acid and Z-Gly-OH) albeit with less promising results. Despite its reactivity, ligand **13** was unselective (entry 11), which suggests that the presence of benzyl-type hydrogen atom is necessary in catalyst structure. Both ligands with shorter arms, that is, **7** and **11**, failed.

With the best ligand in hand, we tested various metal sources. A systematic evaluation of $RE(OTf)_3$ in the condensation of benzaldehyde with 3-pentanone revealed a consistent increase in enantioselectivity as a function of the lanthanide atomic number, with the highest ee of 24% obtained with $Yb(OTf)_3$ (Table 2).

Table 1. Direct aldol-Tishchenko reaction promoted by *O*,*N*-ligands/ytterbium triflate



Entry	Ligand	Catalyst loading, mol %/time, h	Yield, % (**14**/**15**)	Ee
1	**5**	10/20	Trace	—
2	**5**	20/20	75 (1/2)	0
3	**9**	20/20	ND	—
4	**10**	20/20	74 (1/3.3)	5
5	**Ac-10**	20/20	62 (1/7)	7
6	**6**	20/2	96 (2/1)	24
7	**6**	20/4 (−20 °C)	90 (3/1)	10
8	**6**	10/4	97 (2/3)	24
9	**6**	10/4 (40 °C)	90	20
10	**Ac-8**/Et^{i}Pr$_2$N	20/20	13 (1/0)	0
11	**13**	10/20	84 (2/1)	0
12	**11**	20/20	ND	—
13	**7**	20/20	ND	—

Table 2. Optimization on the aldol-Tishchenko reaction of 3-pentanone and benzaldehyde catalyzed by **6** and $RE(OTf)_3$ (10 mol %)

$RE(OTf)_3$	Sc	La	Pr	Sm	Eu	Dy	Er	Yb	Y	In
Yield (%)	ND	ND	15	35	62	83	94	97	95	ND
De (%)	—	—	40	20	28	80	95	99	93	—
Ee (%)	—	—	8	8	10	15	20	24	8	—

In the case of the more reactive 4-chloropropiophenone, as little as 5 mol % of catalyst is sufficient enough for obtaining 63% yield. When 10 mol % of catalyst was used, 98% of the desired product was isolated after 4 h at rt albeit with only 19% ee.

3. Conclusions

In summary, we have demonstrated syntheses of novel chiral ligands, which enable efficient, diastereoselective aldol-Tishchenko condensation. A metal/ligand complexes were designed, which possess two sites of opposite character—a basic site and an acidic site, each capable of independent activation in close proximity the ketone and the aldehyde substrate. Such catalytic systems have been found to be applicable to the difficult aldol reaction of 3-pentanone providing a powerful method for the simultaneous construction of three continuous chiral centers. Gathered data are useful for designing new effective ligands. With these complexes in hand, we are now engaged in evaluating their catalytic activity and the scope of the reaction. These data will be reported elsewhere.

4. Experimental

4.1. General

Ytterbium(III) triflate prepared from ytterbium(III) oxide (Aldrich) and trifluoromethanesulfonic acid (Fluka), was dried for 24 h at 200 °C under vacuum. All other metal triflates were used as delivered (Aldrich) and dried at 200 °C directly before reactions. All reactions were carried out under argon. Optical rotations were measured with a JASCO Dip-360 Digital Polarimeter at room temperature. ^{1}H NMR spectra were recorded on Varian-400 and Bruker-500 spectrometers in $CDCl_3$ with Me_4Si as internal standard. High resolution mass spectra were taken on a Mariner PerSeptive Biosystems mass spectrometer with time-of-flight (TOF) detector. IR spectra were taken with a Perkin Elmer FT-IR-1600 spectrophotometer. Reactions were controlled using TLC on silica [Merck alu-plates (0.2 mm)]. All reagents and solvents were purified and dried according to common methods. All organic solutions were dried over Na_2SO_4. Reaction products were purified by flash chromatography using Merck's Kieselgel 60 (240–400 mesh).

4.2. (1*S*,2*S*)-1,2-Bis[2-(dimethylamino)ethoxy]-1,2-diphenylethanol 5

4.2.1. Preparation of dimethylamino ethanol tosylate. Sodium hydride (50% dispersion in mineral oil, 480 mg, 10 mmol) was weighed into a Schlenk flask containing a magnetic stirring bar under Ar and washed with dry THF. To a stirred suspension of the base in dry THF (5 mL) at 0 °C was added dimethylamino ethanol (500 μL, 5 mmol). After 5 min a solution of tosyl chloride (1.15 g, 6 mmol) in THF (5 mL) was added. Thus a prepared solution of tosylate was directly transferred into the hydrobenzoin dianion.

4.2.2. Preparation of ligands. Potassium hydride (30% dispersion in mineral oil, 480 mg, 3 mmol) was weighed into a Schlenk flask containing a magnetic stirring bar under Ar and washed with dry THF. To a stirred suspension of the base in dry THF (5 mL) at 0 °C, (*S*,*S*)-hydrobenzoin (215 mg, 1 mmol) was added. 18-Crown-6 (790 mg, 3 mmol) was slowly added, and the whole mixture stirred for 15 min. Then dimethylamino ethanol tosylate solution (ca. 5–7 mL) was added to the alkoxide solution. The flask was fitted with a reflux condenser, and reaction mixture heated to 80 °C for 1 h. The reaction mixture was diluted with ethyl acetate, quenched with water, and washed twice with water and brine. The organic phase was evaporated, and the residue submitted to column chromatography (CH_2Cl_2–MeOH, 7:3 + 0.5% Et_3N) to yield 320 mg (89%) of compound **5**; mp 47 °C; $[\alpha]_D = -0.55$ (*c* 1.00, $CHCl_3$); IR (KBr): *v* 3031, 2942, 2868, 2819, 2796, 1454, 1272, 1112, 1073, 1043; ^{1}H NMR (500 MHz): δ 2.23 (s, 12H), 2.45–2.56 (m, 4H), 3.39–3.49 (m, 4H), 4.43 (s, 2H), 7.03–7.06 and 7.13–7.17 (m, 10 H, Ar); ^{13}C NMR (125 MHz): δ 45.6, 58.7, 67.45, 86.2, 127.3, 127.6, 127.7, 138.6; HRMS (ESI) calcd for $C_{22}H_{32}N_2O_2$ $[M+Na]^+$ 379.2356, found 379.2372. When the above reaction was quenched after 30 min without reflux. *(1S,2S)-2-[2-(Dimethylamino)-ethoxy]-1,2-diphenylethanol* **9** was isolated as the main product. Yield: (94%); colorless oil; $[\alpha]_D = -20.2$ (*c* 1.00, $CHCl_3$); IR (KBr): *v* 3369, 3028, 2855, 2822, 2778, 1490, 1453, 1120, 1038, 1024; ^{1}H NMR (500 MHz): δ 2.39 (s, 3H), 2.58–2.64 (m, 1H), 2.67–2.73 (m, 1H), 3.44–3.50 (m, 1H), 3.60–3.65 (m, 1H), 4.22 (d, 1H, $J = 8.3$ Hz), 4.71 (d, 1H, $J = 8.3$ Hz), 6.98–7.20 (m, 10H, Ar); ^{13}C NMR (125 MHz): δ 44.8, 58.3, 65.6, 78.7, 88.5, 127.3, 127.3, 127.6, 127.7, 127.7, 127.9, 138.2, 139.9; HRMS (ESI) calcd for $C_{18}H_{23}NO_2$ $[M+H]^+$ 286.1802, found 286.1816.

4.3. (1*S*,2*S*)-1,2-Diphenylethyl-1,2-dioxy-bis-*N*,*N*-dimethylaminoacetate 6

Dicyclohexylocarbodiimide (3.09 g, 15 mmol), dimethylaminoglycine (1.23 g, 12 mmol), and DMAP (100 mg) were added to a solution of (*S*,*S*)-hydrobenzoin (860 mg, 4 mmol) in dry DCM at 0 °C under Ar. The contents were stirred at rt for 20 h. The solution was diluted with DCM and the precipitate removed by

filtration. The solvent was evaporated and the residue purified on silica gel column (CH_2Cl_2–MeOH, 95:5). Yield 97%; mp 83 °C; $[\alpha]_D$ = +30.7 (*c* 1.00, $CHCl_3$); IR (KBr): *v* 3037, 2932, 2903, 1724, 1243, 1177, 1150, 1068; ^{1}H NMR (500 MHz): δ 2.30 (s, 12H), 3.18 and 3.22 (2 × d, 2 × 2H, *J* = 17.4 Hz), 6.14 (s, 2H), 7.14–7.22 (m, 10H, Ar); ^{13}C NMR (125 MHz): δ 45.0, 60.1, 77.0, 127.4, 128.2, 128.4, 135. 9, 169.4; HRMS (EI) calcd for $C_{22}H_{28}N_2O_4$ $[M]^+$ 384.2049, found 384.2042. When equimolar amount of DMAP was used some amount (7–15%) of *2-[(1S,2S)-2-hydroxy-1,2-diphenylethyl]-oxy-N,N-dimethylaminoacetate* **10** was detected as the first fraction. Mp 93 °C; $[\alpha]_D$ = −7.4 (*c* 1.00, $CHCl_3$); IR (KBr): *v* 3307, 3031, 2848, 1738, 1454, 1204, 1163, 1058; ^{1}H NMR (500 MHz): δ 2.22 (s, 6H), 3.15 and 3.19 (2 × d, 2H, *J* = 15.0 Hz), 4.97 (d, 1H, *J* = 7.27 Hz), 5.91 (d, 1H, *J* = 7.27 Hz), 7.14–7.23 (m, 10H, Ar); ^{13}C NMR (125 MHz): δ 45.2, 60.8, 76.8, 80.5, 127.0, 127.3, 127.9, 128.0, 128.1, 137.0, 139.5, 169.4; HRMS (EI) calcd for $C_{18}H_{21}NO_3$ $[M]^+$ 299.1521, found 299.1525.

4.4. (2*S*,3*S*)-Butyl-2,3-dioxy-bis-*N*,*N*-dimethylacetamide 13

Based on the above procedure D-(−)-2,3-butanediol was transformed into **13**: yield: 63%; oil; $[\alpha]_D$ = +8.5 (*c* 0.75, $CHCl_3$); IR (KBr): *v* 34448, 2984, 2942, 2825, 2774, 1752, 1451, 1381, 1285, 1244, 1197, 1164, 1062; ^{1}H NMR (500 MHz): δ 1.21–1.25 (m, 6H), 2.37 (s, 12H), 3.16 and 3.20 (2 × d, 2H, *J* = 16.3 Hz), 5.03–5.09 (m, 2H); ^{13}C NMR (125 MHz): δ (ppm) 16.2, 45.1, 60.2, 71.6, 169.8; HRMS (ESI) calcd for $C_{12}H_{25}N_2O_4$ $[M+H]^+$ 261.1809, found 261.1817.

4.5. General procedure for the aldol-Tishchenko condensation of benzaldehyde with 3-pentanone[16]

4.5.1. 1-Hydroxy-2-methyl-1-phenylpentylbenzoate 14 and 3-hydroxy-2-methyl-1-phenylpentylbenzoate 15. Ytterbium(III) triflate (62 mg 0.10 mmol) was placed in an oven-dried flask with a magnetic stirring bar and the flask heated at 200 °C for 10 min in vacuo and then flushed with argon. After the flask was cooled down to rt, a solution of ligand **6** (48 mg, 0.12 mmol) in THF (2 mL) was added. The resulting solution was stirred for 10 min at rt under an argon atmosphere. To a solution of the catalyst 3-pentanone (106 μL, 1.00 mmol) and benzaldehyde (101 μL, 1.00 mmol) were added successively. The resulting solution was stirred for 20 h at rt, then dissolved with MTBE, and washed with water and brine. The organic layer was dried over Na_2SO_4, concentrated, and submitted to column chromatography (hexane–ethyl acetate, 9:1). First fraction contained ester **14**:[16] yield 39%, ^{1}H NMR (400 MHz): δ 0.75 (d, 3H, *J* = 6.9 Hz), 0.99 (t, 3H, *J* = 7.4 Hz), 1.55–1.76 (m, 1H), 1.81–2.12 (m, 2H), 3.71 (d, 1H, *J* = 3.8 Hz, OH), 4.19 (dd, 1H, *J* = 3.6, 9.8 Hz), 5.62 (ddd, 1H, *J* = 1.5, 5.6, 8.7 Hz), 7.20–7.64 (m, 8H, Ar), and 8.10 (d, 2H, Ar); ^{13}C NMR (100 MHz): δ 9.9, 10.5, 25.7, 44.3, 75.7, 75.8, 127.0, 127.6, 128.3, 128.4, 129.7, 133.2, 142.8, 167.6. Detection of enantiomers ratio: HPLC on Chiralpak AD-H column: hexane–^{i}PrOH (9:1), 1 mL/min; t^1 = 12.3 min, t_2 = 23.3 min. Second fraction contained ester **15**:[16] yield 58%, ^{1}H NMR (400 MHz): δ 0.75 (d, 3H, *J* = 6.9 Hz), 0.94 (t, 3H, *J* = 7.3 Hz), 1.24–1.69 (m, 2H), 2.02–2.20 (m, 1H), 2.52 (br s, 1H, OH), 3.75 (br t, 1H, *J* = 6.5 Hz), 5.95 (d, 1H, *J* = 9.8 Hz), 7.20–7.68 (m, 8H, Ar), and 8.10 (d, 2H, Ar); ^{13}C NMR (100 MHz): δ 8.8, 10.8, 27.3, 43.0, 71.2, 78.8, 127.4, 128.1, 128.3, 128.4, 129.7, 133.1, 139.4, 166.5. Detection of enantiomers ratio: HPLC on Chiralpak AD-H column: hexane–^{i}PrOH (95:5), 1 mL/min; t^1 = 23.2 min, t_2 = 24.3 min.

Acknowledgements

Financial support by the Polish State Committee for Scientific Research (KBN Grant 3 T09A 126 27) is gratefully acknowledged.

References

1. (a) Schinzer, D. *Selectivities in Lewis Acid Promoted Reactions*; Kluwer Academic: Dordrecht, 1989; (b) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000.
2. (a) Kobayashi, S. In *Lanthanides: Chemistry and Use in Organic Synthesis*; Kobayashi, S., Ed.; Springer: Heidelberg, 1999; (b) Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15–27; (c) Kobayashi, S. *Synlett* **1994**, 689–701.
3. Kobayashi, S.; Suguira, M.; Kitagawa, H.; Lam, W. *Chem. Rev.* **2002**, *102*, 2227–2302.
4. Inanaga, J.; Furuno, H.; Hayano, T. *Chem. Rev.* **2002**, *102*, 2211–2225.
5. Aspinall, H. C. *Chem. Rev.* **2002**, *102*, 1807–1850.
6. (a) Shibasaki, M. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; (b) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595–1601; (c) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65–75.
7. (a) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187–2209; (b) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Adv. Synth. Catal.* **2002**, *344*, 3–15.
8. (a) Trost, B. M.; Ito, H.; Silcoff, E. *J. Am. Chem. Soc.* **2001**, *123*, 3367–3368; (b) Trost, B. M.; Silcoff, E.; Ito, H. *Org. Lett.* **2001**, *3*, 2497–2500.
9. Yamada, M. A.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 5561–5564.
10. Suzuki, T.; Yamagiwa, N.; Matsuo, Y.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M.; Noyori, R. *Tetrahedron Lett.* **2001**, *42*, 4669–4671.
11. (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1871; (b) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168; (c) Yoshikawa, N.; Kumagi, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466.
12. For the first example of direct aldol reaction of ethyl ketones, see: (a) Mahrwald, R. *Org. Lett.* **2000**, *2*, 4011; (b) Mahrwald, R.; Ziemer, B. *Tetrahedron Lett.* **2002**, *43*, 4459.
13. Gnanadesikan, V.; Horiuchi, Y.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7782–7783.
14. For review on aldol-Tishchenko reaction, see: Mahrwald, R. *Curr. Org. Chem.* **2003**, *7*, 1713–1723.
15. Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.

16. Mlynarski, J.; Mitura, M. *Tetrahedron Lett.* **2004**, *45*, 7549–7552.
17. Such a structure was proven by Kobayashi for the binaphthol-based catalytic system: (a) Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083–4084; (b) Kobayashi, S.; Ishitani, H.; Araki, M.; Hachiya, I. *Tetrahedron Lett.* **1994**, *35*, 6325–6328; (c) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840–5841.
18. For binol–amine combination see Ref. 17. For the pybox ligand family, see: Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119–3154, and Ref. 5; For macrocyclic *O*,*N*-donors, see: Hamada, T.; Manabe, K.; Ishikawa, S.; Nagayama, S.; Shiro, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 2989–2996.
19. Aspinall, H. C.; Greeves, N.; Lee, W. M.; McIver, E. G.; Smith, P. M. *Tetrahedron Lett.* **1997**, *38*, 4679–4682.
20. Aspinall, H. C.; Greeves, N.; McIver, E. G. *Tetrahedron* **2003**, *59*, 10453–10463.
21. For a precedent mesylane synthesis in 15% yield, see: Goff, D. A.; Koolpe, G. A.; Kelson, A. B.; Vu, H. M.; Taylor, D. L.; Bedford, C. D.; Musallam, H. M.; Koplovitz, I.; Harris, R. N., III. *J. Med. Chem.* **1991**, *34*, 1363–1368.