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Catalytic enantioselective addition of methyltriisopropoxititanium to aldehydes

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A B S T R A C T

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

1. 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(O*i*Pr)$_4$. In the particular case of MeTi(O*i*Pr)$_3$, 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-ol (Ar-BINMOL)[7b,13] chiral ligands (Scheme 1). High enantioselectivities (up to 99%) are obtained when the reaction is performed in the presence of an excess amount 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 report the results from the enantioselective addition of commercially available MeTi(O*i*Pr)$_3$ to aldehydes, generating versatile methyl carbinol units with high enantioselectivities under mild conditions. No Ti(O*i*Pr)$_4$ is needed and higher, more practical temperatures can be used in contrast to systems using TADDOL ligands.

2. Results and discussion

The optimization process 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 that the use of Et_2O as the 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)

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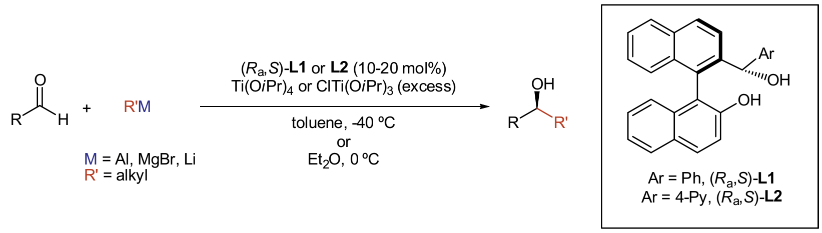
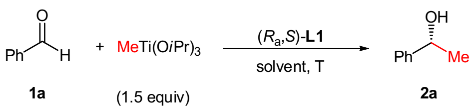


Scheme 1. Previous work on the catalytic enantioselective addition of organolithium, Grignard and organoaluminium reagents to aldehydes using Ar-BINMOL ligands.

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

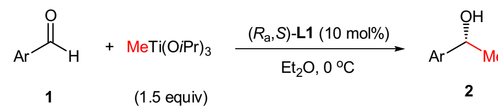
[a] Reaction conditions: **1a** (1 equiv, 0.07 M), MeTi(O*i*Pr)$_3$ (1 M in THF, 1.5 equiv), (R_a,*S*)-**L1**, 1.5 h.
[b] Determined by chiral GC.
[c] (*R*)-BINOL was used as ligand.

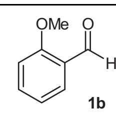
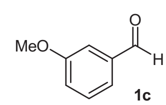
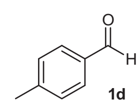
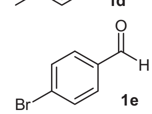
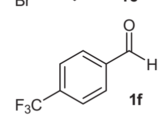
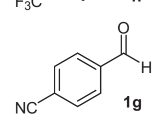
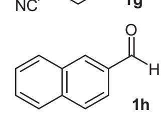
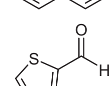
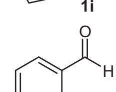
and only a small decrease in enantioselectivity was observed (compare entries 3 and 5). As a means of comparison, we performed the addition of MeTi(O*i*Pr)$_3$ to benzaldehyde **1a** in Et_2O at 0 °C using (*R*)-BINOL as a chiral ligand (entry 6); very low conversion (11%) and enantioselectivity (24%) were obtained.

Under the optimized conditions, the scope of the addition of MeTi(O*i*Pr)$_3$ was examined with different aldehydes (Table 2), which indicated that the system was remarkably efficient. Thus, methyl carbinol units were prepared in good yields (84–96%) and enantioselectivities (56 to >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 with an increased amount 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 the higher steric hindrance around the reactive site. The tolerance of this methodology toward 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 by-product 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 this 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).

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

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

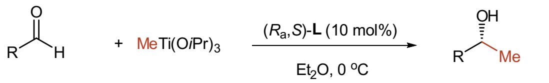


Entry	ArCHO	Conv. (%)[b]	Yield (%)[c]	ee (%)[b]
1	 **1b**	90	n.d.	55
2[d]		>99	96	56
3	 **1c**	82	n.d.	>99
4[d]		99	92	>99
5[d]	 **1d**	99	96	93
6	 **1e**	97	90	97
7	 **1f**	99	89	95
8	 **1g**	97	94	96
9[d]	 **1h**	58	n.d.	86
10[e]		89	84	87
11	 **1i**	67	n.d.	90
12[e]		98	95	94
13[f]	 **1a**	97	95	95

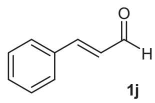
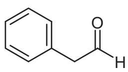
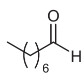
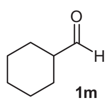
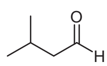
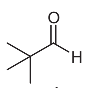
[a] Reaction conditions: **1** (1 equiv, 0.07 M), MeTi(O*i*Pr)$_3$ (1 M in THF, 1.5 equiv), (R_a,*S*)-**L1** (10 mol %), 1.5 h.
[b] Determined by chiral GC or HPLC.
[c] Isolated yield after flash chromatography.
[d] Reaction performed with 1.7 equiv of MeTi(O*i*Pr)$_3$.
[e] Reaction performed with 2.0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

efficiency in the addition of organolithium reagents to aliphatic and α,β-unsaturated aldehydes,[7a] led to a slight improvement in the results (entry 2). Ligand **L2** also proved to be more effective than **L1** when the aliphatic phenylacetaldehyde **1k** was

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



1 (1.5 equiv) 2

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.[f]	94
9[h]		**L1**	78	n.d.[f]	93

[a] Reaction conditions: **1** (1 equiv, 0.07 M), $MeTi(OiPr)_3$ (1 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 $MeTi(OiPr)_3$.
[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 $MeTi(OiPr)_3$.

employed as the substrate (compare entries 3, 4). In general, the addition of $MeTi(OiPr)_3$ to linear-**1l**, and α-branched **1m** proceeded with high enantioselectivities (90 and 94% ee, respectively, entries 5–6) and full conversion in the presence of 10 mol % of **L2** as the 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. The lack of reactivity of pivaldehyde (**1o**) could be rectified by using **L1** as a ligand and 2 equiv of $MeTi(OiPr)_3$ (entry 9).

3. Conclusion

In conclusion, we have developed an efficient catalytic system for the enantioselective addition of methyltriisopropoxititanium to aldehydes. This methodology allows the 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 realized, such as higher, more industrially relevant temperatures, shorter reaction times and no requirement for $Ti(OiPr)_4$ in the reaction media.

4. Experimental

4.1. General

The GC chromatograms (for both conversion and enantioselectivity determination) were recorded using an Agilent Technologies® 7890A GC System and a Hewlett Packard® 5890 Series II GC System, with a CycloSil-β (Agilent Technologies, 30 m × 0.25 mm) and a CP-Chiralsil-DEX CB (Varian, 25 m × 0.25 mm) column, respectively; injector and detector temperatures: 250 °C. HPLC analysis (for enantioselectivity determination) was carried out on a *Agilent 1100 Series* HPLC equipped with a G1315B diode array detector and a Quat Pump G1311A, using the columns Lux 5u Cellulose-1 and Lux 5u Cellulose-3 (Phenomenex®, 250 mm × 4.60 mm). Optical rotations were measured on a Bellingham + Stanley® ADP 440 + Polarimeter with a 0.5 cm cell (*c* given in g/100 mL). All reactions were monitored by thin-layer chromatography using precoated sheets of silica gel 60, 0.25 mm thick (F254 Merck KGaA®). The components were visualized by UV light (254 nm) and phosphomolybdic acid or $KMnO_4$ staining. Flash column chromatography was done using Geduran® Silica gel 60, 40–63 microns RE. The eluent used is mentioned in each particular case. All glassware employed during inert atmosphere experiments was flame-dried under a stream of dry argon. All liquid aldehydes were freshly distilled before use. $MeTi(OiPr)_3$ was purchased from Acros Organics (1 M THF) and used without further purification. Anhydrous DCM, toluene and Et_2O were obtained from a Pure Solv™ Solvent Purification Systems. Ligands (R_a,S)-**L1** and (R_a,S)-**L2** were prepared according to literature procedures[7a] from (*R*)-BINOL, purchased from Manchester Organics.

4.2. General procedure for the addition of methyltriisopropoxititanium to aldehydes—general procedure A

To a stirred solution of **L1** or **L2** (0.2 equiv) in Et_2O (3.0 mL, 0.067 M) at 0 °C, $MeTi(OiPr)_3$ (0.3 mL, 1.5 equiv, 1 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 90 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.

4.2.1. (*R*)-1-Phenylethanol 2a[15]

Following 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 (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.[15] $[\alpha]_D^{26}$ = +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.

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

Following 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.[15] $[\alpha]_D^{26}$ = +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).

4.2.3. (*R*)-1-(3-Methoxyphenyl)ethanol 2c[16]

Following 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.[16] $[\alpha]_D^{20}$ = +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.

4.2.4. (*R*)-1-(4-Methylphenyl)ethanol 2d[17]

Following 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 colorless oil after column chromatography (eluent Hex/EtOAc 9:1). Yield: 96%. *Ee*: 93%. $[\alpha]_D^{25}$ = +39.4 (*c* 0.7, $CHCl_3$) {Lit.[17] $[\alpha]_D^{26}$ = +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.

4.2.5. (*R*)-1-(4-Bromophenyl)ethanol 2e[15]

Following 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.[15] $[\alpha]_D^{20}$ = +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.

4.2.6. (*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.[18] $[\alpha]_D^{20}$ = +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.

4.2.7. (*R*)-4-(1-Hydroxyethyl)benzonitrile 2g[19]

Following 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.[19] $[\alpha]_D^{25}$ = +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.

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

Following 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 chromatography (eluent Hex/EtOAc 8:1). Yield: 92%. *Ee*: 84%. $[\alpha]_D^{24}$ = +31 (*c* 0.4, $CHCl_3$) {Lit.[15] $[\alpha]_D^{28}$ = +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).

4.2.9. (*R*)-1-(Thiophen-2-yl)ethanol 2i[15]

Following 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.[15] $[\alpha]_D^{25}$ = +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.

4.2.10. (*R*,*E*)-4-Phenylbut-3-en-2-ol 2j[20]

Following 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.[20] $[\alpha]_D^{20}$ = +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).

4.2.11. (*R*)-1-Phenylpropan-2-ol 2k[21]

Following 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 colorless oil after column chromatography (Hex/EtOAc 9:1). Yield: 93%. *Ee*: 85%. $[\alpha]_D^{25}$ = −35.4 (*c 0.7*, $CHCl_3$) {Lit.[21] $[\alpha]_D^{28}$ = −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).

4.2.12. (*R*)-2-Nonanol 2l[22]

Following 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 colorless oil. Conversion: 99%. *Ee*: 90%. *Ee* was determined by chiral GC analysis on derivative **3**.

4.2.13. (*R*)-1-Cyclohexylethan-1-ol 2m[23]

Following 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**.

4.2.14. (*R*)-4-Methylpentan-2-ol 2n[5b]

Following 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**.

4.2.15. (*R*)-3,3-Dimethylbutan-2-ol 2o[24]

Following 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.

4.3. 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 after which 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**.

4.3.1. (*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.[25] $[\alpha]_D^{25} = -3.8$ (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).

4.3.2. (*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).

4.3.3. (*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).

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Supplementary data

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