Catalytic enantioselective addition of methyltriisopropoxititanium to aldehydes

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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,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 dimethylzinc3,4 trimethylaluminium5 and, more recently, with the more reactive methyl lithium6 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 carbonyls10 has also been described under catalytic conditions9a,11 using TADDOL,9a,11a,b H8-BINOL11e (for alkyl titanium reagents) or BINOL (for aryltitanium reagents)11c 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 ligands9a,11ab 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 organomagnesium7a,c,j and organoaluminium7c 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 procedures7e and chelating additives.7g 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 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(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)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 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 to cinnamic aldehyde

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>L1 (mol %)</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<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>Et2O</td>
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<td>&gt;99</td>
<td>97</td>
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<td>Et2O</td>
<td>RT</td>
<td>10</td>
<td>&gt;99</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>Et2O</td>
<td>0</td>
<td>100</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.

Under the optimized conditions, the scope of the addition of MeTi(OiPr)3 to benzaldehyde 1a in Et2O at 0 °C using (R)-BINOL as a chiral ligand (entry 6); very low conversion (11%) and enantioselectivity (24%) were obtained.

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(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 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-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 as a ligand and 2 equiv of MeTi(OiPr)₃ could be rectified by using L₁ as a ligand and 1.5 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-Chirasil-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 KGA]). The components were visualized by UV light (254 nm) and phosphomolybdic acid or K MnO₄ staining. Flash column chromatography was done using Geduran silica gel 60, 40–63 microns. 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 (R₅)-L₁ and (R₅)-L₂ were prepared according to literature procedures 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 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 methyltrisopropoxititanium (0.3 mL, 1.5 equiv, 1 M in THF) in the presence of (R₅)-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]D²⁶ = +47 (c 0.7, CHCl₃) [Lit. [α]D²⁶ = +47 (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: t₁(R) = 30.9 min (major enantiomer), t₁(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 methyltrisopropoxititanium (0.34 mL, 1.7 equiv, 1.0 M in THF) in the presence of (R₅)-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]D²⁶ = +33 (c 0.3, CHCl₃) [Lit. [α]D²⁶ = +24 (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: t₁(R) = 9.1 min, t₁(S) = 10.4 min (major enantiomer).

![Chemical structure](image-url)
[eluent Hex/EtOAc 9:1]. Yield: 92%. Ee: 84%. [\(\delta^{25} = +31\) (c 0.4, CHCl\(_3\))] \([\text{Lit.}^{15}][\delta^{25} = +30\) (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: \(t_c(R) = 29.7\) min, \(t_c(S) = 38.7\) min (major enantiomer).

4.2.9. (R)-1-(Thiophen-2-yl)ethanol 2\(I^{15}\)

Following general procedure A, the reaction of thiophene-2-carbaldehyde (9.4 \(\mu\)L, 0.1 mmol) with methyltriisopropoxypotassium (0.4 mL, 2.0 equiv, 1.0 M in THF) in the presence of \((R)_s\)-Py-BINMOL L\(I^{2}\) (7.5 mg, 0.1 equiv) in Et\(_2\)O (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%. [\(\delta^{25} = +12.5\) (c 0.8, CHCl\(_3\))] \([\text{Lit.}^{15}][\delta^{25} = +20\) (c 1.04, CHCl\(_3\))] for 96% ee. Ee determination by chiral GC analysis, CP-Chirasil-DEX CB column, \(T = 125^\circ\) C, \(P = 6\) psi, retention times: \(t_c(R) = 14.5\) min (major enantiomer), \(t_c(S) = 15.9\) min.

4.2.10. (R,E)-4-Phenylbut-3-en-2-ol 2\(J^{20}\)

Following general procedure A, the reaction of trans-cinnamaldehyde (25.2 \(\mu\)L, 0.2 mmol) with methyltriisopropoxypotassium (0.3 mL, 1.5 equiv, 1.0 M in THF) in the presence of \((R)_s\)-Py-BINMOL L\(2\) (7.5 mg, 0.1 equiv) in Et\(_2\)O (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%. [\(\delta^{25} = +35\) (c 0.6, CHCl\(_3\))] \([\text{Lit.}^{20}][\delta^{25} = +23\) (c 1.0, CH\(_2\)Cl\(_2\))] 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: \(t_c(S) = 14.2\) min, \(t_c(R) = 15.3\) min (major enantiomer).

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

Following general procedure A, the reaction of phenylacetaldelyde (12 \(\mu\)L, 0.1 mmol) with methyltriisopropoxypotassium (0.15 mL, 1.5 equiv, 1.0 M in THF) in the presence of \((R)_s\)-Py-BINMOL L\(2\) (3.8 mg, 0.1 equiv) in Et\(_2\)O (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%. [\(\delta^{25} = -35.4\) (c 0.7, CHCl\(_3\))] \([\text{Lit.}^{21}][\delta^{25} = -35.4\) (c 0.8, CHCl\(_3\))] for 99% ee. Ee determination by chiral GC analysis, CycloL\(\beta\) column, \(T = 85^\circ\) C, \(P = 15.9\) psi, retention times: \(t_c(S) = 76.0\) min, \(t_c(R) = 78.2\) min (major enantiomer).

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

Following general procedure A, the reaction of octanal (16.0 \(\mu\)L, 0.1 mmol) with methyltriisopropoxypotassium (0.15 mL, 1.5 equiv, 1.0 M in THF) in the presence of \((R)_s\)-Py-BINMOL L\(2\) (3.8 mg, 0.1 equiv) in Et\(_2\)O (1.5 mL) provided \((R)-2\)-nonanol (21 mg) as a colorless oil. Conversion: 99%. Ee: 90%. Ee was determined by chiral GC analysis on derivative 3.

4.2.13. (R)-1-Cyclohexylmethan-1-ol 2\(M^{23}\)

Following general procedure A, the reaction of cyclohexanecarbaldehyde (24 \(\mu\)L, 0.2 mmol) with methyltriisopropoxypotassium (0.3 mL, 1.5 equiv, 1.0 M in THF) in the presence of \((R)_s\)-Py-BINMOL L\(2\) (7.5 mg, 0.1 equiv) in Et\(_2\)O (1.6 mL) provided \((R)-1\)-cyclohexylmethan-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 2\(N^{2b}\)

Following general procedure A, the reaction of 3-methylbutanol (22 \(\mu\)L, 0.2 mmol) with methyltriisopropoxypotassium (0.3 mL,
1.5 equiv, 1.0 M in THF) in the presence of \((R\_S, S)\)-Py-BINMOL \(L2\) (7.5 mg, 0.1 equiv) in Et\(_2\)O (3.0 mL) provided \((R)\)-3-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 \(20\)\(^{34}\)

Following general procedure A, the reaction of pivaldehyde (11.0 \(\mu\)L, 0.1 mmol) with methyltrisopropoxymethyltin (0.20 mL, 2.0 equiv, 1.0 M in THF) in the presence of \((R\_S, S)\)-Ph-BINMOL \(L1\) (3.8 mg, 0.1 equiv) in Et\(_2\)O (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, \(T = 35^\circ C, P = 6 \text{ psi}\), retention times: \(t_1(R) = 96.3 \text{ min (major enantiomer)}, t_1(S) = 97.0 \text{ min}.

4.3. General procedure for the synthesis of the acetate derivatives—General procedure B

In a flame dried Schlenk tube, the corresponding aliphatic alcohol \(21, 2n\) or \(2n\) (0.2 mmol) was dissolved in anhydrous DCM (2 mL, 0.1 M) at 0 \(^\circ\)C after which Et\(_3\)N (56 \(\mu\)L, 0.4 mmol, 2 equiv), DMAP (2.6 mg, 0.02 mmol, 0.1 equiv) and acetic anhydride (44 \(\mu\)L, 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\(_2\)O (3 \(\times\) 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 \(35\)

Following the general procedure B, the reaction of product \(21\) (0.1 mmol) with Et\(_3\)N (35 \(\mu\)L, 0.25 mmol, 2.5 equiv), DMAP (1.2 mg, 0.01 mmol, 0.1 equiv) and acetic anhydride (24 \(\mu\)L, 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%. \(|\Delta\psi| = 5.6 \text{ (c 0.9, CHCl}_3\text{). Lit.}^{25} \psi = -3.8 \text{ (c 5.3, CHCl}_3\text{) for 91% ee}. Ee determination by chiral GC analysis, CP Chirasil-DEX CB column, \(T = 125^\circ C, P = 6 \text{ psi}\), retention time: \(t_1(S) = 10.6 \text{ min, } t_1(R) = 11.9 \text{ min (major enantiomer)}.

4.3.2. \((R)\)-1-Cyclohexylethyl acetate \(4^{26}\)

Following the general procedure B, the reaction of product 2n (0.2 mmol) with Et\(_3\)N (56 \(\mu\)L, 0.4 mmol, 2 equiv), DMAP (2.6 mg, 0.02 mmol, 0.1 equiv) and acetic anhydride (44 \(\mu\)L, 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, \(T = 100^\circ C, P = 6 \text{ psi}\), retention time: \(t_1(S) = 27.7 \text{ min, } t_1(R) = 34.3 \text{ 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\(_3\)N (56 \(\mu\)L, 0.4 mmol, 2 equiv), DMAP (2.6 mg, 0.02 mmol, 0.1 equiv) and acetic anhydride (44 \(\mu\)L, 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, \(T = 100^\circ C, P = 6 \text{ psi}\), retention time: \(t_1(S) = 4.9 \text{ min, } t_1(R) = 5.3 \text{ 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](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 moiety: see (a) Weber, B.; Seebach, D.

2. For some general reviews on the addition of organozinc reagents to carbonyl derivatives: see (b) Sabitha, G.; Reddy, C. S.; Yadav, J. S.

3. Following the general procedure B, the reaction of product 2l of \((R)\)-3,3-dimethylbutan-2-ol provided \((R)\)-3,3-dimethylbutan-2-ol. This product was volatile and could not be isolated.

4. Conversion: 78%. Ee: 93%. Ee determination by chiral GC analysis, CP Chirasil-DEX CB column, \(T = 35^\circ C, P = 6 \text{ psi}\), retention times: \(t_1(R) = 96.3 \text{ min (major enantiomer)}, t_1(S) = 97.0 \text{ min}.

5. B.M. and M.A.F.I. thank the R.S. for a travel grant. G. P. Howell is thanked for helpful comments on the manuscript.

6. For some general reviews on the use of stoichiometric amounts of ligands in the organocatalysis: see (a) Koga, K.; Tanaka, K.; Mackor, M.; Criegee, R.

7. Following the general procedure B, the reaction of product \(21\) provided \((R)\)-3,3-dimethylbutan-2-ol. This product was volatile and could not be isolated.

8. Conversion: 78%. Ee: 93%. Ee determination by chiral GC analysis, CP Chirasil-DEX CB column, \(T = 35^\circ C, P = 6 \text{ psi}\), retention times: \(t_1(R) = 96.3 \text{ min (major enantiomer)}, t_1(S) = 97.0 \text{ min}.

9. B.M. and M.A.F.I. thank the R.S. for a travel grant. G. P. Howell is thanked for helpful comments on the manuscript.

10. For some general reviews on the use of organocatalysts for asymmetric reactions: see (a) Zhang, Q.; Li, G.-W.; Liu, Z.-K.

11. Following the general procedure B, the reaction of product \(2n\) provided \((R)\)-4-methylpentan-2-ol. This product was volatile and could not be isolated.

12. Conversion: 77%. Ee: 90%. Ee was determined by chiral GC analysis on derivative 5.

13. Following the general procedure B, the reaction of product \(2n\) provided \((R)\)-4-methylpentan-2-ol. This product was volatile and could not be isolated.

14. Conversion: 78%. Ee: 93%. Ee determination by chiral GC analysis, CP Chirasil-DEX CB column, \(T = 35^\circ C, P = 6 \text{ psi}\), retention times: \(t_1(R) = 96.3 \text{ min (major enantiomer)}, t_1(S) = 97.0 \text{ min}.

15. B.M. and M.A.F.I. thank the R.S. for a travel grant. G. P. Howell is thanked for helpful comments on the manuscript.

16. B.M. and M.A.F.I. thank the R.S. for a travel grant. G. P. Howell is thanked for helpful comments on the manuscript.

17. Following the general procedure B, the reaction of product \(2n\) provided \((R)\)-4-methylpentan-2-ol. This product was volatile and could not be isolated.

18. Conversion: 78%. Ee: 93%. Ee determination by chiral GC analysis, CP Chirasil-DEX CB column, \(T = 35^\circ C, P = 6 \text{ psi}\), retention times: \(t_1(R) = 96.3 \text{ min (major enantiomer)}, t_1(S) = 97.0 \text{ min}.

19. B.M. and M.A.F.I. thank the R.S. for a travel grant. G. P. Howell is thanked for helpful comments on the manuscript.


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.


