Enantioselective synthesis of α-hydroxyphosphonates through asymmetric Pudovik reactions with chiral lanthanoid and titanium alkoxides

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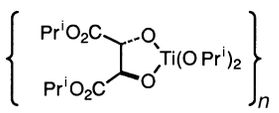
The Pudovik reaction of aromatic aldehydes with diethyl phosphite catalysed by either tartrate-modified titanium(IV) alkoxides or binaphthol-modified lanthanoid alkoxides has been examined. The enantioselectivity for the Pudovik reaction catalysed by tartrate-modified titanium(IV) alkoxide 1 was strongly dependent upon the solvent used. The electronic nature of the carbonyl affected the enantioselectivity for the Pudovik reaction with the La-Li-BINOL complex 2.

Introduction

The synthesis of chiral α-substituted phosphonic acids has become an important area of research, particularly in connection with the search for biologically active surrogates for the corresponding carboxylic acids and phosphoric acids esters.[1] Of such α-substituted phosphonic acids, α-hydroxy phosphonic acid derivatives are compounds attracting increased interest in medicinal chemistry. Interesting inhibitory activity towards renin and HIV protease has been observed upon incorporation of β-amino-α-hydroxy phosphonic acids[2] or the related phosphonic acids[3] into a peptidic framework as a transition-state mimic of dipeptide hydrolysis. Moreover, α-hydroxy phosphonic acids have been proved to act as a hydrolytically stable mimic of phosphoric acid esters; some benzylic α-hydroxy phosphonic acid derivatives have been shown to possess potential inhibitory activity towards EPSP synthase[4] and tyrosine-specific protein kinase.[5] Alternatively, α-hydroxy phosphonates may represent an interesting chiron for the preparation of the parent α-amino phosphonic acids.[6] Despite the number of papers which have appeared on the synthesis of α-amino phosphonic acids,[7] the stereocontrolled synthesis of α-hydroxy phosphonic acid derivatives has only recently begun to receive attention.[8]

Racemic α-hydroxy phosphonate derivatives have been conventionally synthesized through base-catalysed hydrophosphonylation (the Pudovik reaction) of aldehydes with dialkyl phosphites.[9] The asymmetric version of the Pudovik reaction of prochiral aldehydes with chiral phosphorus acid diamides has been extensively studied by Spilling.[10] From the viewpoint of methodology, an enantioselective Pudovik reaction catalysed by a catalytic amount of a chiral base would be both highly desirable and efficient. In this context, Wynberg briefly examined an asymmetric Pudovik reaction using chiral amines derived from quinine as the chiral base.[11] However, the enantiomeric excess (ee) of the products through this method is reported to be rather low. To obtain more efficient asymmetric catalysts for the Pudovik reaction, we have pursued the utility of chiral transition metal catalysts such as titanium alkoxides derived from L-tartrate **1** and binaphthol-modified lanthanoid alkoxides **2**–**5** in the Pudovik reaction and have reported the preliminary results as communications.†[12] In this paper we describe a full account of these experiments.

† After our asymmetric Pudovik reaction with chiral transition-metal catalysts was introduced, Spilling and Shibasaki independently published their results on the asymmetric Pudovik reaction with asymmetric heterobimetallic catalysts.[13]



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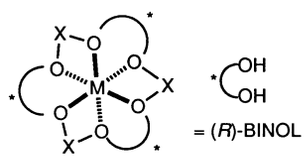
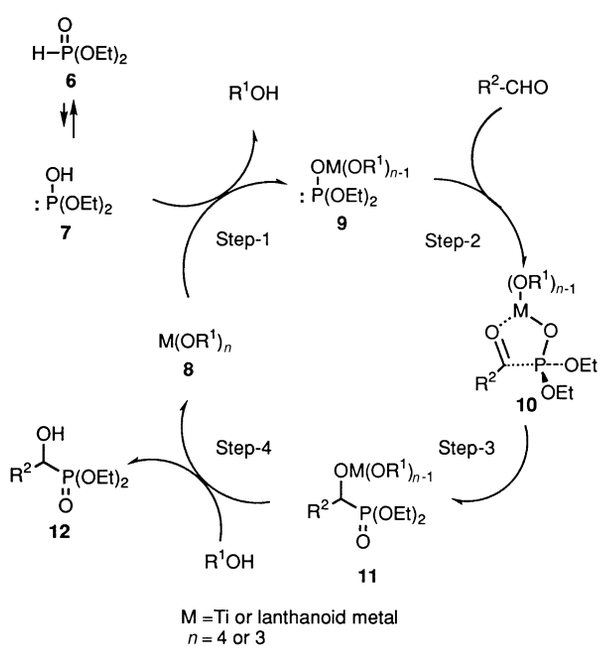


2 X = Li, M = La; **3** X = Na, M = La
4 X = Li, M = Eu; **5** X = Li, M = Sm

Results and discussion

It is commonly accepted that H-phosphonates such as diethyl phosphite exist in two tautomeric forms, the phosphite **7** and the phosphonate **6**, with the latter predominating under neutral conditions (Scheme 1).[7c] However, it is assumed that the anionic

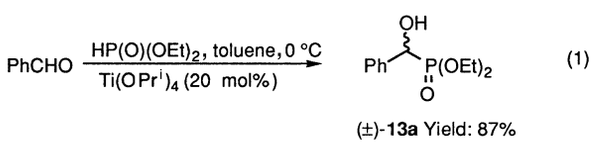


Scheme 1 Schematic drawing for the catalytic Pudovik reaction catalysed by metal alkoxides

form of the phosphite tautomer **7** would be the most nucleophilic and would make the main contribution to the formation of the carbon–phosphorus bond under the basic conditions of the Pudovik reaction.[7c] If transition-metal catalysts **8** such as titanium alkoxides and lanthanoid alkoxides, which are known to act as a weak base,[14,15] are available as an activator of diethyl phosphite through a ligand-exchange reaction as shown in Scheme 1, the resulting organometallic phosphorus species **9** would add to aldehydes to form α-hydroxy phosphonates **12**. In these reactions, the high coordination ability of titanium and lanthanoid atoms would lead to formation of a more intimate contact between the aldehyde and the organometallic phosphorus species **9** *via* a transition state such as **10**. Therefore, introduction of a chiral ligand on the catalysts would provide a favourable chiral environment inducing enantio-differentiation of the prochiral aldehydes.

Pudovik reactions promoted by titanium alkoxy derivatives

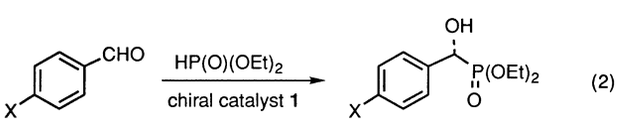
In keeping with the strategy described above for the enantioselective synthesis of chiral α-hydroxy phosphonates, we first examined the possibility of using titanium tetraisopropoxide, $Ti(OPr^i)_4$, as an activator of the Pudovik reaction. Although the reaction proceeded rather slowly, the racemic α-hydroxy phosphonate (±)-**13a** was obtained in 87% yield as expected on treatment of benzaldehyde with diethyl phosphite in the presence of 20 mol% of $Ti(OPr^i)_4$ in toluene at 0 °C [eqn. (1)].‡ The results clearly demonstrated that a catalytic cycle as shown in Scheme 1 actually works well.



(1)

(±)-**13a** Yield: 87%

Encouraged by these findings, we next examined asymmetric Pudovik reactions using the Sharpless catalyst **1**,[15] prepared *in situ* from diisopropyl L-tartrate and $Ti(OPr^i)_4$, because **1** has high potential for differentiating the enantioface in asymmetric epoxidations of allylic alcohols[15a] as well as hydrocyanations of aldehydes.[15b] The Lewis basicity of **1** should affect the tautomerization of diethyl phosphite, which is considered to be crucial for effective incorporation of the phosphoric nucleophile within the chiral titanium species. The Lewis basicity of **1** could be adjusted for the reaction by tuning the donor or acceptor ability of the solvent used.[16] The Pudovik reactions of benzaldehyde as well as the *para*-substituted benzaldehyde with diethyl phosphite were then carried out in the presence of a catalytic amount (20 mol%) of **1** in several kinds of solvents [eqn. (2)]. The results are summarized in Table 1. The reaction



(2)

(+)-**13a–c**

with benzaldehyde in toluene proceeded to give the (*R*)-(+)-α-hydroxy phosphonate (+)-**13a** in 51% yield (36% ee; entry 1). When the reaction was conducted in CH_2Cl_2 as the solvent of acceptor ability, no face selectivity was observed and the chemical yield was low (entry 2). In contrast, when Et_2O or THF was used as the donor solvent, chemical and optical yields of (+)-**13a** increased to 75% (53% ee) and 61% (51% ee), respectively (entries 3 and 4). The same level of asymmetric induction was observed in the hydrophosphonylation of the substituted benzaldehyde having electron-withdrawing chlorine substituents under the same conditions (entry 5). However, low enantioselectivity was observed upon using benzaldehyde having electron-donating substituents such as *p*-anisaldehyde (entry 6).

These data show that efficient incorporation of the chiral titanium alkoxide into diethyl phosphite by increasing the basicity of the catalyst through tuning the donor ability of the solvent used was critical to induce the asymmetric Pudovik reaction; moreover, the enantio-discrimination for these reactions might occur at the phosphorus to carbon bond formation in step 3 as shown in Scheme 1.

Table 1 Enantioselective additions of diethyl phosphite to benzaldehydes and substituted benzaldehydes with the Sharpless catalyst **1**

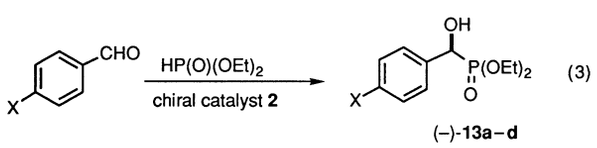
Entry[a]	X	Solvent	Product	Yield (%)	Ee (%)[b]
1	H	Toluene	(*R*)-(+)-**13a**	51	36
2	H	CH_2Cl_2	(±)-**13a**	12	0
3	H	THF	(*R*)-(+)-**13a**	61	51
4	H	Et_2O	(*R*)-(+)-**13a**	75	53
5	Cl	Et_2O	(*R*)-(+)-**13b**	76	52
6	MeO	Toluene	(*R*)-(+)-**13c**	38	21

[a] All reactions were carried out at 0 °C in the presence of 20 mol% of the catalyst for 15 h. [b] Determined by NMR (^{31}P and ^{1}H) analysis of the corresponding MTPA esters.

Asymmetric Pudovik reactions of substituted benzaldehydes catalysed by binaphthol-modified lanthanoid alkoxides

On the basis of the results obtained above, the use of transition-metal catalysts exhibiting a more basic character than the Sharpless catalyst **1** was also considered to be an alternative method to induce the enantioselective Pudovik reaction. In this context, the binaphthol-modified lanthanoid alkoxides, recently introduced by Shibasaki, should be suitable catalysts for the asymmetric Pudovik reaction because of their inherent basic character and potential usefulness for asymmetric synthesis.[14] Accordingly, we examined the catalytic activity of binaphthol-modified lanthanoid alkoxides including La-Li-(*R*)-BINOL (LLB) **2**, La-Na-(*R*)-BINOL (LSB) **3**, Eu-Li-(*R*)-BINOL (EuLB) **4** and Sm-Li-(*R*)-BINOL (SmLB) **5**,[14] prepared from (*R*)-binaphthol by the method of Shibasaki, for the asymmetric Pudovik reactions of benzaldehyde derivatives.

Initially, reactions of several substituted benzaldehydes with diethyl phosphite were examined in the presence of a catalytic amount (20 mol%) of LLB in THF in the range of −20 to −78 °C for 15 h [eqn. (3)]. As summarized in Table 2, all reactions conducted at −40 °C gave the corresponding (*S*)-(−)-α-hydroxy phosphonates (−)-**13a–d** in generally excellent yield (>90%) (entries 3–6). When the reaction was carried out at either −20 or −78 °C, the yield of (−)-**13c** decreased to 87 and 67%, respectively (entries 1 and 2). The results show the catalytic reaction works effectively at around −40 °C. The degree of enantioselectivity for the reactions strongly depended upon the substituent in the *para* position on the aromatic ring. The reactions with *p*-anisaldehyde and *p*-tolualdehyde proceeded with enantioselectivities of 82 and 58% ee, respectively (entries 3 and 4). In contrast, low enantioselectivities were observed with the reaction of benzaldehyde and *p*-chlorobenzaldehyde (entries 5 and 6). To gain insight into the origin of the enantioselectivity, we examined the correlation between the Hammett aromatic substituent constant (σ_p) and the ee. A linear Hammett plot with a relatively large negative ρ value (−1.30, $\gamma = 0.92$) was observed as shown in Fig. 1. The large negative ρ value suggests



(3)

(−)-**13a–d**

‡ It was also found that $La(OPr^i)_3$ and $Al(OPr^i)_3$ catalysed the Pudovik reaction of benzaldehyde with diethyl phosphite in THF and toluene at 0 °C to give (±)-**8a** in 55 and 87% yields, respectively.

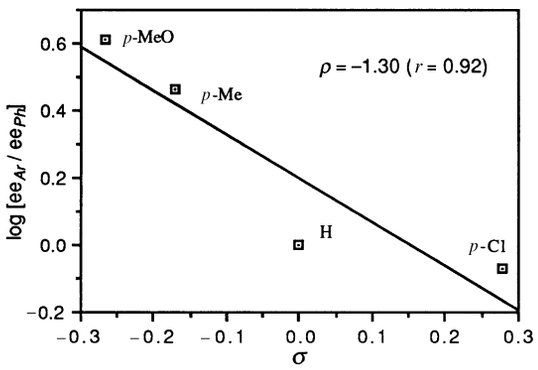


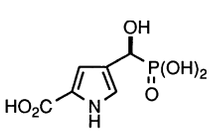
Fig. 1 Hammett plot for enantioselective hydrophosphonylation of substituted benzaldehydes with diethyl phosphite catalysed by **2** at −40 °C

the coordination step (corresponding to step 2 in the schematic catalytic cycle in Scheme 1) of the presumed LLB-HP(O)(OEt)$_2$ complex with aldehydes should be involved in at least the enantio-determination step.

Next, in order to elucidate the effects of metals within the binaphthol-modified lanthanoid catalysts on the asymmetric Pudovik reaction, the hydrophosphonylation reactions of *p*-anisaldehyde with diethyl phosphite catalysed by either LSB, EuLB or SmLB were briefly examined. Although LSB required 0 °C to induce the reaction, EuLB and SmLB exhibited catalytic activity able to induce a good yield of the Pudovik reaction product at −40 °C. However, unfortunately, the enantioselectivities of these reactions were very low (8–15% ee) as shown in Table 3. Although the LSB-catalysed reaction gave (−)-**13c**, the reversed enantio-selection giving (+)-**13c** was observed when either EuLB or SmLB was used as the asymmetric catalyst. The results show that the choice of rare earth metal in a catalyst is a crucial factor in inducing good enantioselectivity; moreover, the alkali metal in the catalyst is significant as a mediator for the effectiveness of the catalytic cycle.

LLB-catalysed Pudovik reactions of heteroaromatic aldehydes

In order to assess the role of the aromatic ring within a substrate during the LLB-catalysed asymmetric Pudovik reactions, as well as to extend the reaction to the enantioselective synthesis of α-hydroxy phosphonates possessing a heteroaromatic ring such as **14**, which is known to exhibit inhibitory activity towards EPSP synthase,[17] our attention was focused on LLB-catalysed hydrophosphonylation of heteroaromatic aldehydes having either a thiophene or furan nucleus.§



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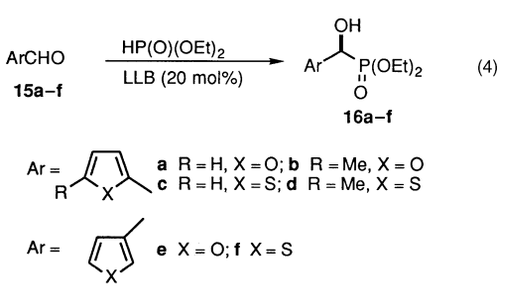
The LLB-catalysed reactions of a range of heteroaromatic aldehydes **15a–f** with diethyl phosphite were examined under exactly the same conditions as described above [eqn. (4)]. The



(4)

§ 1-Methylpyrrole-2-carbaldehyde was found to be a poor substrate for the LLB-catalysed Pudovik reaction under the conditions employed.

Table 2 LLB-catalysed Pudovik reaction of benzaldehyde and substituted benzaldehyde with diethyl phosphite

Entry[a]	X	Temp. (°C)	Product	Yield (%)	Ee (%)[b]
1	MeO	−20	(*S*)-(−)-**13c**	87	74
2	MeO	−78	(*S*)-(−)-**13c**	67	79
3	MeO	−40	(*S*)-(−)-**13c**	95	82
4	Me	−40	(*S*)-(−)-**13d**	94	58
5	H	−40	(*S*)-(−)-**13a**	98	20
6	Cl	−40	(*S*)-(−)-**13b**	99	17

[a] All reactions were carried out in the presence of 20 mol% of the catalyst for 15 h. [b] Determined by NMR (^{31}P and ^{1}H) analysis of the corresponding MTPA esters.

Table 3 Pudovik reactions of *p*-anisaldehyde with diethyl phosphite in the presence of LSB, EuLB or SmLB in THF

Entry[a]	Catalyst	Temp. (°C)	Product	Yield (%)	Ee (%)[b]
1	LSB	0	(*S*)-(−)-**13c**	81	15
2	EuLB	−40	(*R*)-(+)-**13c**	91	9
3	SmLB	−40	(*R*)-(+)-**13c**	89	8

[a] All reactions were carried out in the presence of 20 mol% of the catalyst for 15 h. [b] Determined by NMR (^{31}P and ^{1}H) analysis of the corresponding MTPA esters.

Table 4 LLB-catalysed Pudovik reactions of heteroaromatic aldehydes **15a–f** with diethyl phosphite

Entry[a]	Substrate	$S_r^{(E)}$	Product	Yield (%)	Ee (%)
1	**15a**	0.917	**16a**	74	18
2	**15b**	0.940	**16b**	82	44
3	**15c**	0.959	**16c**	94	41
4	**15d**	0.976	**16d**	57	73
5	**15e**	0.947	**16e**	64	64
6	**15f**	0.975	**16f**	65	67

[a] All reactions were carried out in the presence of 20 mol% of the catalyst for 15 h.

representative results of these reactions are shown in Table 4. All reactions gave the corresponding (*S*)-(−)-α-hydroxy phosphonates **16a–f** with enantioselectivities which, interestingly, varied from 18 to 73% ee in good yields. The highest enantioselectivity (73% ee) was attained in the reaction with 5-methylthiophene-2-carbaldehyde **15d** (entry 4). Obviously, the enantioselectivities obtained from a series of reactions with aldehydes having the thiophene nucleus were found to be higher than those of the corresponding furancarbaldehyde derivatives (entries 1,2,5 *vs.* 3,4,6).

To gain a deeper understanding of the factors governing the enantioselectivity, we examined the correlations between the ee of the products **16a–j** and electrophilic super-delocalizability [$S_r^{(E)}$][18] at the carbonyl oxygen within the substrates. The [$S_r^{(E)}$] would be a measure of the susceptibility of the substrate to attack by the catalyst based on the distribution of electrons in the frontier orbital. As shown in Fig. 2, independent correlations were observed in the series of reactions with aldehydes possessing the same heterocycles, and the numerical value of the ee for the products increased with an increase in the numerical value of $S_r^{(E)}$. The results reveal that electrophilic coordination of the lanthanum atom in the presumed LLB–diethyl phosphite complex to the carbonyl oxygen of the aldehyde might be a critical factor governing the enantioselectivity. This conclusion is consistent with that derived from the LLB-catalysed Pudovik reactions with *para*-substituted benzaldehyde on the basis of the Hammett plots of Fig. 1. However, since the correlation between the [$S_r^{(E)}$] and the ee of **16a–f** is independent of the respective series of thiophene- and

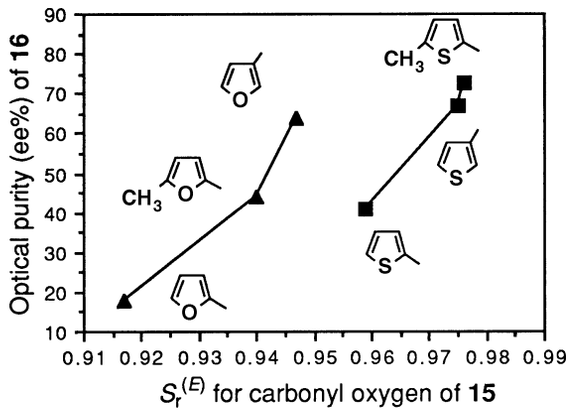


Fig. 2 Plots for optical purities of **16** *vs.* $S_r^{(E)}$ for carbonyl oxygen of **15**

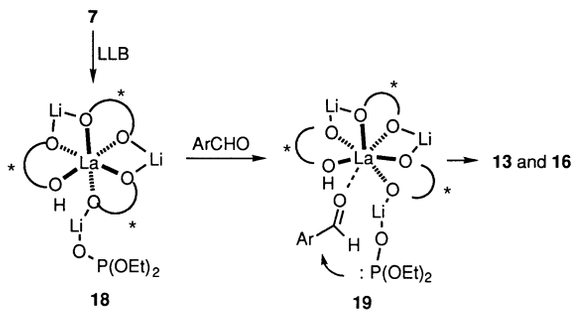
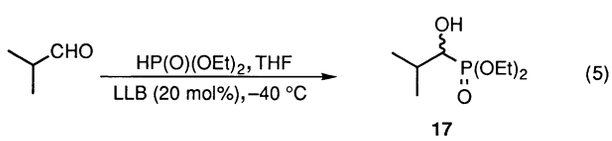


Fig. 3 Possible mechanism for LLB-catalysed asymmetric Pudovik reaction

furan-carbaldehydes, other factors governing the enantioselectivity might be suspected. Since the LLB-catalysed Pudovik reaction with isobutyraldehyde results in an absence of asymmetric induction combined with a high chemical yield (88%) of **17** [eqn. (5)], the aromaticity of the substrate is considered to be



(5)

a significant factor for the LLB-catalysed Pudovik reaction to bring about asymmetric induction.

Determination of the absolute configuration of α-hydroxy phosphonates (−)-13a–d and (−)-16a–f

The absolute stereochemistry of compounds (−)-**13a–d** and (−)-**16a–f** prepared in this study was determined by ^{31}P NMR analysis of their (*R*)-MTPA esters according to the method of Hammerschmidt.[19] Chemical shifts of the ^{31}P NMR spectra for the (*R*)-MTPA esters derived from (−)-**13a–d** and (−)-**16a–f** are summarised in Table 5. In all cases, δ values for the major signals due to the (*R*)-MTPA esters of (−)-**13a–d** and (−)-**16a–f** were observed at lower field, as compared with those arising from the minor enantiomers. The shift differences ($\Delta\delta$) range from 0.28 to 0.50. On the basis of the arguments presented by Hammerschmidt,[19] the ^{31}P NMR signals at lower field in the spectra are assigned to be the (*R*)-MTPA esters derived from the α-hydroxy phosphonates with *S*-configuration. Therefore, the absolute configuration of (−)-**13a–d** and (−)-**16a–f** was unambiguously determined to be *S*.

Mechanistic discussion for the LLB-catalysed asymmetric Pudovik reactions

The following mechanism was considered for the LLB-catalysed asymmetric Pudovik reaction (Fig. 3). The first step in this reaction is the activation of diethyl phosphite with the lithium atom of LLB to generate the lithium salt of diethyl phosphite **18**. Although we could not detect **18** directly by means of spectroscopy, we believe that the phosphorus atom within **18** is trivalent on the basis of a previous report that the predominant form for alkali-metal salts of dialkyl phosphites is considered to be trivalent from the evidence of ^{1}H NMR and IR spectroscopic analyses.[20] The complex **18** then reacts with an aldehyde *via* the transition state **19** to give an α-hydroxy phosphonate. At the transition state of **19**, an intimate coordination contact between an aldehyde and the lanthanum atom arising from basicity of the carbonyl leads to a favourable chiral environment inducing good enantio-differentiation of the carbonyl. These arguments are supported by the Hammett plots as well as the $S_r^{(E)}$–ee correlations (*vide supra*).

Table 5 ^{31}P NMR data of (*R*)-MTPA esters of (−)-**13a–d** and (−)-**16a–f** obtained by the LLB-catalysed Pudovik reaction

(*R*)-MTPA ester	Major (δ ppm)	Minor (δ ppm)	$\Delta\delta$ [δ(major) − δ(minor)]
(*R*)-MTPA-(−)-**13a**	15.77	15.39	0.38
(*R*)-MTPA-(−)-**13b**	15.27	14.89	0.38
(*R*)-MTPA-(−)-**13c**	16.11	15.76	0.35
(*R*)-MTPA-(−)-**13d**	15.97	15.61	0.36
(*R*)-MTPA-(−)-**16a**	13.60	13.13	0.47
(*R*)-MTPA-(−)-**16b**	13.85	13.35	0.50
(*R*)-MTPA-(−)-**16c**	14.39	14.07	0.32
(*R*)-MTPA-(−)-**16d**	14.62	14.30	0.32
(*R*)-MTPA-(−)-**16e**	15.64	15.33	0.31
(*R*)-MTPA-(−)-**16f**	15.28	15.00	0.28

Conclusions

In conclusion, we have realised a catalytic asymmetric Pudovik reaction using either a tartrate-modified titanium alkoxide or a binaphthol-modified lanthanoid alkoxide. The results presented in this paper are likely to be useful in the synthesis of asymmetric α-hydroxy phosphonates which, up to now, have received little attention.

Experimental

General

All mps were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under nitrogen. Solvents were distilled from a suitable drying agent (given in parentheses); THF (sodium benzophenone ketyl), Et_2O (sodium benzophenone ketyl), CH_2Cl_2 (P_2O_5) and toluene (CaH_2). Optical rotations were measured with a JASCO DIP-360 digital polarimeter in a 1-dm cell and are recorded in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded as KBr discs or films on a Perkin-Elmer 1710 FTIR spectrometer. Mass spectra were measured on a Hitachi M-80 or a VG Auto Spec spectrometer at 70 eV. NMR spectra were obtained on a Bruker AM 400 instrument operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C and 160 MHz for ^{31}P. Spectra were referenced internally using either the residual solvent resonance for ^{1}H and ^{13}C, or $SiMe_4$ ($\delta = 0$) and externally for ^{31}P using 85% H_3PO_4 as 0 ppm. *J* Values are given in Hz. The [$S_r^{(E)}$] values for the carbonyl oxygen of compounds **15a–f** were evaluated by MOPAC with AM 1 parameters run on a SONY Tectronix CaChe system.

Reaction of benzaldehyde with diethyl phosphite in the presence of Ti(OPr^i)$_4$ in toluene

To a stirred solution of Ti(OPr^i)$_4$ (191 mg, 0.65 mmol) in toluene (3.3 cm^3) was added a solution of diethyl phosphite (539 mg, 3.9 mmol) in toluene (4 cm^3) at 0 °C. After the mixture had been stirred for 30 min, a solution of benzaldehyde (345 mg, 3.3 mmol) in toluene (3 cm^3) was added to it. The mixture was

stirred at 0 °C for 15 h, after which it was treated with saturated aqueous $NaHCO_3$ to quench the reaction. The biphasic mixture was extracted with Et_2O. The extracts were washed with brine, dried ($MgSO_4$) and evaporated to give a residue. Purification by column chromatography (SiO_2, hexane–EtOAc, 2:1 to 1:20) gave (±)-**13a** (691 mg, 87%), mp 78–80 °C (Found: C, 54.16; H, 6.92. $C_{11}H_{17}O_4P$ requires C, 54.09; H, 7.02%); ν_{max}(KBr)/cm^{-1} 3256 (OH) and 1230 (phosphoryl); δ_H(400 MHz, $CDCl_3$) 7.51–7.40 (2 H, m, Ph), 7.39–7.30 (3 H, m, Ph), 5.03 (1 H, d, *J* 10.8, PhC*H*), 4.10–3.97 (4 H, m, OCH_2CH_3), 1.29 (3 H, t, *J* 7.2, OCH_2CH_3), 1.21 (3 H, t, *J* 7.1, OCH_2CH_3); δ_P(160 MHz; $CDCl_3$) 21.13; δ_C(100 MHz; $CDCl_3$) 128.3 (s, Ph), 128.1 (s, Ph), 127.1 (s, Ph), 127.0 (s, Ph), 71.0 (d, $^1J_{PC}$ 158.5, PHCH), 63.2 (d, $^2J_{PC}$ 7.0, OCH_2CH_3), 63.1 (d, $^2J_{PC}$ 7.3, OCH_2CH_3), 16.4 (s, OCH_2CH_3) and 16.3 (s, OCH_2CH_3); *m/z* 244 (M^+).

General procedure for Pudovik reactions with Sharpless catalyst 1

To a stirred solution of diisopropyl L-tartrate (152 mg, 0.65 mmol) in toluene (3.3 cm^3) was added $Ti(OPr^i)_4$ (191 mg, 0.65 mmol) at room temperature and the mixture was stirred for 2 h. After this, the mixture was treated with a solution of diethyl phosphite (539 mg, 3.9 mmol) in toluene (4 cm^3) at 0 °C and then stirred for 30 min. A solution of the aldehyde (3.3 mmol) in toluene (3 cm^3) was then added to the mixture after which it was stirred for 15 h at the same temperature. The mixture was then treated with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated to give a residue. Purification of this by flash chromatography (SiO_2, hexane–EtOAc, 1:1 to 1:20) gave (+)-**13a–c**. To observe the solvent effects of Et_2O, THF and CH_2Cl_2, the above procedure was followed except for the replacement of toluene by the solvent to be examined. The physical data of compounds (+)-**13a–c** are given below.

(*R*)-Diethyl phenyl(hydroxy)methylphosphonate (*R*)-(+)-13a. Mp 59–61 °C; $[\alpha]_D^{20}$ +19.1 (*c* 1.0, in $CHCl_3$) for a sample of 53% ee; other physical data were identical with those of a racemic standard.

(*R*)-Diethyl hydroxy(4-chlorophenyl)methylphosphonate (*R*)-(+)-13b. Mp 64–66 °C (Found: C, 47.43; H, 5.66. $C_{11}H_{16}ClO_4P$ requires C, 47.40; H, 5.79%); $[\alpha]_D^{20}$ +21.9 (*c* 1.0 in $CHCl_3$) for a sample of 52% ee; ν_{max}(KBr)/cm^{-1} 3251 (OH) and 1234 (phosphoryl); δ_H(400 MHz; $CDCl_3$) 7.44–7.41 (2 H, m, Ph), 7.33 (2 H, d, *J* 8.5, Ph), 4.99 (1 H, d, *J* 10.9, PhC*H*), 4.12–3.96 (4 H, m, OCH_2CH_3), 1.27 (3 H, t, *J* 7.1, OCH_2CH_3) and 1.24 (3 H, t, *J* 7.1, OCH_2CH_3); δ_P(160 MHz; $CDCl_3$) 20.56; δ_C(100 MHz; $CDCl_3$) 135.2 (s, Ph), 133.9 (s, Ph), 128.4 (s, Ph), 128.3 (s, Ph), 70.3 (d, $^1J_{PC}$ 159.0, PHCH), 63.4 (d, $^2J_{PC}$ 7.2, OCH_2CH_3), 63.1 (d, $^2J_{PC}$ 7.0, OCH_2CH_3) and 16.4 (2 C, d, $^3J_{PC}$ 5.4, OCH_2CH_3); *m/z* 278 (M^+).

(*R*)-Diethyl hydroxy(4-methoxyphenyl)methylphosphonate (*R*)-(+)-13c. Mp 120–122 °C (Found: C, 52.72; H, 7.10. $C_{12}H_{19}O_5P$ requires C, 52.55; H, 6.98%); $[\alpha]_D^{20}$ +10.4 (*c* 1.0 in $CHCl_3$) for a sample of 21% ee; ν_{max}(KBr)/cm^{-1} 3256 (OH) and 1252 (phosphoryl); δ_H(400 MHz; $CDCl_3$) 7.40 (2 H, dd, *J* 2.1 and 8.7, Ph), 6.90 (2 H, d, *J* 8.7, Ph), 4.95 (1 H, d, *J* 9.9, PhC*H*), 4.11–3.91 (4 H, m, OCH_2CH_3), 3.81 (3 H, s, MeO), 1.29 (3 H, t, *J* 7.2, OCH_2CH_3), 1.21 (3 H, t, *J* 7.1 OCH_2CH_3); δ_P(160 MHz; $CDCl_3$) 21.36; δ_C(100 MHz; $CDCl_3$) 160.6 (s, Ph), 129.3 (s, Ph), 129.2 (s, Ph), 114.5 (s, Ph), 80.0 (d, $^1J_{PC}$ 160.3, *C*HP), 63.5 (d, $^2J_{PC}$ 7.3, OCH_2CH_3), 63.4 (d, $^2J_{PC}$ 7.5 OCH_2CH_3), 55.6 (s, MeO), 16.50 (d, $^3J_{PC}$ 5.7, OCH_2CH_3) and 16.47 (d, $^3J_{PC}$ 5.0, OCH_2CH_3); *m/z* 274 (M^+).

Representative procedure for Pudovik reactions with LLB

A stock solution of LLB **2** in THF (100 cm^3) was prepared from $LaCl_3 \cdot 7H_2O$ (1.85 g, 5.0 mmol), dilithium (*R*)-binaphthoxide (5 mmol), $NaOBu^t$ (496 mg, 5.0 mmol) and water (3.6×10^{-1} cm^3, 20 mmol) according to the method of Shibasaki.[14b] To a stirred mixture of the aldehyde (2 mmol) and diethyl phosphite (331 mg, 2.4 mmol) in THF (4.5 cm^3) was added the THF solution of LLB (8 cm^3) over 5 min at −40 °C. After being stirred for 15 h at the same temperature, the reaction mixture was treated with 1 M hydrochloric acid and extracted with Et_2O. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated to give a residue. Purification of this by flash chromatography (SiO_2, hexane–EtOAc, 1:1 to 1:20) gave (−)-**13a–d**, (−)-**16a–f** and **17**. The physical data are given below.

(*S*)-Diethyl phenyl(hydroxy)methylphosphonate (*S*)-(−)-13a. Mp 74–76 °C; $[\alpha]_D^{20}$ −6.6 (*c* 1.0 in $CHCl_3$) for a sample of 20% ee. Other physical data were identical with those of a racemic standard and (+)-**13a**.

(*S*)-Diethyl hydroxy(4-chlorophenyl)methylphosphonate (*S*)-(−)-13b. Mp 67–70 °C; $[\alpha]_D^{20}$ −5.5 (*c* 1.0 in $CHCl_3$) for a sample of 17% ee. Other physical data were identical with those of (+)-**13b**.

(*S*)-Diethyl hydroxy(4-methoxyphenyl)methylphosphonate (*S*)-(−)-13c. Mp 120–121 °C; $[\alpha]_D^{20}$ −31.1 (*c* 1.0 in $CHCl_3$) for a sample of 82% ee. Other physical data were identical with those of (+)-**13c**.

(*S*)-Diethyl hydroxy(4-methylphenyl)methylphosphonate (*S*)-(−)-13d. Mp 93–94 °C (Found: C, 55.82; H, 7.43. $C_{12}H_{19}O_4P$ requires C, 55.81; H, 7.42%); $[\alpha]_D^{20}$ −20.0 (*c* 1.0 in $CHCl_3$) for a sample of 58% ee; ν_{max}(KBr)/cm^{-1} 3261 (OH) and 1232 (phosphoryl); δ_H(400 MHz; $CDCl_3$) 7.37 (2 H, d with small splits, *J* 8.0, Ph), 7.17 (2 H, d, *J* 8.0, Ph), 4.97 (1 H, d, *J* 10.5, PhC*H*), 4.10–3.92 (4 H, m, OCH_2CH_3), 2.34 (3 H, d, *J* 1.8, Me), 1.27 (3 H, t, *J* 7.1, OCH_2CH_3) and 1.22 (3 H, t, *J* 7.1, OCH_2CH_3); δ_P(160 MHz; $CDCl_3$) 21.32; δ_C(100 MHz; $CDCl_3$) 137.9 (s, Ph), 133.4 (s, Ph), 129.0 (s, Ph), 127.0 (2 C, s, Ph), 70.8 (d, $^1J_{PC}$ 158.9, PhCH), 63.2 (d, $^2J_{PC}$ 7.3, OCH_2CH_3), 63.0 (d, $^2J_{PC}$ 7.4, OCH_2CH_3), 21.2 (s, Me), 16.40 (d, $^3J_{PC}$ 5.7, OCH_2CH_3) and 16.35 (d, $^3J_{PC}$ 4.7, OCH_2CH_3); *m/z* 258 (M^+).

(*S*)-Diethyl hydroxy(2-furyl)methylphosphonate (*S*)-(−)-16a. Oil (Found: M^+, 234.0635. $C_9H_{15}O_5P$ requires *M*, 234.0657); $[\alpha]_D^{20}$ −4.2 (*c* 1.0 in $CHCl_3$) for a sample of 18% ee; ν_{max}(film)/cm^{-1} 3274 (OH) and 1227 (phosphoryl); δ_H(400 MHz; $CDCl_3$) 7.42 (1 H, m, furan), 6.52–6.50 (1 H, m, furan), 6.38–6.37 (1 H, m, furan), 5.00 (1 H, d, *J* 13.4, C*H*P), 4.30–4.00 (4 H, m, OCH_2CH_3), 1.32 (3 H, t, *J* 7.1, OCH_2CH_3) and 1.24 (3 H, t, *J* 7.1, OCH_2CH_3); δ_P(160 MHz; $CDCl_3$) 19.30; δ_C(100 MHz; $CDCl_3$) 150.0 (s, furan), 142.8 (s, furan), 110.7 (s, furan), 109.3 (d, $^3J_{PC}$ 5.9, furan), 64.7 (d, $^1J_{PC}$ 165.5, CHP), 63.5 (d, $^2J_{PC}$ 6.9, OCH_2CH_3), 63.3 (d, $^2J_{PC}$ 7.0, OCH_2CH_3), 16.4 (d, $^3J_{PC}$ 6.8, OCH_2CH_3) and 16.3 (d, $^3J_{PC}$ 6.6, OCH_2CH_3); *m/z* 234 (M^+).

(*S*)-Diethyl hydroxy(5-methyl-2-furyl)methylphosphonate (*S*)-(−)-16b. Oil (Found: M^+, 248.0813. $C_{10}H_{17}O_5P$ requires *M*, 248.0814); $[\alpha]_D^{20}$ −5.5 (*c* 1.1 in $CHCl_3$) for a sample of 44% ee; ν_{max}(film)/cm^{-1} 3294 (OH) and 1223 (phosphoryl); δ_H(400 MHz; $CDCl_3$) 6.39–6.38 (1 H, m, furan), 5.95–5.94 (1 H, m, furan), 4.92 (1 H, dd, *J* 6.6, 13.3, C*H*P), 4.21–4.01 (4 H, m, OCH_2CH_3), 2.28 (3 H, s, Me), 1.32 (3 H, t, *J* 7.1, OCH_2CH_3) and 1.25 (3 H, t, *J* 7.1, OCH_2CH_3); δ_P(160 MHz; $CDCl_3$) 19.28; δ_C(100 MHz; $CDCl_3$) 152.7 (s, furan), 148.0 (s, furan), 110.4 (d, $^3J_{PC}$ 6.0, furan), 106.7 (s, furan), 64.7 (d, $^1J_{PC}$ 166.3, CHP), 63.3 (d, $^2J_{PC}$ 7.0, OCH_2CH_3), 63.2 (d, $^2J_{PC}$ 7.2, OCH_2CH_3), 16.4 (d, $^3J_{PC}$ 6.0, OCH_2CH_3), 16.3 (d, $^3J_{PC}$ 6.1, OCH_2CH_3) and 13.5 (s, Me); *m/z* 248 (M^+).

(*S*)-Diethyl hydroxy(2-thienyl)methylphosphonate (*S*)-(−)-16c. Mp 32–34 °C (Found: C, 43.31; H, 5.90. $C_9H_{15}O_4PS$ requires C, 43.19; H, 6.04%); $[\alpha]_D^{20}$ −9.3 (*c* 1.0 in $CHCl_3$) for a sample of 41% ee; ν_{max}(film)/cm^{-1} 3271 (OH) and 1237 (phosphoryl); δ_H(400 MHz; $CDCl_3$) 7.31–7.30 (1 H, m, thiophene), 7.20–7.18 (1 H, m, thiophene), 7.01–6.99 (1 H, m, thiophene), 5.23 (1 H, d, *J* 11.0, C*H*P), 4.20–4.01 (4 H, m, OCH_2CH_3), 1.31 (3 H, t, *J* 7.1, OCH_2CH_3) and 1.26 (3 H, t, *J* 7.1, OCH_2CH_3); δ_P(160 MHz; $CDCl_3$) 19.38; δ_C(100 MHz; $CDCl_3$) 126.8 (s, thiophene), 126.23 (s, thiophene), 126.16 (s, thiophene), 125.8 (s, thiophene), 67.1 (d, $^1J_{PC}$ 165.6, CHP), 63.6 (d, $^2J_{PC}$ 6.9,

OCH_2CH_3), 63.3 (d, $^2J_{PC}$ 7.3, OCH_2CH_3), 16.4 (s, OCH_2CH_3) and 16.3 (s, OCH_2CH_3); *m/z* 250 (M^+).

(*S*)-Diethyl hydroxy(5-methyl-2-thienyl)methylphosphonate (*S*)-(−)-16d. Mp 69–70 °C (Found: C, 45.52; H, 6.48. $C_{10}H_{17}O_4PS$ requires C, 45.44; H, 6.48%); $[\alpha]_D^{20}$ −3.8 (*c* 1.0 in $CHCl_3$) for a sample of 73% ee; ν_{max}(KBr)/cm^{-1} 3239 (OH) and 1236 (phosphoryl); δ_H(400 MHz; $CDCl_3$) 6.97–6.96 (1 H, m, thiophene), 6.64–6.63 (1 H, m, thiophene), 5.11 (1 H, dd, *J* 5.8, 10.9, C*H*P) 4.18–4.02 (4 H, m, OCH_2CH_3), 2.46 (3 H, s, Me), 1.31 (3 H, t, *J* 7.1, OCH_2CH_3) and 1.27 (3 H, t, *J* 7.1, OCH_2CH_3); δ_P(160 MHz; $CDCl_3$) 19.63; δ_C(100 MHz; $CDCl_3$) 140.7 (s, thiophene), 136.6 (s, thiophene), 126.5 (d, $^3J_{PC}$ 7.7, thiophene), 124.9 (s, thiophene), 67.1 (d, $^1J_{PC}$ 166.6, *C*HP), 63.5 (d, $^2J_{PC}$ 6.5, OCH_2CH_3), 63.3 (d, $^2J_{PC}$ 7.2, OCH_2CH_3), 16.4 (2 C, s, OCH_2CH_3) and 15.3 (s, Me); *m/z* 264 (M^+).

(*S*)-Diethyl hydroxy(3-furyl)methylphosphonate (*S*)-(−)-16e. Oil (Found: M^+, 234.0631. $C_9H_{15}O_5P$ requires *M*, 234.0657); $[\alpha]_D^{20}$ −11.7 (*c* 1.1 in $CHCl_3$) for a sample of 64% ee; ν_{max}(film)/cm^{-1} 3283 (OH) and 1229 (phosphoryl); δ_H(400 MHz; $CDCl_3$) 7.54–7.53 (1 H, m, furan), 7.38 (1 H, s, furan), 6.54 (1 H, m, furan), 4.93 (1 H, d, 10.3, C*H*P), 4.18–4.01 (4 H, m, OCH_2CH_3), 1.30 (3 H, t, *J* 7.1, OCH_2CH_3) and 1.26 (3 H, t, *J* 7.1, OCH_2CH_3); δ_P(160 MHz; $CDCl_3$) 21.21; δ_C(100 MHz; $CDCl_3$) 143.1 (s, furan), 140.7 (d, $^3J_{PC}$ 10.0, furan), 121.6 (s, furan), 109.7 (d, $^3J_{PC}$ 3.6, furan), 63.8 (d, $^1J_{PC}$ 166.1, *C*HP), 63.3 (d, $^2J_{PC}$ 6.9, OCH_2CH_3), 63.1 (d, $^2J_{PC}$ 7.5, OCH_2CH_3), 16.4 (d, $^3J_{PC}$ 4.7, OCH_2CH_3) and 16.3 (d, $^3J_{PC}$ 4.2, OCH_2CH_3); *m/z* 234 (M^+).

(*S*)-Diethyl hydroxy(3-thienyl)methylphosphonate (*S*)-(−)-16f. Oil (Found: M^+, 250.0439. $C_9H_{15}O_4PS$ requires *M*, 250.0429); $[\alpha]_D^{20}$ −13.4 (*c* 1.0 in $CHCl_3$) for a sample of 67% ee; ν_{max}(film)/cm^{-1} 3282 (OH) and 1236 (phosphoryl); δ_H(400 MHz; $CDCl_3$) 7.42–7.40 (1 H, m, thiophene), 7.31–7.29 (1 H, m, thiophene), 7.21–7.20 (1 H, m, thiophene), 5.09 (1 H, d, *J* 10.6, *C*HP) 4.15–3.93 (4 H, m, OCH_2CH_3), 1.28 (3 H, t, *J* 7.1, OCH_2CH_3) and 1.23 (3 H, t, *J* 7.1, OCH_2CH_3); δ_P(160 MHz; $CDCl_3$) 20.69; δ_C(100 MHz; $CDCl_3$) 137.5 (s, thiophene), 126.7 (d, $^3J_{PC}$ 3.4, thiophene), 125.7 (s, thiophene), 122.9 (d, $^3J_{PC}$ 8.9, thiophene), 67.5 (d, $^1J_{PC}$ 161.9, *C*HP), 63.2 (d, $^2J_{PC}$ 6.9, OCH_2CH_3), 63.1 (d, $^2J_{PC}$ 7.3, OCH_2CH_3), 16.4 (d, $^3J_{PC}$ 5.6, OCH_2CH_3) and 16.3 (d, $^3J_{PC}$ 5.0, OCH_2CH_3); *m/z* 250 (M^+).

Diethyl 1-hydroxy-2-methylpropylphosphonate 17. Oil (Found: M^+, 210.1044. $C_8H_{19}O_4P$ requires *M*, 210.1021); ν_{max}(film)/cm^{-1} 3308 (OH) and 1216 (phosphoryl); δ_H(400 MHz; $CDCl_3$) 4.19–4.11 (4 H, m, OCH_2CH_3), 3.62 (1 H, dd, *J* 6.1, 6.1, C*H*P), 2.10–2.02 [1 H, m, $(CH_3)_2CH$], 1.32 (6 H, t, *J* 7.0, OCH_2CH_3), 1.05 [3 H, d, *J* 6.8, $(CH_3)_2CH$] and 1.04 [3 H, d, *J* 6.8, $(CH_3)_2CH$]; δ_P(160 MHz, $CDCl_3$) 24.92; δ_C(100 MHz; $CDCl_3$) 73.0 (d, $^1J_{PC}$ 156.7, *C*HP), 62.3 (2 C, d, $^2J_{PC}$ 7.0, OCH_2CH_3), 30.2 [s, $(CH_3)_2CH$], 19.8 [d, $^3J_{PC}$ 9.7, $(CH_3)_2CH$], 17.7 [d, $^3J_{PC}$ 7.6, $(CH_3)_2CH$], 16.4 (2 C, d, $^3J_{PC}$ 5.8, OCH_2CH_3); *m/z* 211 ($M^+ + 1$) and 210.

Pudovik reaction catalysed by LSB, EuLB or SmLB

The reactions with LSB, EuLB and SmLB were carried out in an identical fashion to that described for the LLB-catalysed reaction, except for the use of a THF solution of LSB, EuLB or SmLB prepared as follows.

THF solution of LSB. Prepared by the same method as for the preparation of LLB[14d] from $LaCl_3 \cdot 7H_2O$ (1.86 g, 5.0 mmol), disodium (*R*)-binaphthoxide [NaH in 60% mineral oil (400 mg, 10 mmol) and (*R*)-binaphthol (1.43 g, 5 mmol)], $NaOBu^t$ (496 mg, 5.0 mmol) and water (3.6×10^{-1} cm^3, 20 mmol) in THF (100 cm^3).

THF solution of EuLB. Prepared from $EuCl_3$ (1.29 g, 5.0 mmol), dilithium (*R*)-binaphthoxide (10 mmol), $NaOBu^t$ (496 mg, 5.0 mmol) and water (9.0×10^{-1} cm^3, 50 mmol) in THF (100 cm^3) according to the method of Shibasaki.[14c]

THF solution of SmLB. Prepared from $SmCl_3 \cdot 6H_2O$ (1.82 g, 5.0 mmol), dilithium (*R*)-binaphthoxide (10 mmol), $NaOBu^t$ (496 mg, 5.0 mmol) and water (3.6×10^{-1} cm^3, 20 mmol) in THF (100 cm^3) according to the method of Shibasaki.[14c]

General procedure for preparation of (*R*)-MTPA esters of (−)-13a–d and (−)-16a–f

To a stirred solution of (2*R*)-2-methoxy-2-phenyl-3,3,3-trifluoropropanoic acid [(*R*)-MTPA] (91.5 mg, 0.36 mmol), *N*,*N*-dicyclohexylcarbodiimide (DCC) (74.2 mg, 0.36 mmol) and 4-dimethylaminopyridine (DMAP) (4.4 mg, 0.036 mmol) in CH_2Cl_2 (1 cm^3) was added a solution of (−)-**13a–d** or (−)-**16a–f** (0.18 mmol) in CH_2Cl_2 (2 cm^3) at 0 °C.[21] The mixture was stirred at the same temperature for 30 min and then kept at room temperature until the starting material had disappeared as evidenced by TLC (3–24 h). The reaction was quenched by the addition of dilute hydrochloric acid (6 cm^3) to the mixture at 0 °C after which it was extracted with $CHCl_3$. The extracts were washed successively with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was diluted with diethyl ether and the resulting suspension was passed through silica gel (0.5 g). The filtrate was evaporated to leave (*R*)-MTPA esters of (−)-**13a–d** and (−)-**16a–f**, which were analysed by NMR spectroscopy without purification. ^{31}P NMR data of these samples are listed in Table 5.

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