Catalytic enantioselective addition of methyltriisopropoxitanium to aldehydes

M. Veguillas,[a] R. Solà,[a] M. Ángeles Fernández-Ibañez*[b] and B. Maciá*[a]

[a] Division of Chemistry & Environmental Science, Manchester Metropolitan University, Oxford Road, M1 5GD, Manchester, UK. E-mail: b.macia-ruiz@mmu.ac.uk

[b] Van 't Hoff Institute for Molecular Sciences. Science Park 904, 1090 GS, Amsterdam. E-mail: M.A.FernandezIbanez@uva.nl

Keywords: organotitanium • Ar-BINMOL • aldehydes • enantioselective catalysis • methyl carbinol

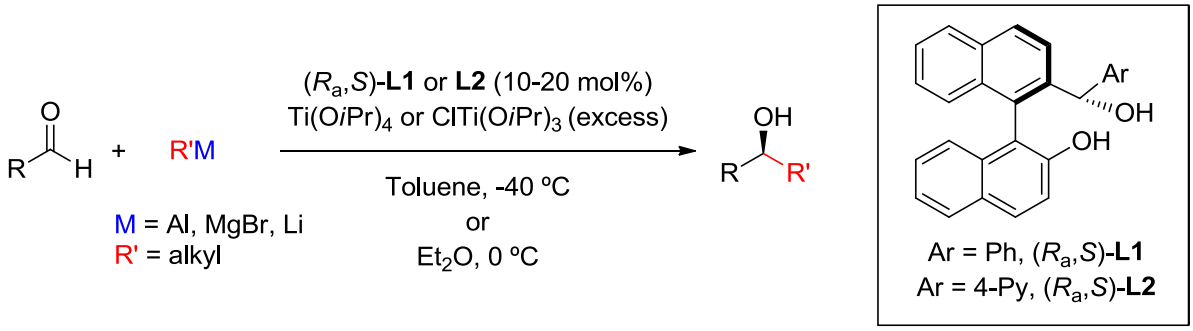
ABSTRACT

An efficient catalyst for the enantioselective synthesis of chiral methyl carbinols from aldehydes is presented. The system uses methyltriisopropoxititanium as nucleophile and a readily available binapthyl derivative as chiral ligand. The enantioselective methylation of both aromatic and aliphatic aldehydes proceeds with good yields and high enantioselectivities under mild conditions.

Introduction

The enantioselective synthesis of the chiral methyl carbinol moiety, present in a large number of natural products and biologically active compounds,[1] is of great importance to both academia and industry. The asymmetric addition of a nucleophilic methyl group to an aldehyde is one of the most efficient and direct approaches to this structural fragment.[2] Enantioselective catalyzed versions of this key transformation have been studied extensively with dimethylzinc[3,4] trimethylaluminium[5] and, more recently, with the more reactive methyllithium[6] and methyl Grignard reagents.[7,8] Many of these methodologies involve the use of $Ti(OR)_4$,[4-8] normally in excess, which generates a titanium-based active species bearing a chiral ligand which is ultimately responsible for the stereocontrol in the addition process. It has also been suggested that these reactions involve the addition of organotitanium species, which are generated *in situ* by transmetallation of the organometallic reagent with $Ti(OR)_4$.[9] The direct asymmetric addition of organotitanium reagents to carbonyls[10] has also been described under catalytic conditions[9a,11] using TADDOL,[9a,11a,b] H_8-BINOL[11e] (for alkyltitanium reagents) or BINOL (for aryltitanium reagents)[11c] derivatives as chiral ligands, in the presence of $Ti(OiPr)_4$. In the particular case of $Me(OiPr)_3$, the only catalytic methodologies reported to date require the use of chiral TADDOL ligands[9a,11a,b] at 20 mol% loading and low temperatures of −70 °C in order to obtain good enantioselectivities.

We have recently developed an efficient catalytic system for the enantioselective addition of organolithium,[6b,c] organomagnesium[7a,c,j] and organoaluminum[5c] reagents to aldehydes,[12] based on the use of Lai's and Xu's 1,1-binaphthalene-2-α-arylmethan-2-ols (Ar-BINMOLs)[7b,13] chiral ligands (Scheme 1). High enantioselectivities (up to 99%) are obtained when the reaction is performed in the presence of an excess of titanium tetraisopropoxide,[14] avoiding salt exclusion procedures[9a] and chelating additives.[7f,g] From these results, we envisioned that organotitanium reagents would also be suitable nucleophiles for use with this class of chiral ligand. Herein, we describe the results from the enantioselective addition of commercially available $Me(OiPr)_3$ to aldehydes, generating versatile methyl carbinol units in high enantioselectivities under mild conditions. No $Ti(OiPr)_4$ is needed and higher, more practical temperatures can be used in contrast to systems using TADDOL ligands.

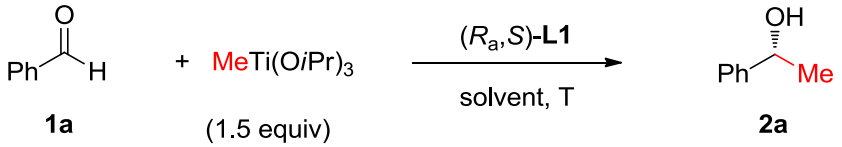


Scheme 1. Previous work on the catalytic enantioselective addition of organolithium, Grignard and organoaluminium reagents to aldehydes using Ar-BINMOL ligands.

Results and Discussion

The process optimization was carried out using benzaldehyde (**1a**) as the model substrate. Our first tests provided very promising results (Table 1). Using 20 mol% of **L1**, the addition of 1.5 equiv of MeTi(O*i*Pr)$_3$ to **1a** in toluene at –40 °C (optimal solvent and temperature for the addition of Grignard reagents to aldehydes using **L1** as ligand)[7c] provided 78% conversion and 94% ee after 1 h (entry 1). In the search for alternative reaction conditions that involve more practical temperatures, we found out that the use of Et_2O as solvent, allowed full conversion and increased enantioselectivity 97% (entry 2) at 0 °C. Under these conditions, the catalyst loading could be reduced to 10 mol% without any significant loss of conversion or enantioselectivity (entry 3). Lower catalyst loadings (5 mol%, entry 4) provided full conversion but lower *ee* (78%). In the presence of 10 mol% of **L1**, the reaction could be carried out at room temperature (entry 5) and only an small decrease in enantioselectivity was observed (compare entries 3 and 5). As a means of comparison, we performed the addition of MeTi(O*i*Pr)$_3$ to benzaldehyde (**1a**) in Et_2O at 0 °C using (*R*)-BINOL as chiral ligand (entry 6); very low conversion (11%) and enantioselectivity (24%) were obtained.

Table 1. Influence of catalyst loading, temperature and solvent[a]



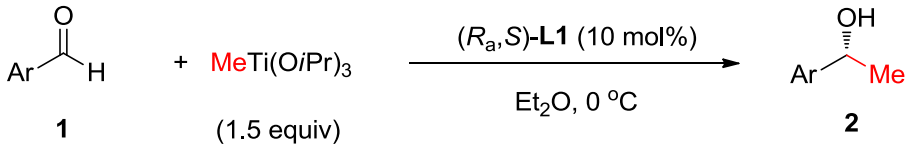
Entry	Solvent	T (°C)	**L1** (mol%)	Conv. (%)[b]	*ee* (%)[b]
1	Toluene	–40	20	78	94
2	Et_2O	0	20	>99	97
3	**Et_2O**	**0**	**10**	**99**	**96**
4	Et_2O	0	5	99	78
5	Et_2O	RT	10	>99	94
6	Et_2O	0	10[c]	11	24

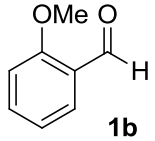
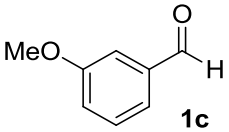
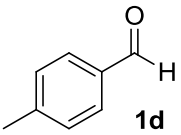
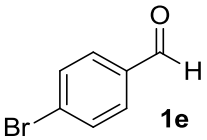
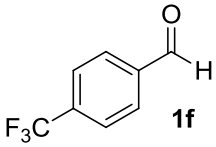
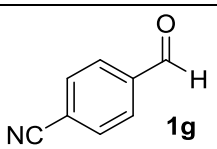
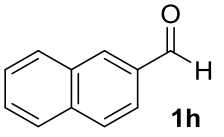
[a] Reaction conditions: **1a** (1 equiv, 0.07 M), MeTi(O*i*Pr)$_3$ (1 M in THF, 1.5 equiv), (*R*$_a$,*S*)-**L1**, 1.5 h. [b] Determined by chiral GC. [c] (*R*)-BINOL was used as ligand.

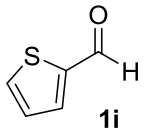
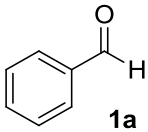
Under the optimized conditions, the scope of the addition of MeTi(O*i*Pr)$_3$ was examined with different aldehydes (Table 2), proving the system as remarkably efficient. Thus, methyl carbinol units were prepare in good yields (84-96%) and enantioselectivities (56->99%, entries 1-13) from a variety of (hetero)aromatic substrates containing both electron-donating and -withdrawing substituents. In some cases, the charge of MeTi(O*i*Pr)$_3$ was increased up to 1.7 equiv. (entries 2, 4, 5 and 9) or 2.0

equiv. (entries 10 and 12), to allow the reaction to reach full conversion. A small increase in enantioselectivity was also observed upon the increased charge of MeTi(O*i*Pr)$_3$ (compare entries 1-2, 9-10 and 11-12). The lower enantioselectivity obtained for *o*-methoxybenzaldehyde (56%, entry 2) might be ascribed to higher steric hindrance around the reactive site. The tolerance of this methodology towards functionalized substrates such as **1e** and **1g** should be emphasized (entries 6 and 8). Remarkably, all reactions were complete in less than 1.5 h without any byproduct formation. Moreover, the unreacted starting material and ligand could be recovered, and the latter, recycled and reused without any loss of activity. The robustness of the method was tested by performing a larger scale reaction with benzaldehyde (**1a**, 47 mmol, 0.5 g, entry 13); no erosion of conversion or enantioselectivity was observed compared to the small scale reaction (compare entry 3, Table 1 with entry 13, Table 2).

Table 2. Enantioselective addition of MeTi(O*i*Pr)$_3$ to aromatic aldehydes: scope of the reaction[a]



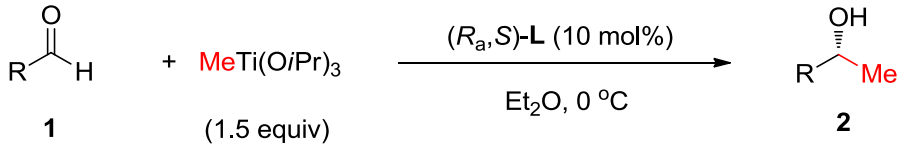
Entry	ArCHO	Conv. (%)[b]	Yield (%)[c]	ee (%)[b]
1	 **1b**	90	n.d.	55
2[d]		>99	96	56
3	 **1c**	82	n.d.	>99
4[d]		99	92	>99
5[d]	 **1d**	99	96	93
6	 **1e**	97	90	97
7	 **1f**	99	89	95
8	 **1g**	97	94	96
9[d]	 **1h**	58	n.d.	86
10[e]		89	84	87

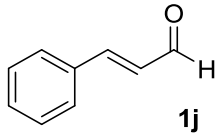
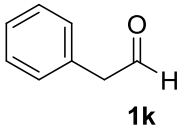
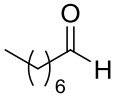
11	 **1i**	67	n.d.	90
12[e]		98	95	94
13[f]	 **1a**	97	95	95

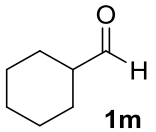
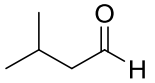
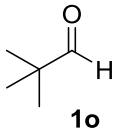
[a] Reaction conditions: **1** (1 equiv, 0.07 M), MeTi(O*i*Pr)$_3$ (1 M in THF, 1.5 equiv), (R_a,*S*)-**L1** (10 mol%), 1.5 h. [b] Determined by chiral GC or HPLC. [c] Isolated yield after flash chromatography. [d] Reaction performed with 1.7 equiv of MeTi(O*i*Pr)$_3$. [e] Reaction performed with 2.0 equiv of MeTi(O*i*Pr)$_3$. [f] Reaction performed using 0.5 g of **1a**.

Next, we examined the substrate generality for aliphatic and α,β-unsaturated aldehydes (Table 3). Ligand **L1** provided moderate conversion and enantioselectivity in the addition of MeTi(O*i*Pr)$_3$ to cinnamic aldehyde (**1j**), even when 1.7 equiv. of nucleophile were employed (entry 1). The use of **L2**, which had shown higher efficiency in the addition of organolithium reagents to aliphatic and α,β-unsaturated aldehydes,[7a] allowed a slight improvement in the results (entry 2). **L2** also proved to be more effective than **L1** when the aliphatic phenylaldehyde (**1k**) was employed as substrate (compare entries 3,4). In general, the addition of MeTi(O*i*Pr)$_3$ to linear-**1l**, and α- branched **1m** proceeds with high enantioselectivities (90 and 94% ee, respectively, entries 5-6) and full conversion in the presence of 10 mol% of **L2** as chiral ligand. Only the β-branched substrate **1n** provided high enantioselectivity, but moderate conversion (entry 7). For the bulkier pivaldehyde (**1o**), high enantioselectivity and very low conversion (94% ee, 20% conv, entry 8), were obtained. Gratifyingly, the lack of reactivity of pivaldehyde (**1o**) could be rectified by using **L1** as a ligand and 2 equiv of MeTi(O*i*Pr)$_3$ (entry 9).

Table 3. Enantioselective addition of MeTi(O*i*Pr)$_3$ to aliphatic and α,β-unsaturated aldehydes: scope of the reaction[a]



Entry	ArCHO	L	Conv. (%)[b]	Yield (%)[c]	ee (%)[b]
1[d]	 **1j**	**L1**	65	n.d.	80
2		**L2**	90	88	82
3	 **1k**	**L1**	99	n.d.	81
4		**L2**	99	93	85
5	 **1l**	**L2**	99	95	90[e]

6	 1m	**L2**	99	n.d.[f]	94[e]
7	 1n	**L2**	77[g]	n.d.[f]	90[e]
8[d]	 1o	**L2**	20	n.d.	94
9[h]		**L1**	78	n.d.	93

[a] Reaction conditions: **1** (1 equiv, 0.07 M), MeTi(O*i*Pr)$_3$ (0.5 M in THF, 1.5 equiv), (R_a,*S*)-**L** (10 mol%), 1 h. [b] Determined by chiral GC or HPLC. [c] Isolated yield after flash chromatography. [d] Reaction performed with 1.7 equiv of MeTi(O*i*Pr)$_3$. [e] Determined by chiral GC on the acetate derivative. [f] Volatile compound. Not isolated. [g] 7% of $(CH_3)_2CHCH_2CH_2OH$ was detected. [h] Reaction performed with 2.0 equiv of MeTi(O*i*Pr)$_3$.

Conclusions

In conclusion, we have developed an efficient catalytic system for the enantioselective addition of methyltriisopropoxititanium to aldehydes. This methodology allows fast and operationally-simple one-pot preparation of highly valuable, optically active methyl carbinols using readily available reagents. In comparison to the existing TADDOL-based procedures, a number of benefits are realised, such as higher, more industrially relevant temperatures, shorter reaction times and no requirement for Ti(O*i*Pr)$_4$ in the reaction media.

Experimental

General: See Supporting Information.

General procedure for the addition of methyltriisopropoxitanium to aldehydes– *General Procedure A.* To a stirred solution of **L1** or **L2** (0.20 equiv.) in Et_2O (3.0 mL, 0.067 M) at 0 ºC, MeTi(*i*-OPr)$_3$ (0.3 mL, 1.5 equiv. 0.5 M in THF, unless stated otherwise) was added. The solution was stirred for 1 min and then the aldehyde (0.1 mmol) was added. The reaction was stirred for 10 min and then quenched with water. The layers were separated and the aqueous layer was extracted three times with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The reaction crude was purified by flash silica gel chromatography.

(*R*)-1-Phenylethanol (2a):[15]
Following the general procedure A, the reaction of benzaldehyde (20 µL, 0.2 mmol) with methyltriisopropoxytitanium (0.3 mL, 1.5 equiv., 1.0 M in THF) in the presence of and (R_a,*S*)-Ph-BINMOL **L1** (7.5 mg, 0.1 equiv.) in Et_2O (3.0 mL) provided (*R*)-1-phenylethanol (23.4 mg) as a colorless oil after column chromatography (Hex/EtOAc 6:1). **Yield:** 96%. ***Ee*:** 96%. $[\alpha]_D^{24}$ = +47 (*c* 0.7, $CHCl_3$) {Lit. $[\alpha]_D^{26}$ = +97 (*c* 0.3, $CHCl_3$) for 95% *ee*}. *Ee* determination by chiral **GC** analysis, Cyclosil β column, T = 100 °C, P = 15.9 psi, retention times: t_r(*R*) = 30.9 min (major enantiomer), t_r(*S*) = 34.8 min.

(*R*)-1-(2-Methoxyphenyl)ethanol (2b):[15]

Following the general procedure A, the reaction of 2-methoxybenzaldehyde (27 mg, 0.2 mmol) with methyltriisopropoxytitanium (0.34 mL, 1.7 equiv., 1.0 M in THF) in the presence of (R_a,*S*)-Ph-BINMOL **L1** (7.5 mg, 0.1 equiv.) in Et_2O (3.0 mL) provided (*R*)-1-(2-methoxyphenyl)ethanol (29 mg) as a colorless oil after column chromatography (Hex/EtOAc 7:1). **Yield:** 95%. ***Ee*:** 56%. $[\alpha]_D^{24}$ = +33 (*c* 0.3, $CHCl_3$) {Lit. $[\alpha]_D^{26}$ = +24 (*c* 1.0, $CHCl_3$) for 99% *ee*}. *Ee* determination by chiral **GC** analysis, Cyclosil β column, T = 150 °C, P = 15.9 psi, retention times: t_r(*R*) = 9.1 min, t_r(*S*) = 10.4 min (major enantiomer).

(*R*)-1-(3-Methoxyphenyl)ethanol (2c):[16]
Following the general procedure A, the reaction of 3-methoxybenzaldehyde (24 µL, 0.2 mmol) with methyltriisopropoxytitanium (0.3 mL, 1.5 equiv., 1.0 M in THF) in the presence of (R_a,*S*)-Ph-BINMOL **L1** (7.5 mg, 0.1 equiv.) in Et_2O (3.0 mL) provided (*R*)-1-(4-methoxyphenyl)ethanol (28 mg) as a colorless oil after column chromatography (Hex/EtOAc 7:1). **Yield:** 92%. ***Ee*:** 99.5%. $[\alpha]_D^{24}$ = +28 (*c* 1.0, $CHCl_3$) {Lit. $[\alpha]_D^{20}$ = +51.2 (*c* 1.0, $CHCl_3$) for 96% *ee*}. *Ee* determination by chiral **GC** analysis, CP-Chirasil-DEX CB column, T = 125 °C, P = 6 psi, retention times: t_r(*R*) = 45.1 min (major enantiomer), t_r(*S*) = 49.4 min.

(*R*)-1-(*4*-Methylphenyl)ethanol (2d):[17]
Following the general procedure A, the reaction of 4-tolualdehyde (12.0 µL, 0.1 mmol) with methyltriisopropoxytitanium (0.15 mL, 1.5 equiv., 1.0 M in THF) in the presence of (R_a,*S*)-Ph-BINMOL **L1** (3.8 mg, 0.1 equiv.) in Et_2O (1.5 mL) provided (*R*)-1-(*4*-methylphenyl)ethanol (13 mg) as a colourless oil after column chromatography (eluent Hex/EtOAc 9:1). **Yield:** 96%. ***Ee*:** 93%. $[\alpha]_D^{25}$ = +39.4 (*c* 0.7, $CHCl_3$) {Lit. $[\alpha]_D^{26}$ = +56 (*c* 1.0, $CHCl_3$) for 96% *ee*}. *Ee* determination by chiral **GC** analysis, CP Chirasil-DEX CB column, T = 130 °C, P = 6 psi, retention times: t_r(*R*) = 14.7 min (major enantiomer), t_r(*S*) = 16.4 min.

(*R*)-1-(4-Bromophenyl)ethanol (2e):[15]
Following the general procedure A, the reaction of 4-bromobenzaldehyde (37 mg, 0.2 mmol) with methyltriisopropoxytitanium (0.3 mL, 1.5 equiv., 1.0 M in THF) in the presence of (R_a,*S*)-Ph-BINMOL **L1** (7.5 mg, 0.1 equiv.) in Et_2O (3.0 mL) provided (*R*)-1-(4-bromophenyl)ethanol (18 mg) as a white solid after column chromatography (Hex/EtOAc 6:1). **Yield:** 90%. ***Ee*:** 97%. $[\alpha]_D^{25}$ = +28 (*c* 0.4, $CHCl_3$) {Lit. $[\alpha]_D^{20}$ = +34.6 (*c* 1.7, $CHCl_3$) for 94% *ee*}. *Ee* determination by chiral **GC** analysis, CP-Chirasil-DEX CB column, 140 °C, P = 6 psi, retention times: t_r(*R*) = 34.3 min (major enantiomer), t_r(*S*) = 39.3 min.

(*R*)-1-[*4*-(Trifluoromethyl)phenyl]ethanol (2f):[18]
Following the general procedure A, the reaction of 4-(trifluoromethyl)benzaldehyde (14 µL, 0.1 mmol) with methyltriisopropoxytitanium (0.15 mL, 1.5 equiv., 1.0 M in THF) in the presence of (R_a,*S*)-Ph-BINMOL **L1** (3.8 mg, 0.1 equiv.) in Et_2O (1.5 mL) provided (*R*)-1-[4-(trifluoromethyl)phenyl]ethanol (17 mg) as a yellow oil after column chromatography (Hex/EtOAc 9:1). **Yield:** 89%. ***Ee*:** 95%. $[\alpha]_D^{25}$ = +28.9 (*c 0.9*, $CHCl_3$) {Lit. $[\alpha]_D^{20}$ = +35.3 (*c 1.6*, $CHCl_3$) for 99% *ee*}. *Ee* determination by chiral **GC** analysis, CP Chirasil-DEX CB column, T = 140 °C, P = 6 psi, retention times: t_r(*R*) = 10.9 min (major enantiomer), t_r(*S*) = 12.5 min.

(*R*)-4-(1-Hydroxyethyl)benzonitrile (2g):[19]
Following the general procedure A, the reaction of 4-formylbenzonitrile (13 mg, 0.1 mmol) with methyltriisopropoxytitanium (0.15 mL, 1.5 equiv., 1.0 M in THF) in the presence of (R_a,*S*)-Ph-BINMOL **L1** (3.8 mg, 0.1 equiv.) in Et_2O (1.5 mL) provided (*R*)-4-(1-hydroxyethyl)benzonitrile (17 mg) as a yellow oil after column chromatography (Hex/EtOAc 8:2). **Yield:** 94%. ***Ee*:** 96%. $[\alpha]_D^{25}$ = +35.3 (*c 0.9*, $CHCl_3$) {Lit. $[\alpha]_D^{25}$ = +43.1 (*c 1.02*, $CHCl_3$) for 96% *ee*}. *Ee* determination by chiral **GC** analysis, CP Chirasil-DEX CB column, T = 170 °C, P = 6 psi, retention times: t_r(*R*) = 18.8 min (major enantiomer), t_r(*S*) = 21.0 min.

(*R*)-1-(Naphthalen-2-yl)ethanol (2h):[15]

Following the general procedure A, the reaction of naphthaldehyde (31.2 mg, 0.2 mmol) with methyltriisopropoxytitanium (0.4 mL, 2.0 equiv., 1.0 M in THF) in the presence of (R_a,*S*)-Ph-BINMOL **L1** (7.5 mg, 0.1 equiv.) in Et_2O (3.0 mL) provided (*R*)-1-(naphthalen-2-yl)ethanol (29.1 mg) as a white solid after column chromat0ography (eluent Hex/EtOAc 8:1). **Yield:** 92%. ***Ee*:** 84%. $[\alpha]_D^{24}$ = +31 (*c* 0.4, $CHCl_3$) {Lit. $[\alpha]_D^{28}$ = +30 (*c* 0.97, $CHCl_3$) for 87% *ee*. *Ee* determination by chiral **HPLC** analysis, Lux 5u Cellulose 3 column, Hex/*i*-PrOH 97:3 flow = 1 mL/min, retention times: t_r(*R*) = 29.7 min, t_r(*S*) = 38.7 min (major enantiomer).

(*R*)-1-(Thiophen-2-yl)ethanol (2i):[15]
Following the general procedure A, the reaction of thiophene-2-carbaldehyde (9.4 µL, 0.1 mmol) with methyltriisopropoxytitanium (0.4 mL, 2.0 equiv., 1.0 M in THF) in the presence of (R_a,*S*)-Ph-BINMOL **L1** (7.5 mg, 0.1 equiv.) in Et_2O (3.0 mL) provided (*R*)-1-(thiophen-2-yl)ethanol (24.3 mg) as a volatile colorless oil after column chromatography (Hex/EtOAc 6:1). **Yield:** 95%. ***Ee*:** 94%. $[\alpha]_D^{24}$ = +12.5 (*c* 0.8, $CHCl_3$) {Lit. $[\alpha]_D^{25}$ = +20 (*c* 1.04, $CHCl_3$) for 96% *ee*}. *Ee* determination by chiral **GC** analysis, CP-Chirasil-DEX CB column, T = 125 °C, P = 6 psi, retention times: t_r(*R*) = 14.5 min (major enantiomer), t_r(*S*) = 15.9 min.

(*R*,*E*)-4-Phenylbut-3-en-2-ol (2j):[20]
Following the general procedure A, the reaction of *trans*-cinnamaldehyde (25.2 µL, 0.2 mmol) with methyltriisopropoxytitanium (0.3 mL, 1.5 equiv., 1.0 M in THF) in the presence of (R_a,*S*)-Py-BINMOL **L2** (7.5 mg, 0.1 equiv.) in Et_2O (3.0 mL) provided (*R*,*E*)-4-phenylbut-3-en-2-ol (26 mg) as a white solid after column chromatography (Hex/EtOAc 5:1). **Yield:** 88%. ***Ee*:** 82%. $[\alpha]_D^{24}$ = +35 (*c* 0.6, $CHCl_3$) {Lit. $[\alpha]_D^{20}$ = +23 (*c* 1.0, CH_2Cl_2) for 99% *ee*. Ee determination by chiral **HPLC** analysis, Lux 5u Cellulose 3 column, Hex/*i*-PrOH 97:3 flow = 1 mL/min, retention times: t_r(*S*) = 14.2 min, t_r(*R*) = 15.3 min (major enantiomer).

(*R*)-1-Phenylpropan-2-ol (2k):[21]
Following the general procedure A, the reaction of phenylacetaldehyde (12 µL, 0.1 mmol) with methyltriisopropoxytitanium (0.15 mL, 1.5 equiv., 1.0 M in THF) in the presence of (R_a,*S*)-Py-BINMOL **L2** (3.8 mg, 0.1 equiv.) in Et_2O (1.5 mL) provided (*R*)-1-phenylpropan-2-ol (13 mg) as a colourless oil after column chromatography (Hex/EtOAc 9:1). **Yield:** 93%. ***Ee*:** 85%. $[\alpha]_D^{25}$ = –35.4 (*c 0.7*, $CHCl_3$) {Lit. $[\alpha]_D^{28}$ = –35.4 (*c 0.8*, $CHCl_3$) for 99% *ee*}. *Ee* determination by chiral **GC** analysis, Cyclosil β column, T = 85 °C, P = 15.9 psi, retention times: t_r(*S*) = 76.0 min, t_r(*R*) = 78.2 min (major enantiomer).

(*R*)-2-Nonanol (2l):[22]
Following the general procedure A, the reaction of octanal (16.0 µL, 0.1 mmol) with methyltriisopropoxytitanium (0.15 mL, 1.5 equiv., 1.0 M in THF) in the presence of (R_a,*S*)-Py-BINMOL **L2** (3.8 mg, 0.1 equiv.) in Et_2O (1.5 mL) provided (*R*)-2-nonanol as a colourless oil. **Conversion:** 99%. ***Ee*:** 90%. *Ee* was determined by chiral **GC** analysis on derivative **3**.

(*R*)-1-Cyclohexylethan-1-ol (2m):[23]
Following the general procedure A, the reaction of cyclohexanecarbaldehyde (24 µL, 0.2 mmol) with methyltriisopropoxytitanium (0.3 mL, 1.5 equiv., 1.0 M in THF) in the presence of (R_a,*S*)-Py-BINMOL **L2** (7.5 mg, 0.1 equiv.) in Et_2O (1.6 mL) provided (*R*)-1-cyclohexylethan-1-ol. This product was volatile and could not be isolated. **Conversion:** 99%. ***Ee*:** 94%. *Ee* was determined by chiral **GC** analysis on derivative **4**.

(*R*)-4-Methylpentan-2-ol (2n):[5b]
Following the general procedure A, the reaction of 3-methylbutanal (22 µL, 0.2 mmol) with methyltriisopropoxytitanium (0.3 mL, 1.5 equiv., 1.0 M in THF) in the presence of (R_a,*S*)-Py-BINMOL **L2** (7.5 mg, 0.1 equiv.) in Et_2O (3.0 mL) provided (*R*)-4-methylpentan-2-ol. This product was volatile and could not be isolated. **Conversion:** 77%. ***Ee*:** 90%. *Ee* was determined by chiral **GC** analysis on derivative **5**.

(*R*)-3,3-Dimethylbutan-2-ol (2o):[24]
Following the general procedure A, the reaction of pivaldehyde (11.0 μL, 0.1 mmol) with methyltriisopropoxytitanium (0.20 mL, 2.0 equiv., 1.0 M in THF) in the presence of (R_a,*S*)-Ph-BINMOL **L1** (3.8 mg, 0.1 equiv.) in Et_2O (1.5 mL) provided (*R*)-3,3-dimethylbutan-2-ol. This product was volatile and could not be isolated. **Conversion:** 78%. ***Ee*:** 93%. *Ee* determination by chiral **GC** analysis, CP Chirasil-DEX CB column, T = 35 °C, P = 6 psi, retention times: t_r(*R*) = 96.3 min (major enantiomer), t_r(*S*) = 97.0 min.

General procedure for the synthesis of acetates derivatives – General Procedure B.
In a flame dried Schlenk tube, the corresponding aliphatic alcohol [**2l**, **2m**, or **2n**] (0.2 mmol) was dissolved in anhydrous DCM (2 mL, 0.1 M) at 0 °C and Et_3N (56 μL, 0.4 mmol, 2 equiv.), DMAP (2.6 mg, 0.02 mmol, 0.1 equiv.) and acetic anhydride (44 μL, 0.4 mmol, 2 equiv.) were added sequentially. The reaction mixture was stirred at RT for 12 h. The reaction was quenched with water (2 mL), extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by chromatographic column to provide the desired products **3-5**.

(*R*)-Nonan-2-yl acetate (3):[25]
Following the general procedure B, the reaction of product **2l** (0.1 mmol) with Et_3N (35 μL, 0.25 mmol, 2.5 equiv.), DMAP (1.2 mg, 0.01 mmol, 0.1 equiv.) and acetic anhydride (24 μL, 0.25 mmol, 2.5 equiv.). Compound **7** was obtained after purification by column chromatography (eluent Hex/EtOAc 97:3) as colorless oil. **Yield**: 95%. ***Ee*:** 90%. $[\alpha]_D^{25}$ = –5.6 (*c* 0.9, $CHCl_3$). {$^{Lit.}$ $[\alpha]_D^{25}$ = –3.8 (*c 5.3*, $CHCl_3$) for 91% *ee*}. *Ee* determination by chiral **GC** analysis, CP Chirasil-DEX CB column, T = 125 °C, P = 6 psi, retention times: t_r(*S*) = 10.6 min, t_r(*R*) = 11.9 min (major enantiomer).

(*R*)-1-Cyclohexylethyl acetate (4):[26]
Following the general procedure B, the reaction of product **2m** (0.2 mmol) with Et_3N (56 μL, 0.4 mmol, 2 equiv.), DMAP (2.6 mg, 0.02 mmol, 0.1 equiv.) and acetic anhydride (44 μL, 0.4 mmol, 2 equiv.). Compound **9** could not be isolated due to the high volatility. ***Ee*:** 94%. *Ee* determination by chiral **GC** analysis, CP-Chirasil-DEX CB column, T = 100 °C, P = 6 psi, retention time: t_r(*S*) = 27.7 min, t_r(*R*) = 34.3 min (major enantiomer).

(*R*)-4-Methylpentan-2-yl acetate (5):[27]
Following the general procedure B, the reaction of product **2n** (0.2 mmol) with Et_3N (56 μL, 0.4 mmol, 2 equiv.), DMAP (2.6 mg, 0.02 mmol, 0.1 equiv.) and acetic anhydride (44 μL, 0.4 mmol, 2 equiv.). Compound **5** could not be isolated due to the high volatility. ***Ee*:** 90%. *Ee* determination by chiral **GC** analysis, CP-Chirasil-DEX CB column, T = 100 °C, P = 6 psi, retention time: t_r(*S*) = 4.9 min, t_r(*R*) = 5.3 min (major enantiomer).

Acknowledgements

BM thanks the European Commission for a Marie Curie Career Integration Grant and the EPSRC for a First Grant. BM and MAFI thank the RS for a travel grant. G. P. Howell is thanked for helpful comments on the manuscript.

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