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Catalytic Enantioselective Addition of Aryl Grignard Reagents to Ketones

Emilio Fernández-Mateos,[a] Beatriz Maciá,*[b] and Miguel Yus*[a]

Dedicated to Professor Santos Fustero on occasion of his 65th birthday

Keywords: Synthetic methods / Homogeneous catalysis / Grignard reaction / Enantioselectivity / Ketones / Titanium

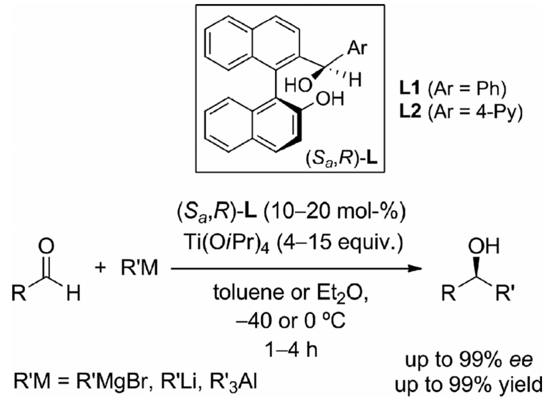
We report a catalytic system for the challenging enantioselective addition of aryl Grignard reagents to ketones. Using a simple, one-pot procedure under mild conditions, a wide range of aromatic ketones are converted into diaryl alcohols in good yields and with good enantioselectivities.

Introduction

The synthesis of chiral tertiary alcohols represents a major challenge in asymmetric catalysis.[1] The enantioselective addition of organometallic reagents to ketones is the most straightforward method for the preparation of this type of valuable motif.[2] For the addition of alkyl groups, this strategy has led to several studies where organozinc,[3] organotitanium,[3] and organoaluminum[4] reagents were effectively used as nucleophiles in catalytic processes. The higher reactivity of readily available and inexpensive Grignard reagents, however, has limited their application in catalytic asymmetric processes. With the exception of a very recent catalytic approach based on the use of a copper-diphosphine ligand,[5] the alkylation of ketones with Grignard reagents requires stoichiometric amounts of chiral ligand.[6]

Catalytic asymmetric propargylation with organoboron[7] or organolithium[8] reagents and allylation of ketones with organosilane[9] reagents have also been successful. For the addition of aryl groups to ketones,[10] some notable enantioselective catalytic methods have been developed in the past decade with organoaluminum,[11] organoboron,[12] organotitanium,[13] and organozinc[3a,14] reagents as the aryl nucleophiles. However, to the best of our knowledge, no catalytic approach allows the enantioselective addition of an aryl Grignard reagent to a ketone.

We have recently developed a catalytic system for the addition of Grignard,[15] organoaluminum,[16] and organolithium[17] reagents to aldehydes, based on the readily available chiral ligand **L1**[18] and an excess of titanium(IV) isopropoxide (Scheme 1). In addition, the challenging alkylation of aliphatic aldehydes with Grignard reagents was successfully achieved using **L2**[19] as ligand (Scheme 1). We envisioned that fine-tuning the ligand structure would further upgrade our catalytic system and make it suitable for less reactive substrates, such as ketones.



Scheme 1. Previous work on the enantioselective addition of organometallic reagents to aldehydes.

Results and Discussion

In this work, we describe the first catalytic approach for the enantioselective arylation of aromatic ketones with Grignard reagents to give valuable diarylmethanols.[20] The

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[a] Departamento de Química Orgánica and Instituto de Síntesis Orgánica, University of Alicante,
Aptdo. 99, 03080 Alicante, Spain
E-mail: yus@ua.es
http://iso.ua.es/personal/investigadores/miguel-yus-astiz.html
[b] Division of Chemistry & Environmental Science Manchester Metropolitan University,
Oxford Road, M1 5GD, Manchester, UK
E-mail: b.macia-ruiz@mmu.ac.uk
http://www.sste.mmu.ac.uk/staff/staffbiog/default.asp?StaffID=853

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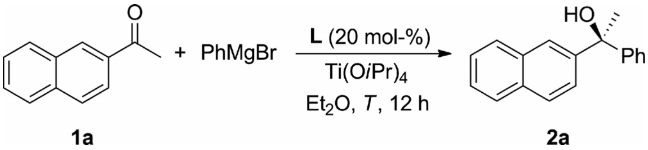
challenging formation of the new quaternary stereocenter takes place with good levels of enantioselectivity, despite the fact that the substrate and the nucleophile both have similar steric and electronic properties. The fact that this method uses readily accessible and inexpensive aryl Grignard reagents as nucleophiles gives it a big advantage over alternative approaches that rely on more expensive diarylzinc or organoboron reagents.

The starting point for our investigation was the modest 27% conversion and 24% *ee* that was obtained for the addition of PhMgBr to 1-(naphthalen-2-yl)ethanone (**1a**) under the previously reported conditions for the addition of Grignard reagents to aldehydes using **L2**[19] (Table 1, entry 1). To improve the conversion of the reaction, we increased the temperature from –20 to 0 °C, and observed not only a higher conversion (68%), but also a higher *ee* (46%; Table 1, entry 2). A thorough screening of solvents (including CH_2Cl_2, toluene, and *t*BuOMe) at different temperatures, was carried out (see the Supporting Information for further details),[21] and the use of diethyl ether at 0 °C gave the highest enantioselectivity. Next, the influence of the ligand was studied using a selection of Ar-BINMOL ligands (Figure 1) with different electronic and steric properties (Table 1, entries 3–9).[22] The use of Ph-BINMOL (**L1**) and the partially hydrogenated version H_8-**L1** gave low conversions and enantiomeric excesses (Table 1, entries 3 and 4). Methoxy-substituted Ar-BINMOLs **L3**–**L5** were also evaluated (Table 1, entries 5–7), but they proved to be inferior ligands to **L2** under the conditions tested. Finally, the arylation reaction of our model substrate **1a** could be improved to give 50% conversion and 74% *ee* (Table 1, entry 8) by using the bulky 1-naphthyl-BINMOL ligand **L6**. Interestingly, when 2-naphthyl-BINMOL ligand **L7** was used, the conversion and the *ee* both dropped, to 27 and 40%, respectively (Table 1, entry 9).

Table 1. Method optimization.[a]



Entry	L	*T* [°C]	Ti(O*i*Pr)$_4$ [equiv.]	PhMgBr [equiv.]	Conversion [%][b]	*ee* [%][c]
1	**L2**	–20	10	2.5	27	24
2	**L2**	0	10	2.5	68	46
3	**L1**	0	10	2.5	32	36
4	H_8-**L1**[d]	0	10	2.5	28	10
5	**L3**	0	10	2.5	30	46
6	**L4**	0	10	2.5	32	26
7	**L5**	0	10	2.5	41	20
8	**L6**	0	10	2.5	50	74
9	**L7**	0	10	2.5	27	40
10	**L6**	0	7.5	2.5	21	28
11	**L6**	0	12	2.5	22	70
12	**L6**	0	15	3.8	66	70

[a] Conditions: **1** (0.05 M; 0.1 mmol), PhMgBr (3 M in Et_2O; 2.5 equiv.), (S_a,*R*)-**L6** (20 mol-%), Ti(O*i*Pr)$_4$ (10 equiv.), Et_2O, 0 °C, 12 h. [b] Determined by GC–MS. [c] Determined by chiral HPLC (see the Supporting Information for details). [d] (S_a,*R*)-2′-[hydroxy(phenyl)methyl]-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthalen-2-ol.

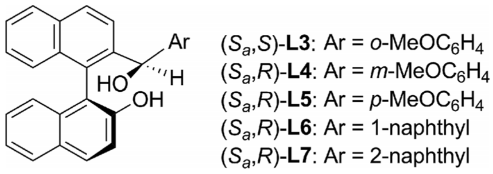


Figure 1. Chiral ligands used in this study.

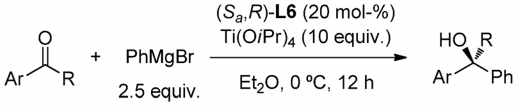
From our previous work on the catalytic enantioselective alkylation of aldehydes with Grignard reagents,[15,19] we know that the relative stoichiometry of Ti(O*i*Pr)$_4$ and RMgBr plays a very important role in the enantioselectivity of the reaction; therefore, we carried out a careful optimization of this parameter (Table 1, entries 10–12 and Tables S1–2 in the Supporting Information). In general, we observed that the use of less than 2.5 equiv. of PhMgBr led to poor conversions (Table S2 in the Supporting Information). For this reason, we set the amount of the nucleophile to this value, and screened different amounts of the titanium source (Table 1, entries 10–11 and Table S2 in the Supporting Information). Unfortunately, the use of less than 10 equiv. of Ti(O*i*Pr)$_4$ led to a detrimental drop in the enantioselectivity (Table 1, entry 10), while the use of a large excess of Ti(O*i*Pr)$_4$ (12 equiv.) impaired the conversion of the reaction (Table 1, entry 11). Increasing the amounts of the both the nucleophile and the Ti(O*i*Pr)$_4$ while keeping fixed optimal ratio of 1:4 resulted in a slightly improved conversion, but caused an small decrease in the enantioselectivity of the reaction (Table 1, entry 12 vs. 8).

Next, using the optimized reaction conditions, we carried out the addition of PhMgBr to different ketones (Table 2). The arylation reaction was achieved with moderate yields and good enantioselectivities (68–80% *ee*) for a wide variety of aryl methyl ketones, with both electron-poor and electron-rich substituents at the *meta* and *para* positions (Table 2, entries 1–7). The arylation of *o*-methylacetophenone was an exception; it gave a very low yield (12%; Table 2, entry 4) that did not improve with longer reaction times (24 h). This is probably due to steric hindrance close to the reactive site.

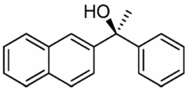
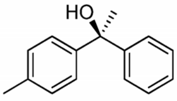
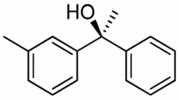
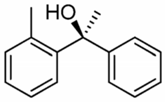
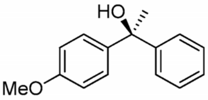
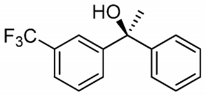
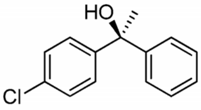
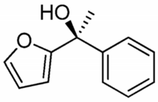
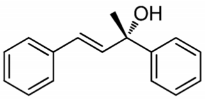
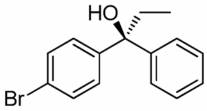
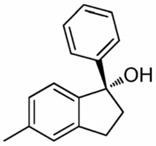
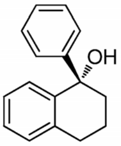
The reaction also worked with heteroaryl and α,β-unsaturated ketones, which gave very good yields in addition reactions with PhMgBr (Table 2, entries 8 and 9), although the enantioselectivities of these reactions were moderate.[23] Other alkyl aryl ketones were also examined. Increasing the size of one of the ketone substituents (an aryl ethyl ketone was used as substrate instead of an aryl methyl ketone) gave a better enantioselectivity but a lower yield (Table 2, entry 10).

Cyclic ketones, such as 5-methylindanone and 1-tetralone, were also tested under the optimized conditions.

Table 2. Addition of PhMgBr to different ketones.[a]



1 **2**

Entry	Product	Yield [%][b]	*ee* [%][c]
1	 **2a**	50	76 (*S*)
2	 **2b**	45	76 (*S*)
3	 **2c**	40	76 (*S*)
4	 **2d**	(12)[d]	n.d.
5	 **2e**	43	72 (*S*)
6	 **2f**	50	80 (*S*)
7	 **2g**	42	68 (*S*)
8	 **2h**	78	46 (*S*)
9	 **2i**	88	59 (*R*)
10	 **2j**	35	84 (*S*)
11	 **2k**	92	76 (*S*)
12	 **2l**	60	92 (*S*)

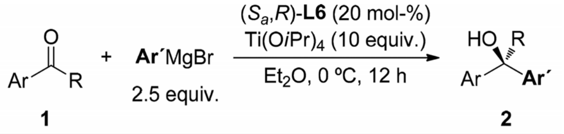
[a] Conditions: **1** (0.06 M; 0.5 mmol), PhMgBr (3 M in Et_2O; 2.5 equiv.), (S_a,*R*)-**L6** (20 mol-%), $Ti(OiPr)_4$ (10 equiv.), Et_2O, 0 °C, 12 h. [b] Isolated yield after flash silica gel chromatography. [c] Determined by chiral HPLC. Configuration based on literature data (see the Supporting Information for details). [d] Conversion determined by GC–MS.

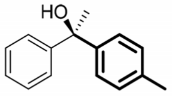
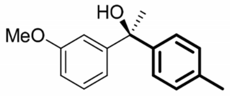
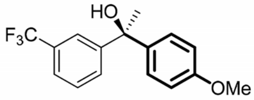
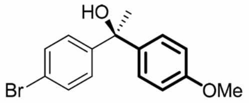
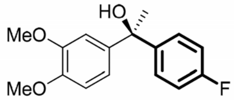
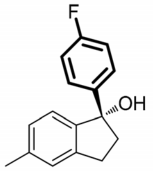
The addition of PhMgBr to the more rigid indanone derivative (Table 2, entry 11) proceeded with good enantioselectivity (76% *ee*) and in very high yield (92%). When the larger six-membered-ring tetralone was used, the best enantioselectivity of the series was obtained (92% *ee*, Table 2, entry 12) but with a decrease in the yield of the reaction (to 60%).

Different aryl Grignard reagents were also evaluated as nucleophiles in the reaction. The synthesis of chiral diaryl tertiary alcohols using Grignard reagents as the aryl source is a very attractive and interesting strategy due to the ready availability, facile synthesis, and inexpensive character of these organometallic species.

The addition of *p*-tolyl-, *p*-methoxy-, and (*p*-fluorophenyl)magnesium bromides to different acetophenone derivatives allowed the synthesis of alcohols **2b** and **2m**–**2p** (Table 3, entries 1–5) with enantioselectivities at the same levels as when PhMgBr was used as the nucleophile. It is worth noting that the addition of *p*-tolylmagnesium bromide to acetophenone gave **2b** with the opposite stereochemistry to when it was formed by the addition of phenylmagnesium bromide to *p*-methylacetophenone (Table 3, entry 1 vs. Table 2, entry 2), using the same chiral ligand [i.e., (S_a,*R*)-**L6**]. The *p*-methoxy-substituted Grignard reagent gave very good yields, the highest of all the experiments carried out in this study (Table 3, entries 3 and 4). The addition of (*p*-fluorophenyl)magnesium bromide to 5-methylindanone gave the corresponding alcohol (i.e., **2q**) in good yield and with good enantioselectivity (Table 3, entry 6).

Table 3. Addition of various Grignard reagents to ketones.[a]



Entry	Product	Yield [%][b]	*ee* [%][c]
1	 **2b**	54	66 (*R*)
2	 **2m**	40	77 (+)
3	 **2n**	96	82 (+)
4	 **2o**	>99	66 (+)
5	 **2p**	38	64 (-)
6	 **2q**	82	80 (+)

[a] Conditions: **1** (0.06 M; 0.5 mmol), ArMgBr (2 M in Et_2O; 2.5 equiv.), (S_a,*R*)-**L6** (20 mol-%), Ti(O*i*Pr)$_4$ (10 equiv.), Et_2O, 0 °C, 12 h. [b] Isolated yield after flash silica gel chromatography. [c] Determined by chiral HPLC. Configuration of known compounds based on literature data (see the Supporting Information for details).

Conclusions

In conclusion, we have developed an efficient enantioselective catalytic system for the addition of aryl Grignard reagents to ketones. This method allows the preparation of challenging optically active diaryl tertiary alcohols in a simple one-pot procedure using cheap and readily available organometallic reagents. A bulky 1-naphthyl-BINMOL ligand **L6** and an excess of titanium tetraisopropoxide were crucial to achieving good enantioselectivities. This work, together with previously developed methods for the addition of different organometallic reagents to aldehydes,[15–17,19] shows the versatility of Ar-BINMOLs for asymmetric additions to carbonyl compounds. We are working towards the expansion of the substrate scope (to include aliphatic ketones), and studying the mechanistic pathway of the reaction.

Experimental Section

General Information: Low-resolution mass spectra were recorded with a GC–MS spectrometer (Agilent Technologies® 6890N Network GC System) equipped with a HP-5MS column (Agilent Technologies®, 30 m × 0.25 mm), connected to an Agilent Technologies® 5973 Network mass-selective detector; or with a mass spectrometer (Agilent Technologies® 5973 Network) with a direct insertion probe (73DIP-1), equipped with a transmission quadrupole analyzer; the samples were ionized with an electron-impact source (70 eV). High-resolution mass spectra were obtained with a Waters® LCT Premier XE apparatus equipped with a time-of-flight (TOF) analyzer; the samples were ionized by ESI techniques, and introduced through an ultra-high pressure liquid chromatography (UPLC) Waters® Acquity H Class model. ^1H and ^{13}C NMR spectra were recorded with a Bruker® AC-300 instrument (300 and 75 MHz, respectively) using $CDCl_3$ as solvent. Chemical-shift values are reported in ppm relative to tetramethylsilane, and residual solvent signals were used as an internal standard ($CDCl_3$: $\delta = 7.26$ for ^1H NMR, $\delta = 77.0$ for ^{13}C NMR). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants [Hz], and integration. Optical rotations were measured with a Jasco® P-1030 Polarimeter with a 5 cm cell (*c* given in g/100 mL). IR spectra were recorded with a Jasco® FTIR – 4100 Fourier transform infrared spectrometer. Melting points were measured with a Reichtert® Thermovar hot-plate apparatus. Enantioselectivities were determined by HPLC analysis with an Agilent Technologies® 1100 Series HPLC instrument equipped with a G1315B diode array detector and a Quat Pump G1311A. The following chiral HPLC columns were used to determine the enantioselectivities of all of the chiral tertiary alcohols: Chiralcel OD-H, Chiralcel OJ, Chiralpak AD-H, Chiralpak AS-H, and Chiralpak IA.

All reactions were carried out under an argon atmosphere unless noted, using flame-dried glassware. Ti(O*i*Pr)$_4$ and anhydrous Et_2O [≥99.7 %, with 1 ppm of BHT (butylated hydroxytoluene) as inhibitor] were purchased from Sigma–Aldrich®, and stored under an argon atmosphere once opened. Panreac® Silica gel 60 (40–63 μm) was used in the purification process of all products. Machery-Nagel® TLC silica gel 60, 0.20 mm, was used, and components were visualized using UV light and phosphomolybdic acid (1 g/24 mL EtOH) staining. Phenylmagnesium bromide (3.0 M in Et_2O), *p*-tolylmagnesium bromide (1.9 M in Et_2O), (4-fluorophenyl)magnesium bromide (2.0 M in Et_2O), and (4-methoxyphenyl)magnesium bromide (1.9 M in Et_2O) were prepared from the corresponding aryl bromide and magnesium turnings in anhydrous Et_2O following standard procedures, and were stored under an argon atmosphere. Grignard reagents were titrated using 2-butanol and catalytic amounts of 1,10-phenanthroline in anhydrous THF. Ketones were used without any purification, except for 2-acetylfuran and 1-tetralone, which were distilled in a Kugelrohr apparatus (Büchi® Glass Oven B-585) immediately before use. Ligands **L1**–**L7** and H_8-**L1** were prepared according to known procedures,[15–17,19] but further details can be also found in the Supporting Information of this manuscript. Racemic tertiary alcohols were synthesized by the reaction of the corresponding ketone (1.0 mmol) and ArMgBr (1.5 mmol) in anhydrous THF at 0 °C.

Synthesis of Chiral Tertiary Alcohols: (S_a,*R*)-**L6** (42.7 mg, 0.1 mmol) was dissolved in anhydrous Et_2O (6.0 mL) in a flame-dried Schlenk tube under an argon atmosphere. The solution was cooled down to 0 °C, and Ti(O*i*Pr)$_4$ (1.53 mL, 5.0 mmol, 10 equiv.) was added. After 5 min, ArMgBr (1.25 mmol, 2.5 equiv.) was added. The mixture was stirred for an additional 15 min, then the corresponding ketone (0.5 mmol) was added. The reaction mixture was stirred at 0 °C for 12 h. The reaction was quenched at 0 °C by the addition of water (5 mL) and HCl (1 M aq.; 3 mL). The mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were neutralized with saturated aqueous $NaHCO_3$ (2 × 10 mL), dried with $MgSO_4$, and concentrated under vacuum. The crude product was purified by chromatography on flash silica gel to give the desired products (i.e., **2a**–**2q**).

(*S*)-1-(Naphthalen-2-yl)-1-phenylethanol (2a):[11a] Compound **2a** was obtained after purification by flash silica gel chromatography (hexane/EtOAc, 100:0 to 96:4) as a colorless viscous oil (50% yield, 76% *ee*). $[\alpha]_D^{25}$ = –9.7 (*c* = 1.0, CH_2Cl_2) {ref. $[\alpha]_D^{25}$ = –16.1 (*c* = 1.0, CH_2Cl_2) for 92% *ee*}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.96 (s, 1 H), 7.87–7.77 (m, 2 H), 7.75 (d, *J* = 8.7 Hz, 1 H), 7.49–7.37 (m, 5 H), 7.36–7.18 (m, 3 H), 2.32 (br. s, 1 H), 2.04 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.7, 145.2, 133.0, 132.4, 129.6, 128.23, 128.20, 127.9, 127.5, 127.0, 126.1, 125.9, 124.9, 123.7, 115.3, 76.4, 30.7 ppm. LRMS (EI-DIP): *m*/*z* (%) = 249 (10) [M + 1]$^+$, 248 (52) [M]$^+$, 234 (18), 233 (100), 205 (11), 155 (15), 128 (11), 127 (23), 105 (74), 77 (20), 43 (19). *ee* determination by chiral HPLC analysis (Chiralcel OJ column, hexane/*i*PrOH, 80:20, flow rate: 1.0 mL/min, λ = 220 nm): $t_R(S)$ = 14.7 min (major enantiomer), $t_R(R)$ = 18.5 min.

(*S*)-1-Phenyl-1-(*p*-tolyl)ethanol (2b):[14b] Compound **2b** was obtained after purification by flash silica gel chromatography (hexane/EtOAc, 100:0 to 95:5) as a pale yellow oil (45% yield, 76% *ee*). $[\alpha]_D^{25}$ = –7.5 (*c* = 1.0, CH_2Cl_2) {ref. $[\alpha]_D^{25}$ = +16.0 (*c* = 1.2, CH_2Cl_2) for 96% *ee*}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.36 (m, 2 H), 7.34–7.19 [m, (including at 7.29 ppm, d, *J* = 8.0 Hz), 5 H], 7.11 (d, *J* = 8.0 Hz, 2 H), 2.32 (s, 3 H), 2.21 (br. s, 1 H), 1.92 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.2, 145.1, 136.6, 128.8, 128.1, 126.8, 125.8, 76.1, 30.8, 21.0 ppm. LRMS (EI): *m*/*z* (%) = 212 (7) [M]$^+$, 198 (16), 197 (100), 194 (11), 179 (14), 178 (11), 119 (22), 105 (35), 91 (14), 77 (13). *ee* determination by chiral HPLC analysis (Chiralpak AD-H column, hexane/*i*PrOH, 99:1, flow rate: 0.5 mL/min, λ = 210 nm): $t_R(R)$ = 46.1 min, $t_R(S)$ = 48.7 min (major enantiomer).

(*S*)-1-Phenyl-1-(*m*-tolyl)ethanol (2c):[14b] Compound **2c** was obtained after purification by flash silica gel chromatography (hexane/EtOAc, 100:0 to 97:3) as a pale yellow oil (40% yield, 76% *ee*). $[\alpha]_D^{27}$ = –4.6 (*c* = 1.0, CH_2Cl_2) {ref. $[\alpha]_D^{25}$ = –14.3 (*c* = 1.2, CH_2Cl_2) for 86% *ee*}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.38 (m, 2 H), 7.35–7.26 (m, 2 H), 7.27–7.22 (m, 2 H), 7.18 (m, 2 H), 7.09–7.02 (m, 1 H), 2.32 (s, 3 H), 2.19 (br. s, 1 H), 1.93 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.1, 147.9, 137.7, 128.1, 128.0, 127.7, 126.9, 126.5, 125.8, 122.9, 76.2, 30.9, 21.6 ppm. LRMS (EI): *m*/*z* (%) = 212 (7) [M]$^+$, 198 (16), 197 (100), 194 (10), 179 (14), 178 (11), 119 (16), 105 (42), 91 (14), 77 (13). *ee* determination by chiral HPLC analysis (Chiralpak IA column, hexane/*i*PrOH, 99:1, flow rate: 0.5 mL/min, λ = 210 nm): $t_R(S)$ = 38.8 min (major enantiomer), $t_R(R)$ = 45.6 min.

(*S*)-1-(4-Methoxyphenyl)-1-phenylethanol (2e):[11a] Compound **2e** was obtained after purification by flash silica gel chromatography (hexane/EtOAc, 100:0 to 94:6) as a pale yellow oil (43% yield, 72% *ee*). $[\alpha]_D^{28}$ = –12.3 (*c* = 1.0, CH_2Cl_2) {ref. $[\alpha]_D^{25}$ = –14.6 (*c* = 0.7, CH_2Cl_2) for 90% *ee*}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.36 (m, 2 H), 7.35–7.27 [m (including at 7.32 ppm, d, *J* = 8.9 Hz), 4 H], 7.27–7.18 (m, 1 H), 6.83 (d, *J* = 8.9 Hz, 2 H), 3.78 (s, 3 H), 2.18 (br. s, 1 H), 1.92 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.5, 148.3, 140.3, 128.1, 127.1, 126.8, 125.7, 113.4, 75.9, 55.2, 31.0 ppm. LRMS (EI): *m*/*z* (%) = 228 (7) [M]$^+$, 213 (46), 211 (17), 210 (100), 209 (12), 195 (52), 179 (12), 178 (11), 167 (15), 166 (11), 165 (33), 152 (23), 151 (10), 135 (12), 105 (16), 77 (10). *ee* determination by chiral HPLC analysis (Chiralcel OJ column, hexane/*i*PrOH, 80:20, flow rate: 1.0 mL/min, λ = 210 nm): $t_R(R)$ = 17.0 min, $t_R(S)$ = 20.7 min (major enantiomer).

(*S*)-1-Phenyl-1-[3-(trifluoromethyl)phenyl]ethanol (2f):[11a] Compound **2f** was obtained after purification by flash silica gel chromatography (hexane/EtOAc, 100:0 to 94:6) as a yellow viscous oil (50% yield, 80% *ee*). $[\alpha]_D^{24}$ = +18.5 (*c* = 1.0, CH_2Cl_2) {ref. $[\alpha]_D^{25}$ = +24.8 (*c* = 4.5, CH_2Cl_2) for 93% *ee*}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.76 (s, 1 H), 7.54 (d, *J* = 7.8 Hz, 1 H), 7.50 (d, *J* = 7.8 Hz, 1 H), 7.44–7.21 (m, 6 H), 2.26 (br. s, 1 H), 1.96 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.0, 147.0, 130.4 (q, $J_{C,F}$ = 32.1 Hz), 129.4, 128.6, 128.4, 127.4, 125.8, 124.3 (q, $J_{C,F}$ = 272.0 Hz), 123.7 (q, $J_{C,F}$ = 3.6 Hz), 122.4 (q, $J_{C,F}$ = 3.5 Hz), 76.0, 30.8 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –62.5 ppm. LRMS (EI): *m*/*z* (%) = 266 (3) [M]$^+$, 252 (16), 251 (100), 173 (49), 145 (17), 105 (9), 77 (9). *ee* determination by chiral HPLC analysis (Chiralcel OD-H column, hexane/*i*PrOH, 96:4, flow rate: 1.0 mL/min, λ = 220 nm): $t_R(R)$ = 9.6 min, $t_R(S)$ = 11.2 min (major enantiomer).

(*S*)-1-(4-Chlorophenyl)-1-phenylethanol (2g):[11a] Compound **2g** was obtained after purification by flash silica gel chromatography (hexane/EtOAc, 100:0 to 97:3) as a colorless oil (42% yield, 68% *ee*). $[\alpha]_D^{28}$ = +6.3 (*c* = 1.0, CH_2Cl_2) {ref. $[\alpha]_D^{25}$ = +8.8 (*c* = 3.2, CH_2Cl_2) for 92% *ee*}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.30 [m (including at 7.33 ppm, d, *J* = 8.9 Hz), 5 H], 7.30–7.19 [m (including at 7.26 ppm, d, *J* = 8.9 Hz, 4 H], 2.24 (br. s, 1 H), 1.92 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.4, 146.5, 132.7, 128.3, 128.2, 127.3, 127.2, 125.7, 75.9, 30.8 ppm. LRMS (EI): *m*/*z* (%) = 232 (7) [M]$^+$, 219 (33), 218 (15), 217 (100), 141 (12), 139 (38), 111 (10), 105 (19), 77 (13). *ee* determination by chiral HPLC analysis (Chiralpak AD-H column, hexane/*i*PrOH, 99:1, flow rate: 1.0 mL/min, λ = 230 nm): $t_R(R)$ = 16.5 min, $t_R(S)$ = 17.8 min (major enantiomer).

(*S*)-1-(Furan-2-yl)-1-phenylethanol (2h):[2b] Compound **2h** was obtained after purification by flash silica gel chromatography (hexane/EtOAc, 100:0 to 95:5) as a yellow oil (78% yield, 46% *ee*). $[\alpha]_D^{29}$ = –16.5 (*c* = 1.0, CH_2Cl_2) {ref. $[\alpha]_D^{22}$ = –34.1 (*c* = 5.4, CH_2Cl_2) for 96% *ee*}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.22 (m, 6 H), 6.33 (dd, *J* = 3.2, 1.8 Hz, 1 H), 6.24 (dd, *J* = 3.2, 0.8 Hz, 1 H), 2.54 (br. s, 1 H), 1.87 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.9, 145.8, 142.1, 128.1, 127.3, 125.2, 110.0, 106.2, 73.0, 29.2 ppm. LRMS (EI): *m*/*z* (%) = 188 (32) [M]$^+$, 174 (12), 173 (100), 171 (12), 170 (36), 169 (12), 141 (28), 115 (23), 111 (15), 105 (16), 95 (65), 77 (17). *ee* determination by chiral HPLC analysis (Chiralcel OD-H column, hexane/*i*PrOH, 99:1, flow rate: 0.5 mL/min, λ = 220 nm): $t_R(R)$ = 30.1 min, $t_R(S)$ = 33.4 min (major enantiomer).

(*R*,*E*)-2,4-Diphenylbut-3-en-2-ol (2i):[24] Compound **2i** was obtained after purification by flash silica gel chromatography (hexane/EtOAc, 100:0 to 95:5) as a pale yellow oil (88% yield, 59% *ee*). $[\alpha]_D^{26}$ = –9.7 (*c* = 1.0, $CHCl_3$) {ref. $[\alpha]_D^{22}$ = –12.7 (*c* = 2.5, $CHCl_3$) for 81% *ee*}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 8.2 Hz, 2 H), 7.41–7.17 (m, 8 H), 6.64 (d, *J* = 16.1 Hz, 1 H), 6.50 (d, *J* = 16.1 Hz, 1 H), 2.06 (br. s, 1 H), 1.75 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.6, 136.7, 136.3, 128.5, 128.3, 127.7, 127.6, 127.1, 126.5, 125.2, 74.7, 29.8 ppm. LRMS (EI): *m*/*z* (%) = 224 (14) [M]$^+$, 209 (12), 206 (48), 205 (24), 203 (12), 202 (10), 191 (21), 182 (17), 181 (100), 178 (10), 166 (12), 165 (15), 131 (15), 129 (12), 128 (18), 105 (20), 103 (22), 91 (29), 77 (21). *ee* determination by chiral HPLC analysis (Chiralpak AS-H column, hexane/*i*PrOH, 99:1, flow rate: 0.5 mL/min, λ = 230 nm): $t_R(S)$ = 20.0 min, $t_R(R)$ = 21.9 min (major enantiomer).

(*S*)-1-(4-Bromophenyl)-1-phenylpropan-1-ol (2j):[14b] Compound **2j** was obtained after purification by flash silica gel chromatography (hexane/EtOAc, 100:0 to 98:2) as a pale yellow oil (35% yield, 84% *ee*). $[\alpha]_D^{29}$ = +8.7 (c = 1.0, CH_2Cl_2) {ref. $[\alpha]_D^{25}$ = +9.9 (c = 1.7, CH_2Cl_2) for 80% *ee*}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.41 (d, J = 8.8 Hz, 2 H), 7.38 (d, J = 8.8 Hz, 2 H), 7.35–7.17 (m, 5 H), 2.28 (q, J = 7.3 Hz, 2 H), 2.05 (s, 1 H), 0.87 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.4, 145.9, 131.1, 128.3, 128.0, 127.0, 126.0, 120.7, 78.2, 34.3, 8.0 ppm. LRMS (EI): m/z (%) = 291 (<1) $[M]^+$, 264 (14), 263 (97), 262 (15), 261 (100), 185 (32), 183 (33), 105 (30), 77 (16). *ee* determination by chiral HPLC analysis (Chiralpak IA column, hexane/*i*PrOH, 99:1, flow rate: 0.5 mL/min, λ = 230 nm): $t_R(R)$ = 48.6 min, $t_R(S)$ = 53.7 min (major enantiomer).

(+)-5-Methyl-1-phenyl-2,3-dihydro-1*H*-inden-1-ol (2k): Compound **2k** was obtained after purification by flash silica gel chromatography (hexane/EtOAc, 100:0 to 95:5) as a yellow viscous oil (92% yield, 76% *ee*). $[\alpha]_D^{29}$ = +13.6 (c = 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.19 (m, 5 H), 7.13 (s, 1 H), 7.02 (d, J = 7.7 Hz, 1 H), 6.96 (d, J = 7.7 Hz, 1 H), 3.21–3.04 (dt, J = 16.0, 7.3 Hz, 1 H), 2.98–2.81 (dt, J = 16.0, 6.4 Hz, 1 H), 2.51–2.41 (m, 2 H), 2.36 (s, 3 H), 2.11 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.5, 145.2, 144.3, 138.3, 128.0, 127.9, 126.8, 125.7, 125.5, 123.7, 85.2, 45.0, 29.8, 21.4 ppm. IR (ATR): $\tilde{\nu}$ = 3381, 2938, 1612, 1492, 1446, 1047 cm^{-1}. LRMS (EI): m/z (%) = 224 (<1) $[M]^+$, 222 (15), 194 (44), 193 (30), 180 (20), 179 (100), 178 (55), 165 (8), 89 (11). HRMS (ESI): calcd. for $C_{16}H_{15}$ $[M - OH]^+$ 207.1174; found 207.1183. *ee* determination by chiral HPLC analysis (Chiralcel OD-H column, hexane/*i*PrOH, 96:4, flow rate: 1.0 mL/min, λ = 220 nm): $t_R(R)$ = 7.8 min, $t_R(S)$ = 10.3 min (major enantiomer).

(*S*)-1-Phenyl-1,2,3,4-tetrahydronaphthalen-1-ol (2l):[25] Compound **2l** was obtained after purification by flash silica gel chromatography (hexane/EtOAc, 100:0 to 97:3) as a yellow viscous oil (60% yield, 92% *ee*). $[\alpha]_D^{27}$ = –29.5 (c = 1.0, $CHCl_3$) {ref. $[\alpha]_D^{22}$ = –32.0 (c = 4.2, $CHCl_3$) for >99% *ee*}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–6.99 (m, 9 H), 2.94–2.84 (m, 2 H), 2.19 (br. s, 1 H), 2.16–2.09 (m, 2 H), 2.05–1.91 (m, 1 H), 1.86–1.70 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.9, 142.0, 137.6, 128.9, 128.8, 127.7, 127.5, 126.6, 126.44, 126.38, 75.3, 41.4, 29.9, 19.6 ppm. LRMS (EI): m/z (%) = 224 (22) $[M]^+$, 207 (14), 206 (75), 205 (11), 196 (22), 195 (100), 191 (16), 178 (14), 165 (12), 147 (59), 146 (15), 129 (11), 128 (11), 105 (10), 91 (26), 77 (15). *ee* determination by chiral HPLC analysis (Chiralcel OD-H column, hexane/*i*PrOH, 99:1, flow rate: 1.0 mL/min, λ = 220 nm): $t_R(R)$ = 9.7 min, $t_R(S)$ = 13.2 min (major enantiomer).

(+)-1-(3-Methoxyphenyl)-1-(*p*-tolyl)ethanol (2m): Compound **2m** was obtained after purification by flash silica gel chromatography (hexane/EtOAc, 100:0 to 96:4) as a yellow oil (40% yield, 77% *ee*). $[\alpha]_D^{29}$ = +15.8 (c = 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.29 (d, J = 8.2 Hz, 2 H), 7.21 (dd, J = 8.2, 7.8 Hz, 1 H), 7.11 (d, J = 8.2 Hz, 2 H), 7.01 (dd, J = 2.6, 1.7 Hz, 1 H), 6.94 (ddd, J = 7.8, 1.7, 0.9 Hz, 1 H), 6.76 (ddd, J = 8.2, 2.6, 0.9 Hz, 1 H), 3.77 (s, 3 H), 2.31 (s, 3 H), 2.21 (br. s, 1 H), 1.91 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4, 149.9, 144.9, 136.6, 129.1, 128.8, 125.7, 118.3, 111.9, 76.0, 55.2, 30.8, 21.0 ppm. IR (ATR): $\tilde{\nu}$ = 3452, 2925, 1600, 1485, 1432, 1253 cm^{-1}. LRMS (EI): m/z (%) = 242 (37) $[M]^+$, 228 (17), 227 (100), 224 (12), 135 (31), 119 (57), 91 (15). HRMS (ESI): calcd. for $C_{16}H_{17}O$ $[M - OH]^+$ 225.1279; found 225.1290. *ee* determination by chiral HPLC analysis (Chiralcel OJ column, hexane/*i*PrOH, 90:10, flow rate: 1.0 mL/min, λ = 210 nm): $t_R(S)$ = 22.1 min (major enantiomer), $t_R(R)$ = 27.3 min.

(+)-1-(4-Methoxyphenyl)-1-[3-(trifluoromethyl)phenyl]ethanol (2n): Compound **2n** was obtained after purification by flash silica gel chromatography (hexane/EtOAc, 100:0 to 91:9) as a yellow viscous oil (96% yield, 82% *ee*). $[\alpha]_D^{29}$ = +32.5 (c = 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.75 (s, 1 H), 7.53 (d, J = 7.7 Hz, 1 H), 7.49 (d, J = 7.7 Hz, 1 H), 7.40 (t, J = 7.7 Hz, 1 H), 7.31 (d, J = 8.9 Hz, 2 H), 6.85 (d, J = 8.9 Hz, 2 H), 3.79 (s, 3 H), 2.22 (br. s, 1 H), 1.94 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.8, 149.4, 139.3, 130.4 (q, $J_{C,F}$ = 32.1 Hz), 129.3, 128.5, 127.2, 124.2 (q, $J_{C,F}$ = 272.3 Hz), 123.6 (q, $J_{C,F}$ = 3.8 Hz), 122.3 (q, $J_{C,F}$ = 3.8 Hz), 113.7, 75.7, 55.3, 31.0 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –62.4 ppm. IR (ATR): $\tilde{\nu}$ = 3456, 2962, 1611, 1510, 1327, 1254, 1162, 1119 cm^{-1}. LRMS (EI): m/z (%) = 296 (19) $[M]^+$, 282 (17), 281 (100), 278 (15), 173 (56), 151 (19), 145 (18), 135 (10). HRMS (ESI): calcd. for $C_{16}H_{14}F_3O$ $[M - OH]^+$ 279.0997; found 279.0995. *ee* determination by chiral HPLC analysis (Chiralcel OD-H column, hexane/*i*PrOH, 99:1, flow rate: 1.0 mL/min, λ = 220 nm): $t_R(R)$ = 18.9 min, $t_R(S)$ = 19.9 min (major enantiomer).

(+)-1-(4-Bromophenyl)-1-(4-methoxyphenyl)ethanol (2o): Compound **2o** was obtained after purification by flash silica gel chromatography (hexane/EtOAc, 100:0 to 90:10) as a yellow viscous oil (>99% yield, 66% *ee*). $[\alpha]_D^{29}$ = +15.8 (c = 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.41 (d, J = 8.8 Hz, 2 H), 7.28 (d, J = 7.2 Hz, 2 H), 7.25 (d, J = 7.2 Hz, 2 H), 6.83 (d, J = 8.8 Hz, 2 H), 3.77 (s, 3 H), 2.26 (br. s, 1 H), 1.88 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.6, 147.4, 139.6, 131.1, 127.6, 127.1, 120.7, 113.5, 75.6, 55.2, 30.8 ppm. IR (ATR): $\tilde{\nu}$ = 3449, 2974, 1608, 1509, 1509, 1248, 1176 cm^{-1}. LRMS (EI): m/z (%) = 308 (17) $[M + 1]^+$, 307 (3) $[M]^+$, 306 (17), 294 (14), 293 (92), 292 (16), 291 (100), 290 (34), 288 (34), 185 (32), 183 (33), 166 (17), 165 (25), 151 (18), 135 (26). HRMS (ESI): calcd. for $C_{15}H_{14}BrO$ $[M - OH]^+$ 289.0228; found 289.0227. *ee* determination by chiral HPLC analysis (Chiralcel OJ column, hexane/*i*PrOH, 97:3, flow rate: 1.0 mL/min, λ = 230 nm): $t_R(S)$ = 58.0 min (major enantiomer), $t_R(R)$ = 63.0 min.

(–)-1-(3,4-Dimethoxyphenyl)-1-(4-fluorophenyl)ethanol (2p): Compound **2p** was obtained after purification by flash silica gel chromatography (hexane/EtOAc, 100:0 to 75:25) as a yellow viscous oil (38% yield, 64% *ee*). $[\alpha]_D^{29}$ = –4.8 (c = 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36 (dd, ^3J = 9.0, $J_{H,F}$ = 5.4 Hz, 2 H), 6.98 (t, $^3J \approx J_{H,F}$ = 9.0 Hz, 2 H), 6.94 (d, J = 2.1 Hz, 1 H), 6.89 (dd, J = 8.4, 2.1 Hz, 1 H), 6.79 (d, J = 8.4 Hz, 1 H), 3.86 (s, 3 H), 3.81 (s, 3 H), 2.28 (br. s, 1 H), 1.91 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.6 (d, $J_{C,F}$ = 245.4 Hz), 148.6, 148.0, 143.9 (d, $J_{C,F}$ = 2.9 Hz), 140.5, 127.5 (d, $J_{C,F}$ = 8.0 Hz), 117.9, 114.7 (d, $J_{C,F}$ = 21.2 Hz), 110.4, 109.5, 75.7, 55.8, 31.2 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –116.2 ppm. IR (ATR): $\tilde{\nu}$ = 3505, 2933, 1735, 1601, 1505, 1255, 1222, 1143 cm^{-1}. LRMS (EI): m/z (%) = 276 (38) $[M]^+$, 261 (50), 259 (19), 258 (100), 243 (13), 183 (19), 171 (13), 170 (11), 123 (75), 121 (14). HRMS (ESI): calcd. for $C_{16}H_{16}FO_2$ $[M - OH]^+$ 259.1134; found 259.1126. *ee* determination by chiral HPLC analysis (Chiralcel OJ column, hexane/*i*PrOH, 85:15, flow rate: 1.0 mL/min, λ = 210 nm): $t_R(R)$ = 21.6 min, $t_R(S)$ = 37.5 min (major enantiomer).

(+)-1-(4-Fluorophenyl)-5-methyl-2,3-dihydro-1*H*-inden-1-ol (2q): Compound **2q** was obtained after purification by flash silica gel chromatography (hexane/EtOAc, 100:0 to 96:4) as a yellow viscous oil (82% yield, 80% *ee*). $[\alpha]_D^{29}$ = +17.5 (c = 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35 (dd, ^3J = 9.0, $J_{H,F}$ = 5.4 Hz, 2 H), 7.14 (s, 1 H), 7.04 (d, J = 7.7 Hz, 1 H), 6.98 (t, $^3J \approx J_{H,F}$ = 9.0 Hz, 2 H), 6.95 (d, J = 7.7 Hz, 1 H), 3.12 (dt, J = 16.0, 7.2 Hz, 1 H), 2.88 (dt, J = 16.0, 6.4 Hz, 1 H), 2.43 (dd, J = 7.2, 6.4 Hz, 2 H), 2.37 (s, 3 H), 2.06 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.8 (d, $J_{C,F}$ = 245.0 Hz), 145.0, 144.3, 142.2 (d, $J_{C,F}$ = 3.0 Hz), 138.6, 128.0, 127.4 (d, $J_{C,F}$ = 8.0 Hz), 125.6, 123.6, 114.7 (d, $J_{C,F}$ = 21.2 Hz), 84.9, 45.1, 29.7, 21.4 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –116.6 ppm. IR (ATR): $\tilde{\nu}$ = 3384, 2940, 1602, 1506, 1221, 1157 cm^{-1}. LRMS (EI-DIP): m/z (%) = 243 (17) $[M + 1]^+$, 242 (100) $[M]^+$, 241 (50), 228 (11), 227 (68), 226 (30), 225 (50), 224 (21), 212 (12), 210 (11), 209 (16), 207 (10), 183 (14), 148 (11), 147 (99), 133 (11), 123 (15), 105 (11), 95 (17), 91 (11). HRMS (ESI): calcd. for $C_{16}H_{14}F$ $[M - OH]^+$ 225.1080; found 225.1078. *ee* determination by chiral HPLC analysis (Chiralcel OD-H column, hexane/*i*PrOH, 96:4, flow rate: 1.0 mL/min, λ = 220 nm): $t_R(R)$ = 7.1 min, $t_R(S)$ = 9.5 min (major enantiomer).

Supporting Information (see footnote on the first page of this article): Synthesis of ligands **L1**–**L7** and H_8-**L1**, additional data (optimization), and spectroscopic and chromatographic data for compounds **2**.

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[1] a) E. N. Jacobsen, A. Pfaltz, H. Yamamoto, *Comprehensive Asymmetric Catalysis*, Suppl. 2, Springer-Verlag, Berlin, **2004**; b) P. J. Walsh, M. C. Kozlowski, *Fundamentals of Asymmetric Catalysis*, University Science Books, California, **2009**; c) V. Caprio, J. M. J. Williams, *Catalysis in Asymmetric Synthesis* 2nd ed., Wiley, Chichester, United Kingdom, **2009**.

[2] a) M. Shibasaki, M. Kanai, *Chem. Rev.* **2008**, *108*, 2853–2873. For alternative methods for the synthesis of chiral tertiary alcohols, see: b) J. L. Stymiest, V. Bagutski, R. M. French, V. K. Aggarwal, *Nature* **2008**, *456*, 778–782; c) H. K. Scott, V. K. Aggarwal, *Chem. Eur. J.* **2011**, *17*, 13124–13132; d) R. Kourist, P. Domínguez de María, U. T. Bornscheuer, *ChemBioChem* **2008**, *9*, 491–498; e) M. Paravidino, J. Holt, D. Romano, N. Singh, I. W. C. E. Arends, A. J. Minnaard, R. V. A. Orru, F. Molinari, U. Hanefeld, *J. Mol. Catal. B* **2010**, *63*, 87–92.

[3] a) P. I. Dosa, G. Fu, *J. Am. Chem. Soc.* **1998**, *120*, 445–446; b) D. J. Ramón, M. Yus, *Tetrahedron Lett.* **1998**, *39*, 1239–1242; c) H. Li, P. J. Walsh, *J. Am. Chem. Soc.* **2004**, *126*, 6538–6539; d) D. J. Ramón, M. Yus, *Angew. Chem. Int. Ed.* **2004**, *43*, 284–287; *Angew. Chem.* **2004**, *116*, 286–289; e) S.-J. Jeon, H. Li, C. García, L. K. LaRochelle, P. J. Walsh, *J. Org. Chem.* **2005**, *70*, 448–455; f) E. F. DiMauro, M. C. Kozlowski, *J. Am. Chem. Soc.* **2002**, *124*, 12668–12669; g) D. K. Friel, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2008**, *130*, 9942–9951; for reviews, see: h) L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757–824; i) C. M. Binder, B. Singaram, *Org. Prep. Proced. Int.* **2011**, *43*, 139–208; j) M. Hatano, K. Ishihara, *Synthesis* **2008**, 1647–1675; k) O. Riant, J. Hannedouche, *Org. Biomol. Chem.* **2007**, *5*, 873–888.

[4] a) J. Siewert, R. Sandmann, P. von Zezschwitz, *Angew. Chem. Int. Ed.* **2007**, *46*, 7122–7124; *Angew. Chem.* **2007**, *119*, 7252–7254; for an example of the addition of vinylboron reagents to ketones, see: b) D. B. Biradar, H.-M. Gau, *Org. Lett.* **2009**, *11*, 499–502.

[5] a) F. Caprioli, A. V. R. Madduri, A. J. Minnaard, S. R. Harutyunyan, *Chem. Commun.* **2013**, *49*, 5450–5452; b) A. V. R. Madduri, A. J. Minnaard, S. R. Harutyunyan, *Angew. Chem. Int. Ed.* **2012**, *51*, 3164–3167; *Angew. Chem.* **2012**, *124*, 3218–3221; c) A. V. R. Madduri, A. J. Minnaard, S. R. Harutyunyan, *Chem. Commun.* **2012**, *48*, 1478–1480; d) A. V. R. Madduri, A. J. Minnaard, S. R. Harutyunyan, *Org. Biomol. Chem.* **2012**, *10*, 2878–2884.

[6] a) R. Noyori, M. Kitamura, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49–69; *Angew. Chem.* **1991**, *103*, 34–55; b) M. R. Luderer, W. F. Bailey, M. R. Luderer, J. D. Fair, R. J. Dancer, M. B. Sommer, *Tetrahedron: Asymmetry* **2009**, *20*, 981–998; c) J. L. von dem Bussche-Huennefeld, D. Seebach, *Tetrahedron* **1992**, *48*, 5719–5730; d) B. Weber, D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 84–86; *Angew. Chem.* **1992**, *104*, 96–97.

[7] K. R. Fandrick, D. R. Fandrick, J. T. Reeves, J. Gao, S. Ma, W. Li, H. Lee, N. Grinberg, B. Lu, C. H. Senanayake, *J. Am. Chem. Soc.* **2011**, *133*, 10332–10335.

[8] a) K. Tanaka, K. Kukita, T. Ichibakase, S. Kotani, M. Nakajima, *Chem. Commun.* **2011**, *47*, 5614–5616; b) S. Kotani, K. Kukita, K. Tanaka, T. Ichibakase, M. Nakajima, *J. Org. Chem.* **2014**, DOI: 10.1021/jo5005394.

[9] For a review of allylation reactions, see: M. Yus, J. C. González-Gómez, F. Foubelo, *Chem. Rev.* **2011**, *111*, 7774–7854.

[10] Some examples of the arylation of aldehydes, with organosilane reagents, see: a) D. Tomita, R. Wada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 4138–4139; with organoboron reagents: b) D. Tomita, M. Kanai, M. Shibasaki, *Chem. Asian J.* **2006**, *1*, 161–166; c) C. Bolm, J. Rudolph, *J. Am. Chem. Soc.* **2002**, *124*, 14850–14851; d) J.-X. Ji, J. Wu, T. T.-L. Au-Yeung, C.-W. Yip, R. K. Haynes, A. S. C. Chan, *J. Org. Chem.* **2005**, *70*, 1093–1095; e) A. L. Braga, D. S. Lüdtke, F. Vargas, M. W. Paixão, *Chem. Commun.* **2005**, 2512–2514; f) S. Özçubukçu, F. Schmidt, C. Bolm, *Org. Lett.* **2005**, *7*, 1407–1409; g) S. Dahmen, M. Lormann, *Org. Lett.* **2005**, *7*, 4597–4600; with Grignard reagents: h) X.-Y. Fan, Y.-X. Yang, F.-F. Zhuo, S.-L. Yu, X. Li, Q.-P. Guo, Z.-X. Du, C.-S. Da, *Chem. Eur. J.* **2010**, *16*, 7988–7991; i) C.-S. Da, J.-R. Wang, X.-G. Yin, X.-Y. Fan, Y. Liu, S.-L. Yu, *Org. Lett.* **2009**, *11*, 5578–5581; Y. Muramatsu, T. Harada, *Chem. Eur. J.* **2008**, *14*, 10560–10563; j) D. Itakura, T. Harada, *Synlett* **2011**, 2875–2879; with organozinc reagents: k) L. Salvi, J. G. Kim, P. J. Walsh, *J. Am. Chem. Soc.* **2009**, *131*, 12483–12493; l) J. G. Kim, P. J. Walsh, *Angew. Chem. Int. Ed.* **2006**, *45*, 4175–4178; *Angew. Chem.* **2006**, *118*, 4281–4284; with organoaluminium reagents: m) K.-H. Wu, H.-M. Gau, *J. Am. Chem. Soc.* **2006**, *128*, 14808–14809; with organotitanium reagents (see also ref.[6c]): n) B. Weber, D. Seebach, *Tetrahedron* **1994**, *50*, 7473−7484; o) K.-H. Wu, S. Zhou, C.-A. Chen, M.-C. Yang, R.-T. Chiang, C.-R. Chen, H.-M. Gau, *Chem. Commun.* **2011**, *47*, 11668−11670; with organolithium: p) Y. Nakagawa, Y. Muramatsu, T. Harada, *Eur. J. Org. Chem.* **2010**, 6535−6538; q) L. Zhang, L. Sun, Y.-Y. Li, Y. Liu, Y.-X. Yang, R. Yuan, P. Wang, C.-S. Da, *ChemCatChem* **2013**, *5*, 3516−3519; r) A. Uenishi, Y. Nakagawa, H. Osumi, *Chem. Eur. J.* **2013**, *19*, 4896−4905.

[11] a) C.-A. Chen, K.-H. Wu, H.-M. Gau, *Adv. Synth. Catal.* **2008**, *350*, 1626–1634; b) C.-A. Chen, K.-H. Wu, H.-M. Gau, *Angew. Chem. Int. Ed.* **2007**, *46*, 5373–5376; *Angew. Chem.* **2007**, *119*, 5469–5472.

[12] a) R. Shintani, M. Inoue, T. Hayashi, *Angew. Chem. Int. Ed.* **2006**, *45*, 3353–3356; *Angew. Chem.* **2006**, *118*, 3431–3434; b) A. Iuliano, S. Facchetti, T. Funaioli, *Chem. Commun.* **2009**, 457–459; c) H. Lai, Z. Huang, Q. Wu, Y. Qin, *J. Org. Chem.* **2009**, *74*, 283–288.

[13] K.-H. Wu, Y.-Y. Kuo, C.-A. Chen, Y.-L. Huang, H.-M. Gau, *Adv. Synth. Catal.* **2013**, *355*, 1001–1008.

[14] a) M. Hatano, T. Miyamoto, K. Ishihara, Org. Lett. **2007**, *9*, 4535–4538; b) V. J. Forrat, O. Prieto, D. J. Ramón, M. Yus, *Chem. Eur. J.* **2006**, *12*, 4431–4445; c) C. García, P. J. Walsh, *Org. Lett.* **2003**, *5*, 3641–3644; d) V. J. Forrat, D. J. Ramón, M. Yus, *Tetrahedron: Asymmetry* **2009**, *20*, 65–67; e) O. Prieto, D. J. Ramón, M. Yus, *Tetrahedron: Asymmetry* **2003**, *14*, 1955–1957.

[15] E. Fernández-Mateos, B. Maciá, D. J. Ramón, M. Yus, *Eur. J. Org. Chem.* **2011**, *34*, 6851–6855.

[16] E. Fernández-Mateos, B. Maciá, M. Yus, *Tetrahedron: Asymmetry* **2012**, *23*, 789–794.

[17] E. Fernández-Mateos, B. Maciá, M. Yus, *Eur. J. Org. Chem.* **2012**, *20*, 3732–3736.

[18] a) L.-S. Zheng, K.-Z. Jiang, Y. Deng, X.-F. Bai, G. Gao, F.-L. Gu, L.-W. Xu, *Eur. J. Org. Chem.* **2013**, *4*, 748–755; b) G. Gao, X.-F. Bai, H.-M. Yang, J.-X. Jiang, G.-Q. Lai, L.-W. Xu, *Eur. J. Org. Chem.* **2011**, 5039–5046; c) G. Gao, F.-L. Gu, J.-X. Jiang, K. Jiang, C.-Q. Sheng, G.-Q. Lai, L.-W. Xu, *Chem. Eur. J.* **2011**, *17*, 2698–2703; d) S.-I. Kiyooka, T. Tsutsui, T. Kira, *Tetrahedron Lett.* **1996**, *37*, 8903–8904.

[19] E. Fernández-Mateos, B. Maciá, M. Yus, *Adv. Synth. Catal.* **2013**, *355*, 1249–1254.

[20] V. Andrushko, N. Andrushko, *Stereoselective Synthesis of Drugs and Natural Products*, Wiley-Blackwell, John Wiley & Sons, Chichester, **2013**.

[21] Different additives [$AlMe_3$, LiBr, and 2,2-oxybis(*N*,*N*-dimethylethanamine) (BDMAEE)] were also tested in the model reaction without any success; see the Supporting Information for further details.

[22] (*S*)-BINOL was also used as a ligand, and no conversion was observed under the optimized reaction conditions {**1a** (0.1 mmol, 0.05 M), PhMgBr (3 M in Et_2O, 2.5 equiv.), (*S*)-BINOL (20 mol-%), Ti(O*i*Pr)$_4$ (10 equiv.), Et_2O, 0 °C, 24 h}.

[23] Lower temperatures (–20 °C) were tested to try to improve the enantioselectivity, but no reaction took place.

[24] T. Ueda, K. Tanaka, T. Ichibakase, Y. Orito, M. Nakajima, *Tetrahedron* **2010**, *66*, 7726–7731.

[25] G. Jaouen, A. Meyer, *J. Am. Chem. Soc.* **1975**, *97*, 4667–4672.

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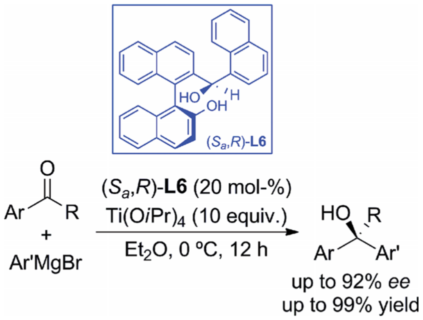
Asymmetric Catalysis

The catalytic enantioselective addition of aryl Grignard reagents to ketones is now possible. Using a readily available Ar-BINMOL ligand and titanium(IV) isopropoxide in a simple, one-pot procedure under mild conditions, a wide range of aromatic ketones are converted into diaryl alcohols in good yields and with good enantioselectivities.



E. Fernández-Mateos, B. Maciá,*
M. Yus* **1–9**

Catalytic Enantioselective Addition of Aryl Grignard Reagents to Ketones

Keywords: Synthetic methods / Homogeneous catalysis / Grignard reaction / Enantioselectivity / Ketones / Titanium