Tetrahedron 71 (2015) 1202–1206

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Catalytic asymmetric arylation of aliphatic aldehydes using a B/Zn exchange reaction

Andressa M.M. Carlos, Maria Eduarda Contreira, Bruna S. Martins, Maira F. Immich, Angélica V. Moro, Diogo S. Lüdtke *

*Instituto de Química, Universidade Federal do Rio Grande do Sul, UFRGS, Av. Bento Gonçalves 9500, 91501-970 Porto Alegre, RS, Brazil*

ARTICLE INFO

*Article history:*
Received 26 November 2014
Received in revised form 8 January 2015
Accepted 9 January 2015
Available online 14 January 2015

*Keywords:*
Boron/zinc exchange
Amino alcohols
Stereoselectivity
Chiral secondary alcohols

ABSTRACT

Herein we describe the arylation of aliphatic aldehydes using the boron/zinc exchange reaction for the generation of transferable aryl groups, in the presence of chiral amino alcohol ligands. For the first time, a systematic investigation of this reaction using aliphatic aldehydes was developed and we have found that it proved to be significantly more challenging than the arylation of aromatic aldehydes. The corresponding chiral secondary alcohols were obtained in up to 73% ee.



## 1. Introduction

The catalytic asymmetric addition of organozinc reagents to aldehydes using is a powerful methodology for the synthesis of enantiopure chiral alcohols.[1] For instance, the reaction of diethylzinc with aldehydes proceeds slowly in the absence of any ligands. However, the addition of substoichiometric amount of a chiral ligand results in the formation of a new catalytic species that accelerates the ethyl transfer to aldehydes and might render it enantioselective.[2] The catalytic asymmetric addition of arylzinc reagents to aldehydes though, poses additional challenges since the uncatalyzed background aryl transfer reaction competes with the catalyzed pathway, requiring an efficient ligand turnover.[3] One of the best ways to perform such a reaction is through the generation mixed arylalkylzinc reagents through a boron/zinc exchange reaction between arylboronic acids and diethylzinc.[4] Using these conditions, a number of aryl groups can be stereoselectively transferred to aldehydes in the presence of catalytic amounts of chiral ligands.[5] Despite the success achieved in such reaction in recent years,[6] the main focus has been the asymmetric arylation of aromatic aldehydes and only scattered examples of the outcome of the arylation of aliphatic aldehydes have been described, usually with diminished enantioselectivities.[7] The main challenge associated with the addition to aliphatic aldehydes is their higher conformational flexibility that decreases the relative energies of the diastereomeric transition states that ultimately lead to the two enantiomers of a given product. Intrigued by the lack of data on the behavior of such aldehydes as electrophiles in asymmetric arylations, we decided to systematically investigate this reaction using easily synthesized chiral ligands that were already successfully employed in the synthesis of diarylmethanols. The ligands chosen possess different chiral backbones, which are based on acyclic amino acids,[8] pyrrolidine[9] and aziridine[10] derivatives, sugar-based amino alcohols,[11] and amino naphthols (Fig. 1).[12]

## 2. Results and discussion

We started our investigation by examining the impact of the ligand structure on the yield and enantioselectivity of the reaction. The phenyl transfer reaction to *n*-hexanal was selected as our standard reaction in order to compare the activities of our selected ligand set (Table 1). In all reactions, the B/Zn exchange was performed using arylboronic acid and diethylzinc, at 60 °C for 0.5 h.

We first tested ligands **L1** and **L2**, derived from L-phenylalanine and L-valine, respectively (Table 1, entries 1 and 7). The phenyl transfer reaction to hexanal was performed in the presence of 20 mol % of the amino alcohol, at 0 °C. Ligand **L1** resulted in better results of yield and enantiomeric excess, delivering the 1-phenyl-1-hexanol product in 80% isolated yield and 62% ee. With this promising result in hands, we changed the reaction conditions in an attempt to improve the performance of our catalytic system.

* Corresponding author. Tel.: +55 51 3308 9637; e-mail address: dsludtke@iq.ufrgs.br (D.S. Lüdtke).

http://dx.doi.org/10.1016/j.tet.2015.01.014
0040-4020/

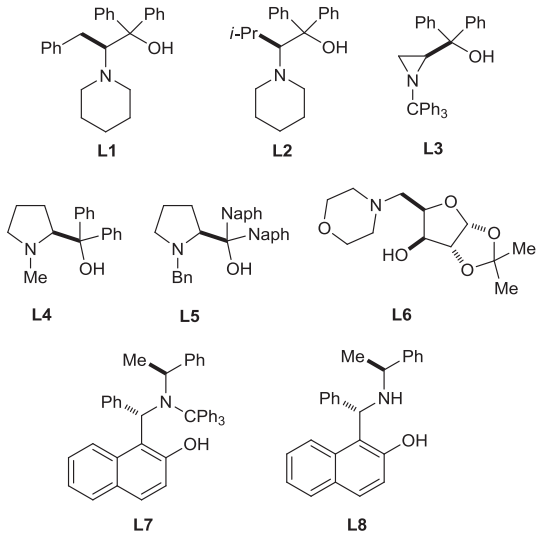
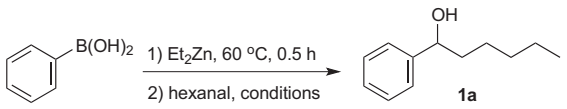



**Fig. 1.** Structures of ligands **L1**–**L8** evaluated.

However, decreasing the arylation temperature from 0 °C to −20 °C (entry 2) or −40 °C (entry 3) resulted in decreased yields and ees. Similarly, keeping the temperature at 0 °C and increasing the arylation time from 1 h to 2 h, resulted in an erosion of the ee of the product (entry 4). We also tried to decrease the ligand loading to 15 mol %, but a sharp decrease of the ee was observed (entry 6). Next, we evaluated three ligands possessing the nitrogen atom embedded in smaller rings: aziridino amino alcohol **L3** and the pyrrolidine amino alcohols **L4** and **L5**, which are derived from L-proline (entries 8–10). These ligands resulted in good conversions to the product, but no further improvement in the enantioselectivity of the arylation reaction was observed. Notably, the chiral secondary alcohol with the opposite absolute configuration was formed as the major product, despite the fact that the all ligands were prepared from the corresponding L-amino acids, the sense of enantioinduction is the opposite for ligands derived from acyclic and cyclic amino acids.[13] The sugar-based 1,3-amino alcohol ligand **L6** was also tested in the reaction and the product was obtained with good yield and modest ee (entry 11). Finally, Chan's amino naphthol ligands **L7** and **L8** were also used and **L8**, with a free N–H group delivered the best results in terms of both yield and ee (entries 12–16). Notably, using **L8**, the ligand loading could be reduced to 10 mol % without any loss of yield and enantioselectivity (entry 16). With **L1** and **L8** identified as the most effective ligands, we next examined their performance in the arylation of a broader range of aliphatic aldehydes. The results of these studies are presented in Table 2.

**Table 1**
Effect of the ligand structure on the arylation of *n*-hexanal




| Entry | Ligand (mol %) | Time (h) | Temperature (°C) | Yield[a] (%) | ee[b] (%) |
|---|---|---|---|---|---|
| 1 | **L1** (20) | 1 | 0 | 80 | 62 (*S*) |
| 2 | **L1** (20) | 4 | −20 | 60 | 55 (*S*) |
| 3 | **L1** (20) | 4 | −40 | 24 | 40 (*S*) |
| 4 | **L1** (20) | 2 | 0 | 85 | 49 (*S*) |
| 5 | **L1** (20) | 1 | 25 | 60 | 36 (*S*) |
| 6 | **L1** (15) | 1 | 0 | 74 | 36 (*S*) |
| 7 | **L2** (20) | 1 | 0 | 60 | 36 (*S*) |
| 8 | **L3** (20) | 2 | 0 | 86 | 61 (*R*) |
| 9 | **L4** (20) | 1 | 0 | 60 | 45 (*R*) |
| 10 | **L5** (20) | 1 | 0 | 58 | 56 (*R*) |
| 11 | **L6** (20) | 1 | 0 | 73 | 40 (*R*) |
| 12 | **L7** (20) | 2 | 0 | 73 | 52 (*S*) |
| 13 | **L8** (20) | 1 | 25 | 68 | 45 (*S*) |
| 14 | **L8** (20) | 1 | 0 | 85 | 62 (*S*) |
| 15 | **L8** (20) | 2 | 0 | 88 | 61 (*S*) |
| 16 | **L8** (10) | 2 | 0 | 84 | 60 (*S*) |

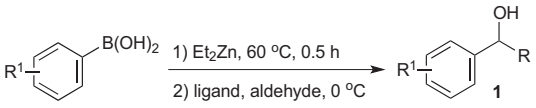
[a] Isolated yield.
[b] Enantiomeric excesses were determined by chiral HPLC, see Supplementary data for details.

We first examined the impact of aldehydes with longer alkyl chains. Therefore, *n*-octanal and *n*-decanal were employed (Table 2, entries 3–6), and we observed that with ligand **L8** the ee was decreased with these longer chain aldehydes, while with **L1** a decrease in the ee was observed for octanal, but essentially the same level of enantioselectivity was obtained with decanal and alcohol **1c** was isolated in 85% yield and 64% ee (entry 5). The same trend was observed with the use of the α-branched aldehyde *iso*-butyraldehyde (entries 7 and 8) whose phenylation resulted in the corresponding alcohol **1d** in 61% ee for **L1** and 40% ee for **L8**. An increase in the bulky of the side chain, by using pivalaldehyde, resulted in sluggish arylation and alcohol **1e** was obtained in disappointingly low yields, alongside with decomposition of the aldehyde (entries 9 and 10). On the other hand, *cyclo*-hexylcarboxaldehyde and *trans*-cinnamaldehyde underwent smooth arylation (entries 11–14) and the best results were achieved using ligand **L8**, which resulted in products **1f** and **1g** in 71% and 73% ee, respectively. Finally, we examined the scope of the arylation reaction regarding the substitution pattern of the starting arylboronic acid. Therefore, we performed the arylation of hexanal and *cyclo*-hexylcarboxaldehyde using 4-methoxyphenyl boronic acid, 4-chlorophenyl boronic acid, and 2-tolyl boronic acid, in order to evaluate the influence of electronic and steric effects on the arylation reagent. We have found that the presence of substituents at the transferable aryl group was best tolerated when using ligand **L1** and hexanal as the electrophile. When the electron-donating group methoxy was present, we observed an increase in the reactivity of the arylating agent and the products were obtained with higher yields, albeit with decreased ees (see entries 16, 21, and 22). Exception to this trend was observed with the reaction between 4-methoxyphenyl boronic acid and hexanal in the presence of **L1**, which resulted in product **1h** in 90% yield and an increased ee of 69% (entry 15). For the transfer of a 4-chlorophenyl group to hexanal, **L1** has shown the best results (entry 17, 65% yield, 69% ee) while for *cyclo*-hexylcarboxaldehyde **L8** was the most efficient (entry 24, 88% yield, 62% ee). Finally, the enantioselectivity of the reaction proved to be sensitive to steric effects at the aryl group and in all cases studied the products **1j** and **1m** were isolated in very low enantiomeric excesses (see entries 19, 20 and 25, 26).

## 3. Conclusions

In summary, we have studied the arylation of aliphatic aldehydes using the boron/zinc exchange reaction for the generation of transferable aryl groups, in the presence of chiral amino alcohol ligands. For the first time, a systematic investigation of this reaction using aliphatic aldehydes was developed and we have found that it proved to be significantly more challenging than the arylation of aromatic aldehydes. The lower reactivity toward nucleophilic addition, together with the higher conformational flexibility of the alkyl side chain, imposed additional hurdles that are reflected in small energetic differences in the diastereomeric transition states that lead to each enantiomers of the chiral secondary alcohol. Of significant note is that all ligands tested have been previously used in the arylation of aryl aldehydes, delivering the corresponding diarylmethanols in ees higher than 90%, therefore confirming that the arylation of more conformationally flexible electrophiles is far

**Table 2**
Scope of the arylation[a]



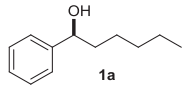
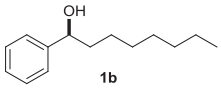
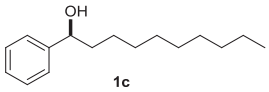
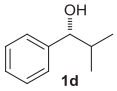
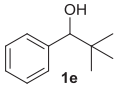
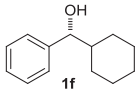
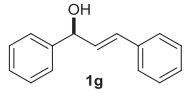
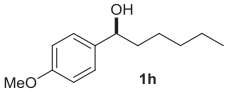
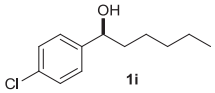
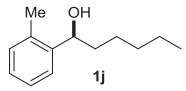
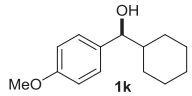
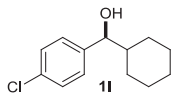
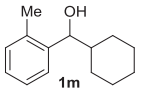

| Entry | Product | Ligand (mol %) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 |  | **L1** (20) | 80 | 62 |
| 2 | **1a** | **L8** (10) | 84 | 60 |
| 3 |  | **L1** (20) | 70 | 51 |
| 4 | **1b** | **L8** (10) | 75 | 41 |
| 5 |  | **L1** (20) | 85 | 64 |
| 6 | **1c** | **L8** (10) | 83 | 51 |
| 7 |  | **L1** (20) | 60 | 61 |
| 8 | **1d** | **L8** (10) | 57 | 40 |
| 9 |  | **L1** (20) | <10 | n.d. |
| 10 | **1e** | **L8** (10) | <10 | n.d. |
| 11 |  | **L1** (20) | 96 | 68 |
| 12 | **1f** | **L8** (10) | 80 | 71 |
| 13 |  | **L1** (20) | 68 | 24 |
| 14 | **1g** | **L8** (10) | 73 | 73 |
| 15 |  | **L1** (20) | 90 | 69 |
| 16 | **1h** | **L8** (10) | 63 | 41 |
| 17 |  | **L1** (20) | 65 | 69 |
| 18 | **1i** | **L8** (10) | 88 | 53 |
| 19 |  | **L1** (20) | 76 | 21 |
| 20 | **1j** | **L8** (10) | 90 | 2 |
| 21 |  | **L1** (20) | 80 | 27 |
| 22 | **1k** | **L8** (10) | 97 | 21 |
| 23 |  | **L1** (20) | 75 | 23 |
| 24 | **1l** | **L8** (10) | 88 | 62 |

**Table 2** (*continued*)

| Entry | Product | Ligand (mol %) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 25 |  | **L1** (20) | 37 | 21 (*S*) |
| 26 | **1m** | **L8** (10) | 83 | 14 (*R*) |

n.d.=not determined. Absolute configurations were assigned based on comparison with the literature.

[a] All reactions were performed on a 0.5 mmol scale with $PhB(OH)_2$ (2.4 equiv), $Et_2Zn$ (7.2 equiv) in toluene. For reactions performed using ligand **L1** (20 mol %) the reaction mixture was stirred at 0 °C for 1 h. For ligand **L8** (10 mol %), the reaction mixture was stirred at 0 °C for 2 h.

[b] Isolated yield.

[c] Enantiomeric excesses were determined by chiral HPLC, see Supplementary data for details.

from being just a mere extension of substrate scope. Further studies toward a better understanding of this behavior are underway.

## 4. Experimental

### 4.1. General

Hydrogen nuclear magnetic resonance spectra ($^1$H NMR) were obtained at 300 MHz and 400 MHz. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts ($\delta$) are reported in parts per million (ppm), referenced to the solvent peak of residual $CHCl_3$ or tetramethylsilane (TMS) as reference. Data are reported as follows: chemical shift ($\delta$), multiplicity, coupling constant ($J$) in hertz (Hz), and integrated intensity. Carbon-13 nuclear magnetic resonance spectra ($^{13}$C NMR) were obtained at 75 and 100 MHz. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in parts per million (ppm), referenced to the solvent peak $CDCl_3$. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), dd (double doublet), m (multiplet), and br s (broad singlet). Optical rotations were obtained on a Perkin Elmer 341 Polarimeter. Column chromatography was performed using silica gel (230–400 mesh) following the methods described by Still.[14] Thin layer chromatography (TLC) was performed using silica gel $GF_{254}$, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or phosphomolibdic acid, followed by heating. Air- and moisture-sensitive reactions were conducted in oven-dried glassware equipped with tightly fitted rubber septa and under a positive atmosphere of dry argon. Reagents and solvents were handled using standard syringe techniques. The chiral ligands used were prepared according to the following literature procedures, which are also described in Supplementary data: **L1** and **L2**;[8] **L3**;[11a] **L4**;[9] **L5**; **L6**;[10] **L7**[15] and **L8**.[12d]

### 4.2. General experimental procedure for the arylation reaction

In an atmosphere of argon 1.5 M solution of $Et_2Zn$ (7.2 equiv, 3.6 mmol, 2.4 mL) was slowly added to a solution of arylboronic acid (2.4 equiv, 1.2 mmol, 146 mg) in dry toluene (2 mL). The mixture was stirred at 60 °C for 0.5 h and after this period, cooled at room temperature and a solution of ligand (20 mol % **L1** and 10 mol % **L8**) in 1 mL of dry toluene was added. The reaction mixture was stirred for 15 min followed by addition of the aldehyde (0.5 mmol). After stirred at 0 °C for the time indicate in Table 2 the reaction mixture was carefully quenched at 0 °C by the addition of $NH_4Cl$ solution (satd, 10 mL) or HCl 1 M solution (**L8**). The aqueous layer was extracted with dichloromethane (3×15 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered,

and the solvent was evaporated in vacuum. The crude product was purified by flash chromatography using hexane/ethyl acetate (90:10) when **L1** was used or dichloromethane, when **L8** was used.

*4.2.1. (S)-1-Phenyl-1-hexanol (**1a**).* Colorless liquid.[7]
With **L1**: yield: 80%, 62% ee; $[\alpha]_D^{20}$ −20 (*c* 1, $CHCl_3$).
With **L8**: yield: 84%, 60% ee; $[\alpha]_D^{20}$ −20 (*c* 1, $CHCl_3$).
HPLC conditions: Chiralcel OD-H, hexane/IPA=99:1, 0.9 mL/min, UV 254 nm, (*R*): 19.2; (*S*): 22.4 min.
$^1$H NMR (300 MHz, $CDCl_3$): δ 7.33–7.26 (m, 5H), 4.62 (t, *J*=6.0, 1H), 2.08 (br s, 1H), 1.78–1.66 (m, 2H), 1.30–1.26 (m, 6H), 0.87 (t, *J*=6.8, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 144.9, 128.3, 127.3, 125.8, 74.6, 39.0, 31.6, 25.4, 22.5, 14.0.

*4.2.2. (S)-1-Phenyl-1-octanol (**1b**).* Colorless liquid.[16]
With **L1**: yield: 70%, 51% ee; $[\alpha]_D^{20}$ −16 (*c* 1, $CHCl_3$).
With **L8**: yield: 75%, 41% ee; $[\alpha]_D^{20}$ −8 (*c* 1, $CHCl_3$).
HPLC conditions: Chiralcel OD-H, Hexane/IPA=99:1, 0.9 mL/min, UV 254 nm, (*R*): 19.2; (*S*): 22.4 min.
$^1$H NMR (300 MHz, $CDCl_3$): δ 7.38–7.22 (m, 5H), 4.64 (t, *J*=5.8, 1H), 2.00 (br s, 1H), 1.88–1.59 (m, 2H), 1.51–1.16 (m, 10H), 0.86 (t, *J*=6.8, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 144.9, 128.3, 127.4, 125.8, 74.6, 39.0, 31.8, 29.4, 29.1, 25.8, 22.6, 14.0.

*4.2.3. (S)-1-Phenyl-1-decanol (**1c**).* Colorless liquid.[17]
With **L1**: yield: 85%, 64% ee; $[\alpha]_D^{20}$ −14 (*c* 1, $CHCl_3$).
With **L8**: yield: 83%, 51% ee; $[\alpha]_D^{20}$ −7 (*c* 1, EtOH).
HPLC conditions: Chiralcel OD-H, hexane/IPA=98:2, 1.0 mL/min, UV 254 nm, (*R*): 7.4 min; (*S*): 8.6 min.
$^1$H NMR (300 MHz, $CDCl_3$): δ 7.35–7.23 (m, 5H), 4.61 (t, *J*=6.5, 1H), 2.11 (br s, 1H), 1.79–1.63 (m, 2H), 1.38–1.24 (m, 14H), 0.88 (t, *J*=6.5, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 144.9, 128.3, 127.3, 125.8, 74.6, 39.0, 31.8, 29.5, 29.2, 25.8, 22.6, 14.0.

*4.2.4. (R)-2-Methyl-1-phenylpropan-1-ol (**1d**).* Colorless liquid.[18]
With **L1**: yield: 60%, 61% ee; $[\alpha]_D^{20}$ −15 (*c* 1, AcOEt).
With **L8**: yield: 57%, 40% ee; $[\alpha]_D^{20}$ −30 (*c* 1, $CHCl_3$).
HPLC conditions: Chiracel OD-H, hexane/IPA=90:10, 0.5 mL/min, UV 254 nm, (*R*): 11.8; (*S*): 10.8 min.
$^1$H NMR (300 MHz, $CDCl_3$): δ 7.33–7.25 (m, 5H), 4.34 (d, *J*=6.9, 1H), 2.02–1.87 (m, 2H), 0.99 (d, *J*=6.7, 3H), 0.78 (d, *J*=6.8, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 143.5, 128.1, 127.3, 126.5, 80.0, 35.2, 18.9, 18.2.

*4.2.5. (R)-1-Phenyl-1-cyclohexanol (**1f**).* White solid.[19]
With **L1**: yield: 96%, 68% ee; $[\alpha]_D^{20}$ −26 (*c* 1, $CHCl_3$).
With **L8**: yield: 80%, 71% ee; $[\alpha]_D^{20}$ −28 (*c* 1, $CHCl_3$).
HPLC conditions: Chiracel OD-H, hexane/IPA=99:1, 0.4 mL/min, UV 254 nm, (*S*): 46.0, (*R*): 60.1 min.
$^1$H NMR (300 MHz, $CDCl_3$): δ 7.34–7.25 (m, 5H), 4.36 (d, *J*=5.5, 1H), 2.03–1.92 (m, 1H), 1.82–1.57 (m, 5H), 1.40–0.94 (m, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 143.6, 128.1, 127.4, 126.6, 79.3, 44.9, 29.3, 28.8, 26.4, 26.1, 26.0.

*4.2.6. (S)-(E)-1,3-Diphenyl-prop-2-en-1-ol (**1g**).* Colorless liquid.[18]
With **L1**: yield: 68%, 24% ee; $[\alpha]_D^{20}$ −15 (*c* 1, $CHCl_3$).
With **L8**: yield: 73%, 73% ee; $[\alpha]_D^{20}$ −14 (*c* 1, EtOH).
HPLC conditions: Chiralcel OD-H, hexane/IPA=88:12, 1.0 mL/min, UV 254 nm, (*S*): 10.6, (*R*): 13.4 min.
$^1$H NMR (300 MHz, $CDCl_3$): δ 7.37–7.22 (m, 10H), 6.62 (dd, *J*=15.8, 0.6, 1H), 6.33 (dd, *J*=15.8, 6.5, 1H), 5.30 (d, *J*=6.5, 1H), 2.4 (br s, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 142.6, 136.4, 131.4, 130.4, 128.5, 128.4, 127.6, 126.5, 126.2, 74.9.

*4.2.7. (S)-1-(4-Methoxyphenyl)hexan-1-ol (**1h**).* White solid.[20]
With **L1**: yield: 90%, 69% ee; $[\alpha]_D^{20}$ −20 (*c* 1, $CHCl_3$).
With **L8**: yield: 66%, 41% ee; $[\alpha]_D^{20}$ −18 (*c* 1, $CHCl_3$).
HPLC conditions: Chiracel OB-H, hexane/IPA=95:5, 1.0 mL/min, UV, 254 nm, (*S*): 9.34; (*R*): 10.8 min.
$^1$H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, *J*=8.1, 2H), 6.88 (d, *J*=8.1, 2H), 4.61 (t, *J*=6.7, 1H), 3.81 (s, 3H), 1.85–1.56 (m, 4H), 1.34–1.27 (m, 5H), 0.86 (t, *J*=6.9, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 159.0, 137.1, 127.1, 113.8, 74.3, 55.3, 38.9, 31.7, 25.6, 22.6, 14.0.

*4.2.8. (S)-1-(4-Chlorophenyl)hexan-1-ol (**1i**).* White solid.[21]
With **L1**: yield: 65%, 69% ee; $[\alpha]_D^{20}$ −19 (*c* 1, $CHCl_3$).
With **L8**: yield: 63%, 53% ee; $[\alpha]_D^{20}$ −18 (*c* 1, $CHCl_3$).
HPLC conditions: Chiralcel AD-H, hexane/IPA=98:2, 0.5 mL/min, UV 254 nm, 36.32, 40.68 min.
$^1$H NMR (300 MHz, $CDCl_3$): δ 7.31–7.23 (m, 4H), 4.62 (t, *J*=6.6, 1H), 2.00 (br s, 1H), 1.77–1.61 (m, 2H), 1.40–1.26 (m, 6H), 0.86 (t, *J*=6.6, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 143.3, 133, 128.5, 127.2, 73.9, 39, 31.6, 25.3, 22.5, 13.9.

*4.2.9. (S)-1-(2-Methylphenyl)hexan-1-ol (**1j**).* White solid.[21]
With **L1**: yield: 76%, 21% ee; $[\alpha]_D^{20}$ −15 (*c* 1, $CHCl_3$).
With **L8**: yield: 68%, 2% ee; $[\alpha]_D^{20}$ −7 (*c* 1, $CHCl_3$).
HPLC conditions: Chiralcel AD-H, hexane/IPA=99:1, 0.8 mL/min, UV 254 nm, 15.70, 18.58 min.
$^1$H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, *J*=7.3, 1H), 7.23–7.09 (m, 3H), 4.90 (dd, *J*=7.3, 5.3, 1H), 2.32 (s, 3H), 1.89 (br s, 1H), 1.73–1.62 (m, 2H), 1.41–1.25 (m, 6H), 0.88 (t, *J*=6.5, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 143.0, 134.3, 130.2, 127.0, 126.0, 125.0, 70.6, 38.0, 31.7, 25.7, 22.5, 19.0, 14.0.

*4.2.10. (S)-1-(4-Methoxyphenyl)cyclohexan-1-ol (**1k**).* White solid.[22]
With **L1**: yield: 80%, 27% ee; $[\alpha]_D^{20}$ −13 (*c* 1, THF).
With **L8**: yield: 97%, 21% ee; $[\alpha]_D^{20}$ −21 (*c* 1, THF).
HPLC conditions: Chiralcel AS-H, hexane/IPA=97:3, 0.5 mL/min, UV 254 nm, 12.5, 18.3 min.
$^1$H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, *J*=8.5, 2H), 6.86 (d, *J*=8.5, 2H), 4.27 (d, *J*=7.4, 1H), 3.78 (s, 3H), 2.07–1.97 (m, 2H), 1.77–1.51 (m, 4H), 1.36–0.84 (m, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 158.8, 135.7, 127.7, 113.4, 78.9, 55.1, 44.8, 29.1, 29.0, 26.3, 26, 25.9.

*4.2.11. (S)-1-(4-Chlorophenyl)cyclohexan-1-ol (**1l**).* Colorless oil.[23]
With **L1**: yield: 75%, 23% ee; $[\alpha]_D^{20}$ −9 (*c* 1, $CHCl_3$).
With **L8**: yield: 88%, 62% ee; $[\alpha]_D^{20}$ −19 (*c* 1, $CHCl_3$).
HPLC conditions: Chiralcel OD-H, hexane/IPA=98:2, 0,5 L/min, UV 254 nm, (*S*) 19.83, (*R*) 25.02 min.
$^1$H NMR (300 MHz, $CDCl_3$): δ 7.29 (d, *J*=8.4, 2H), 7.20 (d, *J*=8.4, 2H), 4.32 (d, *J*=6.9, 1H), 2.10 (br s, 1H), 1.93–1.89 (m, 1H), 1.77–1.48 (m, 4H), 1.38–0.87 (m, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 141.9, 132.9, 128.2, 127.9, 78.5, 44.9, 29.1, 28.6, 26.3, 25.98, 25.90.

*4.2.12. (2-Methylphenyl)cyclohexan-1-ol (**1m**).* White solid.[22]
With **L1**: yield: 37%, 21% ee (*S*); $[\alpha]_D^{20}$ −21 (*c* 1, $CHCl_3$).
With **L8**: yield: 83%, 14% ee (*R*); $[\alpha]_D^{20}$ +4 (*c* 1, $CHCl_3$).
HPLC conditions: Chiralcel OD-H, hexane/IPA=97:3, 0.5 L/min, UV 254 nm, (*S*): 14.77, (*R*): 16.6 min.
$^1$H NMR (300 MHz, $CDCl_3$): δ 7.41 (d, *J*=7.2, 1H), 7.16–7.13 (m, 3H), 4.62 (d, *J*=7.1, 1H), 2.34 (s, 3H), 2.04–2.01 (m, 1H), 1.80–1.77 (m, 1H), 1.71–1.26 (m, 3H), 1.40–1.37 (m, 1H), 1.26–1.03 (m, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 141.9, 135.0, 130.2, 127.0, 126.2, 126.0, 75.1, 44.5, 29.5, 28.5, 26.4, 26.3, 26.0, 19.5.

## Acknowledgements

We are grateful to the following agencies for financial support: FAPERGS, CNPq, and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior.

## Supplementary data

Copies of NMR and IR spectra and HPLC chromatograms. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.01.014.

## References and notes


1. (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69; (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856; (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, NY, 1994. ISBN:978-0-471-57267-1; (d) Pu, L. *Tetrahedron* **2003**, *59*, 9873–9886; (e) Lemire, A.; Cote, A.; Janes, M. K.; Charette, A. B. *Aldrichimica Acta* **2009**, *43*, 71–83; (f) Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757–824; (g) Binder, C. M.; Singaram, B. *Org. Prep. Proced. Int.* **2011**, *43*, 139–208.
2. Walsh, P. J.; Kozlowski, M. C. *Fundamentals of Asymmetric Catalysis*; University Science Books: Sausalito, CA, 2009.
3. For leading references, see: (a) Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284–3308; (b) Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444–445; (c) Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7940–7956; (d) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muñiz, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3465–3467; (e) Fontes, M.; Verdaguer, X.; Solà, L.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 2532–2543.
4. (a) Seminal reference: Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850–14851; For earlier reports on the B/Zn exchange, see: (b) Srebnik, M. *Tetrahedron Lett.* **1991**, *32*, 2449–2452; (c) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*, 170–173; (d) Oppolzer, W.; Radinov, R. N. *J. Am. Chem. Soc.* **1993**, *115*, 1593–1594; (e) Langer, F.; Schwink, L.; Devasagayaraj, A.; Chavant, P. Y.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 8229–8243; (f) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4414–4435.
5. (a) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454–470; (b) Dimitrov, V.; Kostova, K. *Lett. Org. Chem.* **2006**, *3*, 176–182; (c) Paixão, M. W.; Braga, A. L.; Lüdtke, D. S. *J. Braz. Chem. Soc.* **2008**, *19*, 813–830.
6. For recent publications on the catalytic asymmetric arylation, see: (a) Pisani, L.; Bochicchio, C.; Superchi, S.; Scafato, P. *Eur. J. Org. Chem.* **2014**, 5939–5945; (b) Song, X.; Hua, Y.-Z.; Shi, J.-G.; Sun, P.-P.; Wang, M.-C.; Chang, J. *J. Org. Chem.* **2014**, *79*, 6087–6093; (c) Hatano, M.; Gouzu, R.; Mizuno, T.; Abe, H.; Yamada, T.; Ishihara, K. *Catal. Sci. Technol.* **2011**, *1*, 1149–1158; (d) Infante, R.; Nieto, J.; Andrés, C. *Org. Biomol. Chem.* **2011**, *9*, 6691–6699; (e) Schwab, R. S.; Soares, L. C.; Dornelles, L.; Rodrigues, O. E. D.; Paixão, M. W.; Godoi, M.; Braga, A. L. *Eur. J. Org. Chem.* **2010**, 3574–3578; (f) Godoi, M.; Alberto, E. E.; Paixão, M. W.; Soares, L. A.; Schneider, P. H.; Braga, A. L. *Tetrahedron* **2010**, *66*, 1341–1345; (g) DeBerardinis, A. M.; Turlington, M.; Ko, J.; Sole, M.; Pu, L. *J. Org. Chem.* **2010**, *75*, 2836–2850; For the use of the B/Zn exchange reaction in diastereoselective reactions, see: (h) Martins, B. S.; Lüdtke, D. S. *Eur. J. Org. Chem.* **2014**, 5364–5369; (i) Wouters, A. D.; Bessa, A. B.; Sachini, M.; Wessjohann, L. A.; Lüdtke, D. S. *Synthesis* **2013**, *45*, 2222–2233; (j) Wouters, A. D.; Lüdtke, D. S. *Org. Lett.* **2012**, *14*, 3962–3965; (k) Stanton, G. R.; Kauffman, M. C.; Walsh, P. J. *Org. Lett.* **2012**, *14*, 3368–3371; (l) Stanton, G. R.; Norrby, P.-O.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2012**, *134*, 17599–17604; (m) Stanton, G. R.; Koz, G.; Walsh, P. J. *J. Am. Chem. Soc.* **2011**, *133*, 7969–7976; (n) Stanton, G. R.; Johnson, C. N.; Walsh, P. J. *J. Am. Chem. Soc.* **2010**, *132*, 4399–4408.
7. For a related study on the Ru-catalyzed arylation of aliphatic aldehydes using aryl boronic acids see: Yamamoto, Y.; Shirai, T.; Watanabe, M.; Kurihara, K.; Miyaura, N. *Molecules* **2011**, *16*, 5020–5034.
8. Braga, A. L.; Lüdtke, D. S.; Vargas, F.; Paixão, M. W. *Chem. Commun.* **2005**, 2512–2514.
9. Braga, A. L.; Lüdtke, D. S.; Schneider, P. H.; Vargas, F.; Schneider, A.; Wessjohann, L. A.; Paixão, M. W. *Tetrahedron Lett.* **2005**, *46*, 7827–7830.
10. Wouters, A. D.; Trossini, G. H. G.; Stefani, H. A.; Lüdtke, D. S. *Eur. J. Org. Chem.* **2010**, 2351–2356.
11. (a) Braga, A. L.; Paixão, M. W.; Westermann, B.; Schneider, P. H.; Wessjohann, L. A. *J. Org. Chem.* **2008**, *73*, 2879–2882; (b) Braga, A. L.; Paixão, M. W.; Westermann, B.; Schneider, P. H.; Wessjohann, L. A. *Synlett* **2007**, 917–920.
12. (a) Ji, J. X.; Wu, J.; Au-Yeung, T. T. L.; Yip, C. W.; Haynes, K. R.; Chan, A. S. C. *J. Org. Chem.* **2005**, *70*, 1093–1095; (b) Lu, G.; Kwong, F. Y.; Ruan, J. W.; Li, Y. M.; Chan, A. S. C. *Chem.—Eur. J.* **2006**, *12*, 4115–4120; (c) Ruan, J. W.; Lu, G.; Xu, L.; Li, Y.; Chan, A. S. C. *Adv. Synth. Catal.* **2008**, *350*, 76–84; (d) Wei, H.; Yim, L.; Luo, H.; Li, X.; Chan, A. S. C. *Chirality* **2011**, *23*, 222–227.
13. Compare for example: (a) Ref. 8 and (b) Jimeno, C.; Sayalero, S.; Fjermestad, T.; Colet, G.; Maseras, F.; Pericàs, M. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 1098–1101 with: (c) Ref. 9 and (d) Moro, A. V.; Tiekink, E. R. T.; Zukerman-Schpector, J.; Lüdtke, D. S.; Correia, C. R. D. *Eur. J. Org. Chem.* **2010**, 3696–3703.
14. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
15. Trost, B. M.; Ngai, M.; Dong, G. *Org. Lett.* **2011**, *13*, 1900–1903.
16. Yong, H. K.; Taylor, J. N.; Chong, M. J. *Org. Lett.* **2002**, *4*, 3553–3556.
17. Fan, X. Y.; Yang, Y. X.; Zhuo, F. F.; Yu, S. L.; Li, X.; Guo, Q. P.; Du, Z. X.; Da, C. S. *Chem.—Eur. J.* **2010**, *16*, 7988–7991.
18. Diaz-Valenzuela, B. M.; Phillips, D. S.; France, B. M.; Gunn, E. M.; Clarke, L. M. *Chem.—Eur. J.* **2009**, *15*, 1227–1232.
19. Pu, L.; Qin, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 273–277.
20. Adair, G. R. A.; Williams, J. M. J. *Chem. Commun.* **2007**, 2608–2609.
21. Onodera, G.; Nishibayashi, Y.; Uemura, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3819–3822.
22. Kim, J. G.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4175–4178.
23. Li, Q.; Gau, H. M. *Chirality* **2011**, *23*, 929–939.