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Catalytic enantioselective addition of methyltriisopropoxititanium to aldehydes

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A R T I C L E   I N F O

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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 methyltriisopropoxititanium as a nucleophile and a readily available binaphthyl ligand. The enantioselective methylation of both aromatic and aliphatic aldehydes proceeds with good yields and high enantioselectivities under mild conditions.

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1. Introduction

The enantioselective synthesis of the chiral methyl carbinol moiety, present in a large number of natural products and biologically active compounds, 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. Enantioselective catalyzed versions of this key transformation have been studied extensively with dimethylzinc, methyl Grignard, and dimethylaluminium reagents. Many of these methodologies involve the use of Ti(OjPr) 4 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 reactant with Ti(OjPr) 4. The direct asymmetric addition of organotitanium reagents to carbonyls has also been described under catalytic conditions using TADDOL, H-BINOL derivatives as chiral ligands, in the presence of Ti(OjPr) 4. In the particular case of MeTi(OjPr) 3 as the model substrate. Our first tests provided very promising results (Table 1). Using 20 mol % of L 1, the addition of 1.5 equiv of MeTi(OjPr) 3 to 1a in toluene at −40 °C (optimal solvent and temperature for the addition of Grignard reagents to aldehydes) 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 3O 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 L 1, the reaction could be carried out at room temperature (entry 5)

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 L 1, the addition of 1.5 equiv of MeTi(OjPr) 3 to 1a in toluene at −40 °C (optimal solvent and temperature for the addition of Grignard reagents to aldehydes) 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 3O 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 L 1, the reaction could be carried out at room temperature (entry 5)
Influence of catalyst loading, temperature and solvent on the reaction of MeTi(O\(i\)Pr\(_3\)) to cinnamic aldehyde 1j. As a means of comparison, we observed with an increased amount of MeTi(O\(i\)Pr\(_3\)) conversion. A small increase in enantioselectivity was also obtained 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(OiPr\(_3\)) 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(OiPr\(_3\)) to aromatic aldehydes: scope of the reaction (Table 2).

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 \(\alpha,\beta\)-unsaturated aldehydes (Table 3). Ligand L1 provided moderate conversion and enantioselectivity in the addition of MeTi(OiPr\(_3\)) 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 \(\alpha,\beta\)-unsaturated aldehydes,\(^2\) 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 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>(T) (°C)</th>
<th>(L1) (mol %)</th>
<th>Conv. (%)b</th>
<th>ee (%)b</th>
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<tr>
<td>1</td>
<td>Toluene</td>
<td>-40</td>
<td>20</td>
<td>78</td>
<td>94</td>
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<td>2</td>
<td>(Et_{2}O)</td>
<td>0</td>
<td>20</td>
<td>&gt;99</td>
<td>97</td>
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<tr>
<td>3</td>
<td>(Et_{2}O)</td>
<td>0</td>
<td>10</td>
<td>99</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>(Et_{2}O)</td>
<td>0</td>
<td>5</td>
<td>99</td>
<td>78</td>
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<tr>
<td>5</td>
<td>(Et_{2}O)</td>
<td>RT</td>
<td>10</td>
<td>&gt;99</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>(Et_{2}O)</td>
<td>0</td>
<td>10</td>
<td>11</td>
<td>24</td>
</tr>
</tbody>
</table>

\(a\) Reaction conditions: 1a (1 equiv, 0.07 M), MeTi(OiPr\(_3\)) (1 M in THF, 1.5 equiv), \((R,S)-L1\), 1.5 h.

\(b\) Determined by chiral GC.

\(c\) \([R]-\)BINOL was used as ligand.

Table 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArCHO</th>
<th>Conv. (%)b</th>
<th>Yield (%)c</th>
<th>ee (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Ar_{CHO})</td>
<td>90</td>
<td>n.d.</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>(Ar_{CHO})</td>
<td>&gt;99</td>
<td>96</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>(Ar_{CHO})</td>
<td>82</td>
<td>n.d.</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>(Ar_{CHO})</td>
<td>99</td>
<td>96</td>
<td>93</td>
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<tr>
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<td>90</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td>(Ar_{CHO})</td>
<td>99</td>
<td>89</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>(Ar_{CHO})</td>
<td>97</td>
<td>94</td>
<td>96</td>
</tr>
<tr>
<td>9</td>
<td>(Ar_{CHO})</td>
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<tr>
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<td>(Ar_{CHO})</td>
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<td>84</td>
<td>87</td>
</tr>
<tr>
<td>11</td>
<td>(Ar_{CHO})</td>
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<td>n.d.</td>
<td>90</td>
</tr>
<tr>
<td>12</td>
<td>(Ar_{CHO})</td>
<td>98</td>
<td>95</td>
<td>94</td>
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<tr>
<td>13</td>
<td>(Ar_{CHO})</td>
<td>97</td>
<td>95</td>
<td>95</td>
</tr>
</tbody>
</table>

\(a\) Reaction conditions: 1 (1 equiv, 0.07 M), MeTi(OiPr\(_3\)) (1 M in THF, 1.5 equiv), \((R,S)-L1\) (10 mol %), 1.5 h.

\(b\) Determined by chiral GC.

\(c\) Isolated yield after flash chromatography.

\(d\) Reaction performed with 1.7 equiv of MeTi(OiPr\(_3\)).

\(e\) Reaction performed with 2.0 equiv of MeTi(OiPr\(_3\)).

\(f\) Reaction performed using 0.5 g of 1a.
Table 3
Enantioselective addition of MeTi(OIPr)3 to aliphatic and α,β-unsaturated aldehydes: scope of the reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArCHO</th>
<th>L</th>
<th>Conv. (%)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>L1</td>
<td>65</td>
<td>90</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>L2</td>
<td>99</td>
<td>n.d.</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>L1</td>
<td>99</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>L2</td>
<td>99</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>L2</td>
<td>99</td>
<td>95</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>L2</td>
<td>99</td>
<td>n.d.</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>L2</td>
<td>77</td>
<td>n.d.</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>L2</td>
<td>20</td>
<td>n.d.</td>
<td>94</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>L1</td>
<td>78</td>
<td>n.d.</td>
<td>93</td>
</tr>
</tbody>
</table>

* Reaction conditions: 1 (1 equiv, 0.07 M), MeTi(OIPr)3 (1 M in THF, 1.5 equiv), (R,S)-L (10 mol %), 1 h.

* Determined by chiral GC or HPLC.

* Isolated yield after flash chromatography.

* Reaction performed with 1.1 equiv of MeTi(OIPr)3.

* Determined by chiral GC on the acetate derivative.

* Volatile compound. Not isolated.

* 7% of (CH3)2CHCHO was detected.

* 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-11, 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 methyltrisopropoxititanium 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)3 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 + Polariometer 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 KMnO4 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 Et2O were obtained from a Pure Solv Solvent Purification Systems. Ligands (R,S)-L1 and (R,S)-L2 were prepared according to literature procedures from (R)-BINOL, purchased from Manuget Organics.

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

To a stirred solution of L1 or L2 (0.2 equiv) in Et2O (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 Et2O. The combined organic layers were dried over anhydrous MgSO4 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

Following general procedure A, the reaction of benzaldehyde (20 μL, 0.2 mmol) with methyltrisopropoxytitanium (0.3 mL, 1.5 equiv, 1.0 M in THF) in the presence of (R,S)-Ph-BINMOL L1 (7.5 mg, 0.1 equiv) in Et2O (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%. [α]D24 = +47 (c 0.7, CHCl3) [Lit. [α]D24 = +497 (c 0.3, CHCl3) for 95% ee]. Ee determination by chiral GC analysis, Cyclosil β column, T = 100 °C, P = 15.9 psi, retention times: tR(R) = 30.9 min (major enantiomer), tR(S) = 34.8 min.

4.2.2. (R)-1-(2-Methoxyphenyl)ethanol 2b

Following general procedure A, the reaction of 2-methoxybenzaldehyde (27 mg, 0.2 mmol) with methyltrisopropoxytitanium (0.34 mL, 1.7 equiv, 1.0 M in THF) in the presence of (R,S)-Ph-BINMOL L1 (7.5 mg, 0.1 equiv) in Et2O (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%. [α]D24 = +43 (c 0.3, CHCl3) [Lit. [α]D24 = +243 (c 1.0, CHCl3) for 99% ee]. Ee determination by chiral GC analysis, Cyclosil β column, T = 150 °C, P = 15.9 psi, retention times: tR(R) = 9.1 min, tR(S) = 10.4 min (major enantiomer).
4.2.3. (R)-1-(3-Methoxyphenyl)ethanol 2c

Following general procedure A, the reaction of 3-methoxybenzaldehyde (24 μL, 0.2 mmol) with methyltrisopropoxypentanium (0.3 mL, 1.5 equiv, 1.0 M in THF) in the presence of (R,S)-Ph-BINMOL L1 (7.5 mg, 0.1 equiv) in Et2O (3.0 mL) provided (R)-1-(3-methoxyphenyl)ethanol (28 mg) as a colorless oil after column chromatography (Hex/EtOAc 9:1). Yield: 92%. Ee: 95%. [α]D+36 = +28 (c 1.0, CHCl3) [Lit.16] [α]D+36 = +52.1 (c 1.0, CHCl3) for 96% ee. 

4.2.4. (R)-1-(4-Methylphenyl)ethanol 2d

Following general procedure A, the reaction of 4-tolualdehyde (12.0 μL, 0.1 mmol) with methyltrisopropoxypentanium (0.15 mL, 1.5 equiv, 1.0 M in THF) in the presence of (R,S)-Ph-BINMOL L1 (3.8 mg, 0.1 equiv) in Et2O (1.5 mL) provided (R)-1-(4-methylphenyl)ethanol (13 mg) as a colorless oil after column chromatography (eluents Hex/EtOAc 9:1). Yield: 96%. Ee: 93%. [α]D+35 = +39.4 (c 0.7, CHCl3) [Lit.16] [α]D+35 = +56 (c 1.0, CHCl3) for 96% ee. 

4.2.5. (R)-1-(4-Bromomethyl)ethanol 2e

Following general procedure A, the reaction of 4-bromobenzaldehyde (37 mg, 0.2 mmol) with methyltrisopropoxypentanium (0.3 mL, 1.5 equiv, 1.0 M in THF) in the presence of (R,S)-Ph-BINMOL L1 (7.5 mg, 0.1 equiv) in Et2O (3.0 mL) provided (R)-1-(4-bromomethyl)ethanol (18 mg) as a white solid after column chromatography (Hex/EtOAc 6:1). Yield: 90%. Ee: 97%. [α]D+28 = +28 (c 0.4, CHCl3) [Lit.16] [α]D+28 = +34.6 (c 1.7, CHCl3) for 94% ee. 

4.2.6. (R)-1-[4-(Trifluoromethyl)phenyl]ethanol 2f

Following the general procedure A, the reaction of 4-(trifluoromethyl)benzaldehyde (14 μL, 0.1 mmol) with methyltrisopropoxypentanium (0.15 mL, 1.5 equiv, 1.0 M in THF) in the presence of (R,S)-Ph-BINMOL L1 (3.8 mg, 0.1 equiv) in Et2O (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%. [α]D+28 = +28.9 (c 0.9, CHCl3) [Lit.16] [α]D+28 = +35.3 (c 1.6, CHCl3) for 99% ee. 

4.2.7. (R)-4-(1-Hydroxyethyl)benzonitrile 2g

Following general procedure A, the reaction of 4-formylbenzonitrile (13 mg, 0.1 mmol) with methyltrisopropoxypentanium (0.15 mL, 1.5 equiv, 1.0 M in THF) in the presence of (R,S)-Ph-BINMOL L1 (3.8 mg, 0.1 equiv) in Et2O (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%. [α]D+28 = +35.3 (c 0.9, CHCl3) [Lit.16] [α]D+28 = +43.1 (c 1.02, CHCl3) for 96% ee. 

4.2.8. (R)-1-(Naphthalen-2-yl)ethanol 2h

Following general procedure A, the reaction of naphthaldehyde (31.2 mg, 0.2 mmol) with methyltrisopropoxypentanium (0.4 mL, 2.0 equiv, 1.0 M in THF) in the presence of (R,S)-Ph-BINMOL L1 (7.5 mg, 0.1 equiv) in Et2O (3.0 mL) provided (R)-1-(naphthalen-2-yl)ethanol (29.1 mg) as a white solid after column chromatography (eluents Hex/EtOAc 8:1). Yield: 92%. Ee: 84%. [α]D+31 = +31 (c 0.4, CHCl3) [Lit.15] [α]D+31 = +30 (c 0.97, CHCl3) for 87% ee. 

4.2.9. (R)-1-(Thiophen-2-yl)ethanol 2i

Following general procedure A, the reaction of thiophene-2-carbaldehyde (9.4 μL, 0.1 mmol) with methyltrisopropoxypentanium (0.4 mL, 2.0 equiv, 1.0 M in THF) in the presence of (R,S)-Ph-BINMOL L1 (7.5 mg, 0.1 equiv) in Et2O (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%. [α]D+35 = +125 (c 0.8, CHCl3) [Lit.15] [α]D+35 = +20 (c 1.04, CHCl3) for 96% ee. 

4.2.10. (R,E)-4-Phenylbut-3-en-2-ol 2j

Following general procedure A, the reaction of trans-cinnamaldehyde (25.2 μL, 0.2 mmol) with methyltrisopropoxypentanium (0.3 mL, 1.5 equiv, 1.0 M in THF) in the presence of (R,S)-Py-BINMOL L2 (7.5 mg, 0.1 equiv) in Et2O (3.0 mL) provided (R,E)-4-phenylbut-3-en-2-ol (26 mg) as a white solid after column chromatography (Hex/EtOAc 6:1). Yield: 88%. Ee: 82%. [α]D+28 = +35 (c 0.6, CHCl3) [Lit.20] [α]D+28 = +23 (c 1.0, CH2Cl2) for 99% ee. 

4.2.11. (R)-1-Phenylpropan-2-ol 2k

Following general procedure A, the reaction of phenylacetaldheyde (12 μL, 0.1 mmol) with methyltrisopropoxypentanium (0.15 mL, 1.5 equiv, 1.0 M in THF) in the presence of (R,S)-Py-BINMOL L2 (3.8 mg, 0.1 equiv) in Et2O (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%. [α]D+28 = -35.4 (c 0.7, CHCl3) [Lit.21] [α]D+28 = -35.4 (c 0.8, CHCl3) for 99% ee. 

4.2.12. (R)-2-Nonanol 2l

Following general procedure A, the reaction of octanal (16.0 μL, 0.1 mmol) with methyltrisopropoxypentanium (0.15 mL, 1.5 equiv, 1.0 M in THF) in the presence of (R,S)-Py-BINMOL L2 (3.8 mg, 0.1 equiv) in Et2O (1.5 mL) provided (R)-2-nonanol (26 mg) as a colorless oil. Conversion: 99%. Ee: 90%. Ee was determined by chiral GC analysis on derivative 3.

4.2.13. (R)-1-Cyclohexylethanol-1-ol 2m

Following general procedure A, the reaction of cyclohexanecarbaldehyde (24 μL, 0.2 mmol) with methyltrisopropoxypentanium (0.3 mL, 1.5 equiv, 1.0 M in THF) in the presence of (R,S)-Py-BINMOL L2 (7.5 mg, 0.1 equiv) in Et2O (1.6 mL) provided (R)-1-cyclohexylethanol-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

Following general procedure A, the reaction of 3-methylbutanal (22 μL, 0.2 mmol) with methyltrisopropoxypentanium (0.3 mL,
4.3.1. (R)-Nonan-2-yl acetate 32

Following the general procedure B, the reaction of product 21 (0.1 mmol) with Et3N (35 μL, 0.25 mmol, 2.5 equiv), DMAP (1.2 mg, 0.01 mmol, 1 equiv) and acetic anhydride (24 μL, 0.25 mmol, 2.5 equiv), Compound 7 was obtained after purification by column chromatography (elucent Hex/EtOAc 97:3) as colorless oil. Yield: 95%. Ee: 90%. |x|αD 15 = 5.6 (c 0.9, CHCl3). Lit. 25 |x|αD 15 = 3.8 (c 5.3, CHCl3) for 91% ee. Ee determination by chiral GC analysis, CP Chirasil-DEX CB column, T = 125 °C, P = 6 psi, retention times: tR(S) = 10.6 min, tR(R) = 11.9 min (major enantiomer).

4.3.2. (R)-1-Cyclohexylethyl acetate 426

Following the general procedure B, the reaction of product 21 (0.2 mmol) with Et3N (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) was added sequentially. The reaction mixture was stirred at RT for 12 h. The reaction was quenched with water (2 ml), extracted with EtOAc (3 × 5 ml) and the combined organic layers were dried over MgSO4 and concentrated under vacuum. The crude product was purified by chromatographic column to provide the desired products 3-5.

4.3.3. (R)-4-Methylpentan-2-yl acetate 327

Following the general procedure B, the reaction of product 2n (0.2 mmol) with Et3N (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: tR(S) = 4.9 min, tR(R) = 5.3 min (major enantiomer).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2016.06.001.

References

2. For some examples on the use of stoichiometric amounts of ligands in the catalytic addition of other alkyl Grignard reagents to carbonyl compounds, see: (a) Binder, C. M.; Singaram, B. J. Org. Chem. 1986, 51, 1090–1092; (b) Ramón, D. J.; Yus, M. Org. Lett. 2001, 3, 1785–1788;
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5. (a) M. Veguillas et al. / Tetrahedron: Asymmetry 2016, 27, 643–648


12. This methodology is also applicable to ketones when aryl Grignard reagents are used as nucleophiles. See reference 7j.


14. A lower excess of chlorotitanium trisopropoxide can be used instead for the addition of organolithium reagents to aldehydes.


