Catalytic enantioselective addition of methyltriisopropoxititanium to aldehydes

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Catalytic enantioselective addition of methyltriisopropoxititanium to aldehydes

Marcos Veguillas, Ricard Solà, M. Ángeles Fernández-Ibáñez, Beatriz Maciá

Abstract

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 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, 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, trimethylaluminium, and more recently, with the more reactive methylithium and methyl Grignard reagents. Many of these methodologies involve the use of Ti(OR)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 reagent with Ti(OR)₄. The direct asymmetric addition of organotitanium reagents to carbonyls has also been described under catalytic conditions using TADDOL, HBINOL (for alkyltitanium reagents) or BINOL (for aryltitanium reagents) derivatives as chiral ligands, in the presence of Ti(OiPr)₄. In the particular case of MeTi(OiPr)₃, the only catalytic methodologies reported to date require the use of chiral TADDOL ligands 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 and organoaluminum reagents to aldehydes, based on the use of Lai’s and Xu’s 1,1-binaphthalene-2-α-arylmethan-2-ol (Ar-BINMOL) chiral ligands. High enantioselectivities (up to 99%) are obtained when the reaction is performed in the presence of an excess amount of titanium tetraisopropoxide, avoiding salt exclusion procedures and chelating additives. 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(OiPr)₃ to aldehydes, generating versatile methyl carbinol units with 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.

2. Results and discussion

The optimization process was carried out using benzaldehyde 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(OiPr)₃ to 1a in toluene at −40 °C (optimal solvent and temperature for the addition of Grignard reagents to aldehydes using L₁ as ligand) 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 Et₂O 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)
Influence of catalyst loading, temperature and solvent:

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>L1 (mol %)</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
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<td>10</td>
<td>11</td>
<td>24</td>
</tr>
</tbody>
</table>

* Reaction conditions: 1a (1 equiv, 0.07 M), MeTi(O(i-Pr)₃) (1 M in THF, 1.5 equiv), (R,S)-L1, 1.5 h.

Enantioselective addition of MeTi(O(i-Pr)₃) to aromatic aldehydes: scope of the reaction:

<table>
<thead>
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<th>Entry</th>
<th>ArCHO</th>
<th>Conv. (%)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
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<td>55</td>
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<tr>
<td>2</td>
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<td>96</td>
<td>56</td>
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<td>3</td>
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<td>&gt;99</td>
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<td>4</td>
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<td>99</td>
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<td>&gt;99</td>
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<td>96</td>
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<td>9</td>
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<td>58</td>
<td>n.d.</td>
<td>86</td>
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<td>10</td>
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<td>11</td>
<td></td>
<td>67</td>
<td>n.d.</td>
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<td>12</td>
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<tr>
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<td></td>
<td>97</td>
<td>95</td>
<td>95</td>
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</tbody>
</table>

* Reaction conditions: 1 (1 equiv, 0.07 M), MeTi(O(i-Pr)₃) (1 M in THF, 1.5 equiv), (R,S)-L1 (10 mol %), 1.5 h.

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 benzyaldehyde 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 cinnamaldehyde 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, 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...
employed as the substrate (compare entries 3, 4). In general, the addition of MeTi(OiPr)$_3$ to linear-$\text{L}$ and $\alpha$-branched $1\text{m}$ proceeded with high enantioselectivities (90 and 94% ee, respectively, entries 5–6) and full conversion in the presence of $10\text{ mol}\%$ of $\text{L}$ as the chiral ligand. Only the $\beta$-branched substrate $1\text{n}$ provided high enantioselectivity, but moderate conversion (entry 7). For the bulkier pivaldehyde $1\text{o}$, high enantioselectivity and very low conversion (94% ee, 20% conv, entry 8), were obtained. The lack of reactivity of pivaldehyde ($1\text{o}$) could be rectified by using $\text{L}$ 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 carbinals 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$^\text{a}$ 7890A GC System and a Hewlett Packard$^\text{b}$ 5890 Series II GC System, with a CycloSil-$\beta$ (Agilent Technologies, 30 m $\times$ 0.25 mm) and a CP-ChiralSIL-DEX CB (Varian, 25 m $\times$ 0.25 mm) column, respectively; injector and detector temperatures: 250 $^\circ$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$^\text{c}$, 250 mm $\times$ 4.60 mm). Optical rotations were measured on a Bellingham + Stanley$^\text{d}$ 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 (EUR 254 Merck KGA$^\text{e}$). The components were visualized by UV light (254 nm) and phosphomolybdic acid or KMnO$_4$ staining. Flash column chromatography was done using Geduran$^\text{f}$ 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 EtO$_2$ were obtained from a Pure Solv$^\text{g}$ Solvent Purification Systems. Ligands ($R_S$-$\text{L}$) and ($R_S$-$\text{L}$-$\text{L}$) were prepared according to literature procedures$^\text{h}$ from ($R$-)BINOL, purchased from Manchester Organics.

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

To a stirred solution of $\text{L}$ or $\text{L}$ (0.2 equiv) in Et$_2$O (3.0 mL, 0.067 M) at 0 $^\circ$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 EtO$_2$. 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 $2\text{a}^\text{15}$

Following general procedure A, the reaction of benzaldehyde (20 $\mu$L, 0.2 mmol) with methyltrisopropoxititanium (0.3 mL, 1.5 equiv, 1.0 M in THF) in the presence of ($R_S$)-Ph-BINMOL $\text{L}$ (7.5 mg, 0.1 equiv) in Et$_2$O (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%. $[x]_D^{24} = +47$ (c 0.7, CHCl$_3$) [Lit.$^\text{i}$ $[x]_D^{24} = +97$ (c 0.3, CHCl$_3$) for 95% ee]. Ee determination by chiral GC analysis, Cyclosil $\beta$ column, $T = 100^\circ$C, $P = 15.9$ psi, retention times: $t(R) = 30.9$ min (major enantiomer), $t(S) = 34.8$ min.

#### 4.2.2. ($R$)-1-(2-Methoxyphenyl)ethanol $2\text{b}^\text{15}$

Following general procedure A, the reaction of 2-methoxybenzaldehyde (27 mg, 0.2 mmol) with methyltrisopropoxititanium (0.34 mL, 1.7 equiv, 1.0 M in THF) in the presence of ($R_S$)-Ph-BINMOL $\text{L}$ (7.5 mg, 0.1 equiv) in Et$_2$O (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%. $[x]_D^{24} = +33$ (c 0.3, CHCl$_3$) [Lit.$^\text{i}$ $[x]_D^{24} = +24$ (c 1.0, CHCl$_3$) for 99% ee]. Ee determination by chiral GC analysis, Cyclosil $\beta$ column, $T = 150^\circ$C, $P = 15.9$ psi, retention times: $t(R) = 9.1$ min, $t(S) = 10.4$ min (major enantiomer).

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArCHO</th>
<th>$\text{L}$</th>
<th>Conv. (%)$^b$</th>
<th>Yield (%)$^c$</th>
<th>ee (%)$^e$</th>
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<tbody>
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<td>1a</td>
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<td></td>
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<td></td>
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</tr>
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<td>95</td>
<td>90%</td>
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<td>$L_2$</td>
<td>99</td>
<td>n.d.$^d$</td>
<td>94%</td>
</tr>
<tr>
<td>7</td>
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<td>$L_2$</td>
<td>77$^e$</td>
<td>n.d.$^d$</td>
<td>90%</td>
</tr>
<tr>
<td>8d</td>
<td></td>
<td>$L_2$</td>
<td>20</td>
<td>n.d.$^d$</td>
<td>94%</td>
</tr>
<tr>
<td>9h</td>
<td></td>
<td>$L_2$</td>
<td>78</td>
<td>n.d.$^d$</td>
<td>93%</td>
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</tbody>
</table>

$^a$ Reaction conditions: 1 (1 equiv, 0.07 M), MeTi(OiPr)$_3$ (1 M in THF, 1.5 equiv), ($R_S$-$\text{L}$-$\text{L}$) (10 mol %), 1 h. $^b$ Isolated yield after flash chromatography. $^c$ Volatile compound. Not isolated. $^d$ Reaction performed with 1.7 equiv of MeTi(OiPr)$_3$. $^e$ Determined by chiral GC on the acetate derivative. $^f$ Determined by chiral GC or HPLC.

Table 3

Enantioselective addition of MeTi(OiPr)$_3$ to aliphatic and $\alpha$-$\beta$-unsaturated aldehydes: scope of the reaction$^a$
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 methyltrisopropoxypotassium (0.3 mL, 1.5 equiv, 1.0 M in THF) in the presence of \((R_S)-\text{Ph-BINMOL} \ L_1\) (7.5 mg, 0.1 equiv) in EtO\(_2\) (3.0 mL) provided \((R)-1-(3-\text{methoxyphenyl})\)ethanol (28 mg) as a colorless oil after column chromatography (Hex/EtOAc 9:1). Yield: 96%. \(\text{Ee}: 99.5\%\). \[\text{Ee} = 1\%\]

4.2.4. (R)-1-(4-Methylphenyl)ethanol 2d\(^{17}\)

Following general procedure A, the reaction of 4-toludehyde (12.0 μL, 0.1 mmol) with methyltrisopropoxypotassium (0.15 mL, 1.5 equiv, 1.0 M in THF) in the presence of \((R_S)-\text{Ph-BINMOL} \ L_1\) (3.8 mg, 0.1 equiv) in EtO\(_2\) (1.5 mL) provided \((R)-1-(4-\text{methylphenyl})\)ethanol (13 mg) as a colorless oil after column chromatography (eluent Hex/EtOAc 7:1). Yield: 96%. \(\text{Ee}: 93\%\). \[\text{Ee} = 7\%\]

4.2.5. (R)-1-(4-Bromomethyl)ethanol 2e\(^{15}\)

Following general procedure A, the reaction of 4-bromobenzaldehyde (37 mg, 0.2 mmol) with methyltrisopropoxypotassium (0.3 mL, 1.5 equiv, 1.0 M in THF) in the presence of \((R_S)-\text{Ph-BINMOL} \ L_1\) (7.5 mg, 0.1 equiv) in EtO\(_2\) (3.0 mL) provided \((R)-1-(4-\text{bromomethyl})\)ethanol (18 mg) as a white solid after column chromatography (Hex/EtOAc 6:1). Yield: 90%. \(\text{Ee}: 94\%\). \[\text{Ee} = 6\%\]

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 methyltrisopropoxypotassium (0.15 mL, 1.5 equiv, 1.0 M in THF) in the presence of \((R_S)-\text{Ph-BINMOL} \ L_1\) (3.8 mg, 0.1 equiv) in EtO\(_2\) (1.5 mL) provided \((R)-1-(4-\text{trifluoromethylphenyl})\)ethanol (17 mg) as a yellow oil after column chromatography (Hex/EtOAc 9:1). Yield: 90%. \(\text{Ee}: 95\%\). \[\text{Ee} = 5\%\]

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 methyltrisopropoxypotassium (0.15 mL, 1.5 equiv, 1.0 M in THF) in the presence of \((R_S)-\text{Ph-BINMOL} \ L_1\) (3.8 mg, 0.1 equiv) in EtO\(_2\) (1.5 mL) provided \((R)-4-(1-\text{hydroxyethyl})\)benzonitrile (17 mg) as a yellow oil after column chromatography (Hex/EtOAc 8:2). Yield: 94%. \(\text{Ee}: 96\%\). \[\text{Ee} = 4\%\]

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 methyltrisopropoxypotassium (0.4 mL, 2.0 equiv, 1.0 M in THF) in the presence of \((R_S)-\text{Ph-BINMOL} \ L_1\) (7.5 mg, 0.1 equiv) in EtO\(_2\) (3.0 mL) provided \((R)-1-(\text{naphthalen-2-yl})\)ethanol (29.1 mg) as a white solid after column chromatography (eluent Hex/EtOAc 8:1). Yield: 92%. \(\text{Ee}: 84\%\). \[\text{Ee} = 6\%\]

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 methyltrisopropoxypotassium (0.4 mL, 2.0 equiv, 1.0 M in THF) in the presence of \((R_S)-\text{Ph-BINMOL} \ L_1\) (7.5 mg, 0.1 equiv) in EtO\(_2\) (3.0 mL) provided \((R)-1-(\text{thiophen-2-yl})\)ethanol (24.3 mg) as a volatile colorless oil after column chromatography (Hex/EtOAc 6:1). Yield: 95%. \(\text{Ee}: 94\%\). \[\text{Ee} = 6\%\]

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 methyltrisopropoxypotassium (0.3 mL, 1.5 equiv, 1.0 M in THF) in the presence of \((R_S)-\text{Ph-Py-BINMOL} \ L_2\) (7.5 mg, 0.1 equiv) in EtO\(_2\) (3.0 mL) provided \((R,E)-4-\text{phenylbut-3-en-2-ol}\) (26 mg) as a white solid after column chromatography (Hex/EtOAc 5:1). Yield: 95%. \(\text{Ee}: 95\%\). \[\text{Ee} = 5\%\]

4.2.11. (R)-1-Phenylpropan-2-ol 2k\(^{21}\)

Following general procedure A, the reaction of phenylacetaldehyde (12 μL, 0.1 mmol) with methyltrisopropoxypotassium (0.15 mL, 1.5 equiv, 1.0 M in THF) in the presence of \((R_S)-\text{Ph-Py-BINMOL} \ L_2\) (3.8 mg, 0.1 equiv) in EtO\(_2\) (1.5 mL) provided \((R)-1-\text{phenylpropan-2-ol}\) (13 mg) as a colorless oil after column chromatography (Hex/EtOAc 9:1). Yield: 90%. \(\text{Ee}: 85\%\). \[\text{Ee} = 15\%\]

4.2.12. (R)-2-Nonanol 2l\(^{22}\)

Following general procedure A, the reaction of octanal (16.0 μL, 0.1 mmol) with methyltrisopropoxypotassium (0.15 mL, 1.5 equiv, 1.0 M in THF) in the presence of \((R_S)-\text{Ph-Py-BINMOL} \ L_2\) (3.8 mg, 0.1 equiv) in EtO\(_2\) (1.5 mL) provided \((R)-2-\text{nonanol}\) (26 mg) as a white oil. Conversion: 99%. \(\text{Ee}: 90\%\). \[\text{Ee} = 5\%\]

4.2.13. (R)-1-Cyclohexylethan-1-ol 2m\(^{23}\)

Following general procedure A, the reaction of cyclohexanecarbaldehyde (24 μL, 0.2 mmol) with methyltrisopropoxypotassium (0.3 mL, 1.5 equiv, 1.0 M in THF) in the presence of \((R_S)-\text{Ph-Py-BINMOL} \ L_2\) (7.5 mg, 0.1 equiv) in EtO\(_2\) (1.6 mL) provided \((R)-1-\text{cyclohexylethan-1-ol}\). This product was volatile and could not be isolated. Conversion: 99%. \(\text{Ee}: 94\%\). \[\text{Ee} = 6\%\]

4.2.14. (R)-4-Methylpentan-2-ol 2n\(^{2b}\)

Following general procedure A, the reaction of 3-methylbutanal (22 μL, 0.2 mmol) with methyltrisopropoxypotassium (0.3 mL,
For some examples of natural product syntheses with a chiral methyl carbinol (a) Hatano, M.; Miyamoto, T.; Ishihara, K.
(b) Sokeirik, Y. S.; Mori, H.; Omote, M.; Sato, K.; Tarui, A.; Kumadaki, I.; Lecachey, B.; Fressigné, C.; Oulyadi, H.; Harrison-Marchand, A.; Maddaluno, T.
(c) Sato, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K.
(d) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R.
(e) Da, C.-S.; Wang, J.-R.; Yin, X.-G.; Fan, X.-Y.
(f) Harada, T.; Hiraoka, Y.; Kusukawa, T.
(g) Da, C.-S.; Yu, S.-L.; Yin, X.-G.; Wang, J.-R.
(h) Harada, T.; Hiraoka, Y.; Kusukawa, T.
(j) Madruga, M. A.; Riera, V.; Harutyunyan, S. R.; Minnaard, A. J.
(k) Nakajima, M.; Tomioka, K.; Koga, K.

**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**

1. For some examples of natural product syntheses with a chiral methyl carbinol majorite see: (a) Fernández-Mateos, E.; Maciá, B.; Yus, M.
2. For some general reviews on the addition of organozinc reagents to carbonyl derivatives—General procedure B
3. For some examples of the enantioselective addition of Me2Zn, see: (a) Wang, M. C.; Zhang, Q.-J.; Li, G.-W.; Liu, Z.-K.
4. Acknowledgements
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12. This methodology is also applicable to ketones when aryl Grignard reagents are used as nucleophiles. See reference.7


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


