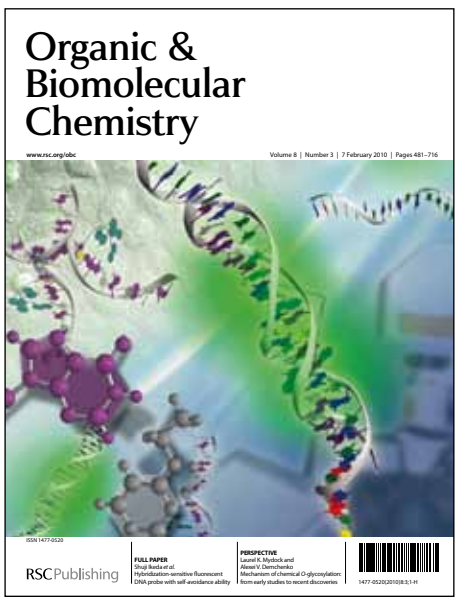
Organic & Biomolecular Chemistry

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the RSC Publishing peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, which is prior to technical editing, formatting and proof reading. This free service from RSC Publishing allows authors to make their results available to the community, in citable form, before publication of the edited article. This *Accepted Manuscript* will be replaced by the edited and formatted *Advance Article* as soon as this is available.

To cite this manuscript please use its permanent Digital Object Identifier (DOI®), which is identical for all formats of publication.

More information about *Accepted Manuscripts* can be found in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics contained in the manuscript submitted by the author(s) which may alter content, and that the standard **Terms & Conditions** and the **ethical guidelines** that apply to the journal are still applicable. In no event shall the RSC be held responsible for any errors or omissions in these *Accepted Manuscript* manuscripts or any consequences arising from the use of any information contained in them.

Organic & Biomolecular Chemistry

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

PAPER

Copper-dipyridylphosphine-catalyzed hydrosilylation: Enantioselective synthesis of aryl- and heteroaryl cycloalkyl alcohols†

Shan-Bin Qi,[a] Min Li,[a] Shijun Li,[a] Ji-Ning Zhou,[a] Jun-Wen Wu,[a] Feng Yu,[a] Xi-Chang Zhang,[a] Albert S. C. Chan[b] and Jing Wu*[a]

Received (in XXX, XXX) Xth XXXXXXXXX 200X, Accepted Xth XXXXXXXXX 200X
DOI: 10.1039/b000000x

The non-precious metal copper-catalyzed enantioselective hydrosilylation of a vast array of aryl cycloalkyl ketones with different ring sizes was studied systematically for the first time (up to 99% enantiomeric excess). The results demonstrated that the steric size of cycloalkyl group has a significant influence on the reaction outcomes. The first stereoselective formation of a selection of cyclohexyl heteroaryl alcohols of up to 97% enantiopurity was realized as well. Dramatic temperature effects on both the enantiopurity and the absolute configuration of the alcohol products were observed in the reduction of some cyclohexyl pyridyl ketones.

Introduction

Enantioenriched secondary alcohols constitute significant intermediates and ubiquitous structural elements not only in medicinal chemistry but also in the fields of agrochemicals, fragrances and flavors.[1] Among them, chiral aryl- or heteroaryl cycloalkyl methanol derivatives form the core of several physiologically active molecules such as the matrix metalloprotease inhibitor [2] and the glucocorticoid receptor Scanlan [3] (Fig. 1). Whereas, the reports on the catalytic asymmetric synthesis of aryl or heteroaryl cycloalkyl alcohols are relatively limited. The efficient approaches involve (1) the addition of appropriate aryl organometallic nucleophiles to cycloalkyl aldehydes,[4,5] (2) the di(cycloalkyl)zinc addition to aromatic aldehydes,[6] and (3) the catalytic reduction of the corresponding prochiral ketones.[7] From both the scientific and commercial points of view, the asymmetric reduction of aryl cycloalkyl ketones offers a straightforward and especially attractive entry to single enantiomer alcohols. In 1994, Takaya and co-workers disclosed a catalyst system derived from [Ir((*S*)-BINAP)(cod)]BF_4 or [Ir((*S*)-H_8-BINAP)(cod)]BF_4 and bis(*o*-dimethylaminophenyl)phenylphosphine, which allowed the effective enantioselective hydrogenation of cycloalkyl (*c*-C_3H_5, *c*-C_4H_7, *c*-C_5H_9, *c*-C_6H_{11}) phenyl ketones, and the highest ee of 80% was achieved when the alkyl group was *c*-C_6H_{11}.[8] Later, a Ru-BINAP-diamine system was developed by Noyori et al. for the hydrogenation of cyclopropyl or cyclohexyl phenyl ketone with 96%[9] and 92% ee,[10] respectively. In 2003, using Ru-Xyl-P-Phos-diamine catalyst, we described the asymmetric hydrogenation of a selection of cyclopropyl *para*-substituted phenyl ketones in up to 97.6% ee values.[11] Additionally, the transfer hydrogenation of cycloalkyl (*c*-C_3H_5, *c*-C_4H_7, *c*-C_5H_9, *c*-C_6H_{11}) phenyl ketones (78–94% ee) mediated by a chiral Ru catalyst was reported by Wills and co-workers.[12]

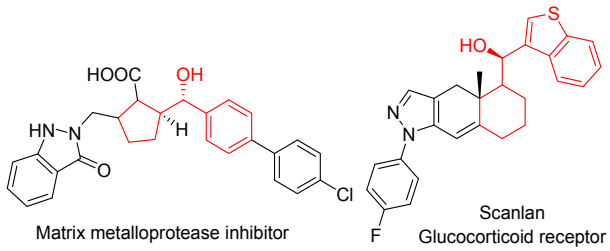


Fig. 1 Selected valuable bioactive targets derived from chiral aryl-and heteroaryl cycloalkyl alcohols.

In the past decade, non-noble copper-catalyzed asymmetric hydrosilylation has become an especially powerful and appealing tool for directing chirality in prochiral ketones owing to the economic benefits, the high efficiency, and the smooth reaction conditions.[13,14] Nevertheless, the application of chiral copper catalysts in the hydrosilylation of aryl cycloalkyl ketones remained relatively unexplored. By employing 3,5-Xyl-MeO-BIPHEP [15] or DTBM-SEGPHOS [16] ligated chiral CuH hydrosilylation system, Lipshutz et al. reported the reduction of cyclohexyl phenyl ketone to the corresponding alcohol of 93% enantiopurity.[14b,d] Herein, the copper-catalyzed enantioselective hydrosilylation of a wide spectrum of aryl cycloalkyl ketones

[a] *College of Material, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 310036, China.*
E-mail: jingwubc@hznu.edu.cn; Fax : (+86)-571-2886-8023
[b] *Institute of Creativity, Hong Kong Baptist University, Hong Kong*
† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/b000000x/

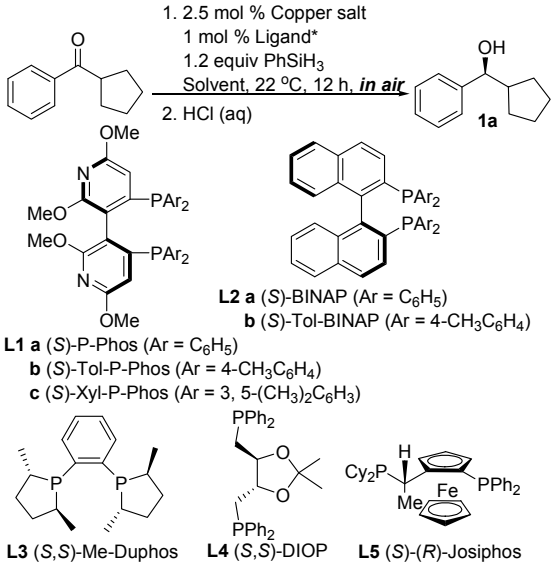
with different ring sizes was systematically studied. The first example of highly enantioselective formation of a series of cyclohexyl heteroaryl alcohols of up to 97% ee under air was described as well.

Results and discussion

Our studies were initiated by examining the ability of non-racemic dipyridylphosphine ligand P-Phos (Table 1, **L1a**),[17] which was previously demonstrated to be remarkably reactive (substrate to ligand ratio up to 100,000) yet selective (ee up to 99.9%) for effecting copper-,[14f, 18] cobalt-[19a] or nickel-[19b] catalyzed asymmetric hydrosilylation of a broad assortment of ketones as well as 1,4-reduction of *β*-(acylamino)acrylates,[19c] to promote the reduction of the model substrate cyclopentyl phenyl ketone. As shown in entry 1 of Table 1, when cyclopentyl phenyl ketone was subjected to a premixed solution of 2.5 mol % of $Cu(OAc)_2•H_2O$, 1 mol % of **L1a** and 1.2 equivalent of hydride resource $PhSiH_3$ in toluene, the reaction was completed at room temperature in air after 12 h to furnish (*S*)-**1a** in 77% ee. Next, various copper precursors were tested in detail (entries 2–7) under a given set of conditions and the results indicated that the counterion of copper salts had a pronounced influence on both the reactivity and the enantioselectivity. Similar to the previous findings,[14c,14f] except for the use of CuF_2 (entry 2), all copper(I) or copper(II) halides such as $CuCl_2$, $CuBr_2$ and CuI exhibited poor activities (<5% conversion). Although promising results were also achieved by applying $Cu(OAc)_2$, CuOAc and Cu(TC) (entries 3–5), $Cu(OAc)_2•H_2O$ appears to be the most preferable choice in terms of both the easiness of handling and the substantially low cost. Among the chiral diphosphine ligands screened (entries 8–14), (*S*)-Xyl-P-Phos (**L1c**, entry 9) gave the comparative levels of activity and asymmetric induction with those of P-Phos. Besides, the reaction was also strongly solvent-dependent and toluene was much more conducive than other solvents (entries 15–17 vs entry 9).

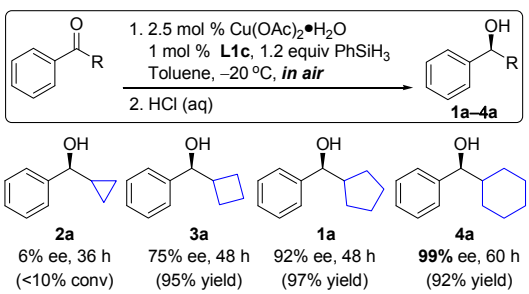
With a reasonably effective Cu-catalyzed protocol identified, further optimization of conditions was performed. As depicted in Scheme 1, full conversion and 92% ee were realized at –20 °C in the presence of **L1c** simply by prolonging the reaction time while 89% ee was obtained by employing **L1a**. Particularly noteworthy was the observation that both the reactivity and the enantioselectivity of the reduction of cycloalkyl phenyl ketones were largely dependent on the steric size of the cycloalkyl group.[8] For instance, reactions with substrates bearing a *c*-C_4H_7, *c*-C_5H_9 or *c*-C_6H_{11} group afforded the desired products in 92–95% yield, albeit a longer reaction time was demanded for the complete conversion of cyclohexyl phenyl ketone. In contrast, however, the reduction of cyclopropyl phenyl ketone was found to be rather sluggish (<10% conversion). Interestingly, when the size of cycloalkyl group was increased from three-membered ring to six-membered ring, the enantioselectivity dramatically improved from 6% (**2a**) to 99% (**4a**), which may be because the difference of energy between the two enantiotopic faces of ketone in the transition state largely relies on the asymmetric bias generating from the phenyl and cycloalkyl groups connected to the C=O function.

Table 1 Selected optimization conditions for the copper-catalyzed asymmetric hydrosilylation of cyclopentyl phenyl ketone in air.[a]



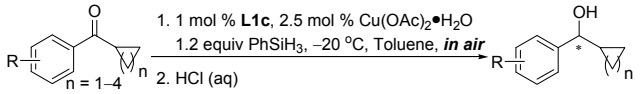
Entry	Copper salt	Ligand	Solvent	Yield (%)[b]	ee (%)[c]
1	$Cu(OAc)_2•H_2O$	**L1a**	Toluene	99	77
2	CuF_2	**L1a**	Toluene	96	76
3	$Cu(OAc)_2$	**L1a**	Toluene	99	77
4	CuOAc	**L1a**	Toluene	99	76
5	Cu(TC)	**L1a**	Toluene	97	74
6	$Cu(acac)_2$	**L1a**	Toluene	10	55
7	$Cu(OCH_3)_2$	**L1a**	Toluene	<1	n.d.[d]
8	$Cu(OAc)_2•H_2O$	**L1b**	Toluene	73	71
9	$Cu(OAc)_2•H_2O$	**L1c**	Toluene	99	76
10	$Cu(OAc)_2•H_2O$	**L2a**	Toluene	99	73
11	$Cu(OAc)_2•H_2O$	**L2b**	Toluene	86	73
12	$Cu(OAc)_2•H_2O$	**L3**	Toluene	66	39
13	$Cu(OAc)_2•H_2O$	**L4**	Toluene	18	5
14	$Cu(OAc)_2•H_2O$	**L5**	Toluene	<5	n.d.
15	$Cu(OAc)_2•H_2O$	**L1c**	THF	81	76
16	$Cu(OAc)_2•H_2O$	**L1c**	CH_3CN	34	35
17	$Cu(OAc)_2•H_2O$	**L1c**	CH_2Cl_2	<5	n.d.

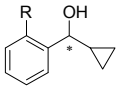
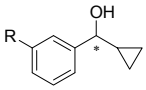
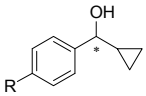
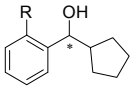
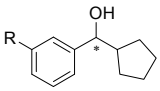
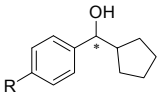
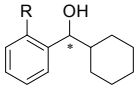
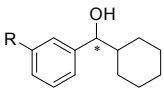
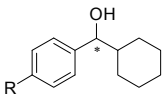
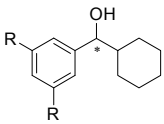
[a] Reaction conditions: 35 mg substrate, substrate concentration = 0.3–0.5 mol•L^{-1}. [b] Determined by NMR and GC analysis. [c] The ee values were determined by chiral HPLC analysis. The absolute configuration was determined by comparing the optical rotation with known data. [d] n.d. = not determined.



Scheme 1 Asymmetric hydrosilylation of cycloalkyl phenyl ketones in air.

Table 2 Cu(II)-catalyzed asymmetric hydrosilylation of aryl cycloalkyl ketones in air.[a]

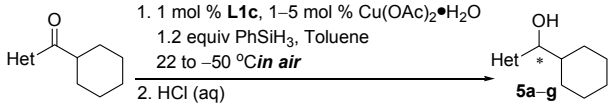


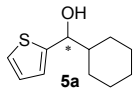
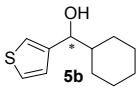
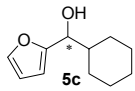
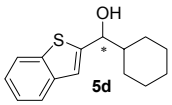
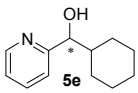
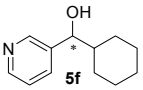
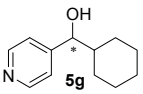
Entry	Alcohols	R	Time (h)	Yield (%)[b]	ee (%)[c]
1		**2b**, Cl	60	97	10 (–)
2		**2c**, CH_3	36	10	n.d.
3		**2d**, Br	65	96	31 (+)
4		**2e**, OCH_3	65	33	28 (+)
5		**2f**, Cl	36	93	57(+)
6		**2g**, OCH_3	36	5	n.d.
7		**1b**, Cl	48	97	61 (–)
8		**1c** OCH_3	48	90	54 (–)
9		**1d**, Br	48	96	92 (–)
10		**1e**, OCH_3	36	96	91 (–)
11		**1f**, CF_3	36	97	91 (–)
12		**1g**, CH_3	36	96	93 (–)
13		**4b**, Cl	48	97	72 (–)
14[d]		**4c**, CH_3	60	92	57 (–)
15		**4d**, Br	48	93	94 (–)
16		**4e**, OCH_3	60	96	95 (*S*)
17		**4f**, CF_3	40	96	95 (–)
18		**4g**, CH_3	72	95	95 (–)
19		**4h**, Ph	40	93	95 (–)
20		**4i**, OCH_3	40	96	92 (–)

[a] Reaction conditions: 37–108 mg substrate, substrate concentration = 0.3–0.5 mol•L^{-1} in toluene. [b] Isolated yields. [c] The ee values were determined by chiral HPLC analysis. The absolute configurations were determined by comparing the retention times or optical rotations with known data. [d] The ligand was **L1a**.

To access a wider scope of aryl cycloalkyl alcohols of high enantiomeric purity, we turned to the reaction of other substrate classes possessing various substituted aryl or cycloalkyl groups with different ring sizes. The results of these studies are summarized in Table 2. Transformation with cyclopropyl ketone substrates possessing an *o*-chloro, *m*-bromo or *p*-chloro aryl group proceeded to provide the corresponding alcohols in 93–97% yield and 10–57% ee (entries 1, 3 and 5). As illustrated in entry 5, the introduction of an electron-withdrawing substituent on the *para*-position of cyclopropyl phenyl ketones (Scheme 1) enhanced the ee from 6% to 57%. The aryl cyclopropyl ketones bearing an electron-donating substituent (**2c**, **2e** and **2g**) all exhibited poor reactivity (5–33% yield, entries 2, 4 and 6) as that

Table 3 Cu(II)-catalyzed asymmetric hydrosilylation of cyclohexyl heteroaryl ketones in air.[a]



Entry	Alcohols	T (°C)	Time (h)	Yield (%)	ee (%)
1	 **5a**	–50	72	94	95 (–)
2	 **5b**	–50	72	97	87 (–)
3	 **5c**	22	16	96	84 (*S*)
4		–50	72	97	90 (*S*)
5	 **5d**	22	3	90	92 (+)
6		–20	40	90	**97** (+)
7	 **5e**	22	3	95	27 (–)
8		–50	48	88	63 (–)
9	 **5f**	50	2	80	62 (–)
10		22	3	90	58 (–)
11		–20	20	97	0
12		–50	48	93	48 (+)
13	 **5g**	50	2	94	52 (–)
14		–50	48	92	53 (+)

[a] Reaction conditions: 36–135 mg substrate, substrate concentration = 0.3–0.5 mol•L^{-1} in toluene.

of cyclopropyl phenyl ketones. At this stage, what is the role of the electron-withdrawing substituent on the phenyl ring of the ketonic substrates for the increased rates remains unclear. It appeared that, in the catalytic cycle, the σ-bond metathesis between Cu-O and Si-H bonds leading to the active species copper hydride is the rate limiting step and the electron-withdrawing groups on the copper alkoxide intermediate [(Ar)(R)C(H)O]CuL*(OAc) [L* = **L1c**] might be favorable for the transmetallation between copper and silicon. In a likewise manner for cycloalkyl phenyl ketones (Scheme 1), the cycloalkyl ring effect was still obvious on the reduction of the substituted phenyl cycloalkyl ketones. When the size of cycloalkyl group was increased to five-membered ring, substrates with a *meta*- or *para*-substituted electron-deficient or electron-rich aryl group all underwent facile hydrosilylation in air, providing the desired alcohols of 91–93% ee in high isolated yield (entries 9–12), whilst the *ortho*-substituted ketones gave moderate stereoselectivities (entries 7 and 8). Similar substituent effects were also observed in the reduction of substituted phenyl cyclohexyl ketones. In general, substrates with *meta*- or *para*-substitution on the phenyl group reacted favorably to give products of consistently higher enantiopurity (94–95% ee, entries 15–19) when compared with substrates bearing *ortho*-substituents (entries 13 and 14). In addition, when the reaction in entry 20 was conducted at –20 °C, disubstituted phenyl

cyclohexyl alcohol **4i** was provided quantitatively in 92% ee after 40 h.

Furthermore, as part of our continuing efforts to broaden the generality of the present catalyst system, we were interested in the extension of our system to the enantioselective reduction of cycloalkyl hetero-aromatic ketones, the products of which can serve as crucial intermediates for the synthesis of some physiologically active targets.[1b,3] The chiral dipyridylphosphine ligated Cu-H acted as an efficacious catalyst, rendering high yields (90–97%) and good to excellent ee values (up to 97%) for the hydrosilylation of cyclohexyl ketones with 2-thienyl, 3-thienyl, 2-furyl or benzo[*b*]2-thienyl group (Table 3, entries 1, 2, 4 and 6) under optimized conditions. To our best knowledge, this was the first highly efficient catalytic asymmetric reduction of such a class of substrates.

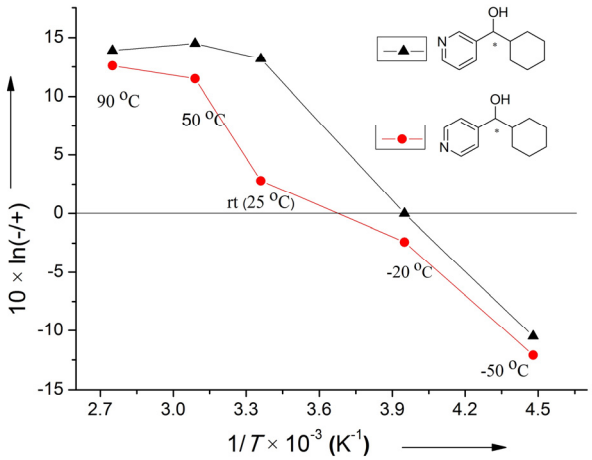


Fig. 2 Temperature effect on the enantioselectivities of **5f** and **5g**.

Our previous studies on the copper catalyzed hydrosilylation of pyridyl methyl ketones indicated that the reaction temperature had a dramatic effect on both the configuration and the enantiopurity of the alcohol products.[18a] Interestingly, this phenomenon was again observed in the reduction of cyclohexyl pyridyl ketones. The representative results were summarized as entries 7–14 of Table 3 and the plots of ln(–/+) (ln(–/+) = ln[(1+ee)/(1–ee)] if (–)-enantiomer is excess; ln(–/+) = ln[(1–ee)/(1+ee)] if (+)-enantiomer is excess.) versus 1/*T* (Eyring's curves) were drawn as well (Fig. 2). For example, when cyclohexyl 3-pyridyl ketone was treated with 5 mol % of $Cu(OAc)_2$•H_2O and 1 mol % of **L1c** ligand plus 1.2 equivalent of $PhSiH_3$ in air, the ee of **5f** remained almost unchanged from 90 °C (–60% ee, Fig. 2) to room temperature (–58% ee, Table 3, entry 10). Then, the ee rapidly fell to 0% at –20 °C (entry 11). Surprisingly, further lowering the reaction temperature to –50 °C led to an asymmetric induction of the opposite sense to give the (+)-enantiomer of **5f** in 48% ee (entry 12). As illustrated in Figure 2, 4-pyridyl ketone also exhibited a similar interesting tendency. Nonetheless, the inversion in the sense of chiral induction did not appear in the case of 2-pyridyl ketone (entries 7 and 8), likely because the potential formation of bidentate complex (N and O atoms) with cupric ion may make the substrate show totally different behaviour from that of 3-pyridyl or 4-pyridyl ketone.

Conclusion

In conclusion, by using a commercially available and air-stable chiral dipyridylphosphine (*S*)-Xyl-Phos, a substantially inexpensive and easy-to-handle copper salt $Cu(OAc)_2$•H_2O as well as the hydride source $PhSiH_3$, the enantioselective formation of a broad spectrum of aryl cycloalkyl alcohols with good to excellent degrees of optical purity (up to 99% ee) was realized in air. The results demonstrated that the steric size of cycloalkyl groups has a significant influence on the reaction outcomes. The first highly stereoselective reduction of a selection of cyclohexyl heteroaryl ketones was achieved with up to 97% ee. Dramatic temperature effects on the enantiopurity as well as the absolute configuration of the alcohol products were observed in the reduction of some cyclohexyl pyridyl ketones. The present catalyst system features high air-stability, good to excellent enantioselectivity and cost efficiency, and thus offers a great opportunity for the practical preparation of structurally diverse chiral secondary alcohols embodying cyclic alkyl moieties.

Experimental Section

General Information

^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker advance spectrophotometer (400 and 100 MHz) at room temperature. Chemical shifts (δ) are given in ppm and are referenced to residual solvent peaks. HRMS spectra were recorded on a Waters Micromass® GCT Premier™ orthogonal acceleration time-of-flight (oa-TOF) GC mass spectrometer with EI resource and are reported as m/z (relative intensity). Low resolution mass spectra were obtained with an Agilent Technologies 5975C. Conversions were determined by ^1H NMR and gas chromatographic analyses (Capillary GC, J&W Scientific INNOWAX column, 30 m × 0.25 mm, carrier gas, N_2). Enantiomeric excesses of the asymmetric hydrosilylation products were determined by chiral GC (Capillary GC, Chirasil-DEX CB column; 25 m × 0.25 mm, carrier gas, N_2) or HPLC (25 cm × 4.6 mm Chiralcel OB-H, OD or OD-H column). GC analyses were conducted on a Fuli 9790 with an FID detector. HPLC analyses were performed using an Agilent 1200 with a UV detector. Optical rotations were measured on a Perkin-Elmer Model 341 polarimeter in a 10 cm cell. Optically pure P-Phos, Xyl-P-Phos, BINAP, Tol-BINAP and (*S,S*)-Me-Duphos were purchased from Strem or Aldrich. (*S*)-Tol-P-Phos was prepared according to previous reported procedure.[20] Substrates were prepared and characterized according to the literature procedures.[21,22] All solvents were purified and dried according to standard methods prior to use. Copper salts, phenylsilane, some ketone substrates, and other reagents were purchased from Aldrich, Alfa aesar or Acros organics and used as received without further purification unless otherwise stated.

General procedure of asymmetric hydrosilylation in air (Scheme 1, cyclopentyl phenyl ketone): $Cu(OAc)_2$•H_2O (2.0 mg, 1.0×10^{-2} mmol), (*S*)-Xyl-P-Phos (2.8 mg, 4.0×10^{-3} mmol) were weighed under air and placed in a 25 mL round-bottomed flask equipped with a magnetic stirrer bar. Toluene (0.6 mL) was added and the mixture was stirred at room temperature for 10 min.

Then $PhSiH_3$ (60 μL, 0.48 mmol) in toluene (0.3 mL) was added under vigorous stirring and the mixture was cooled to –20 °C. A solution of cyclopentyl phenyl ketone (69.6 mg, 0.40 mmol) in toluene (0.4 mL) was added and the flask was stoppered. The reaction was monitored by TLC. Upon completion, the reaction mixture was treated with 1 mol•L^{-1} HCl (1 mL) and the organic product was extracted with ethyl acetate (3 × 5 mL). The combined extract was washed with water, dried with anhydrous sodium sulfate, filtered through a plug of silica and concentrated *in vacuo* to give the crude product. The conversion and the enantiomeric excess of the product (*S*)-(cyclopentyl)phenylmethanol **1a** was determined by NMR, GC (Capillary GC, INNOWAX column, 30 m × 0.25 mm, carrier gas, N_2) and chiral HPLC (25 cm × 4.6 mm Chiralcel OB-H column) analysis to be 99% and 92%, respectively. The pure product was isolated (68 mg, 97% yield) by column chromatography (ethyl acetate:petroleum ether = 1:10).

(*S*)-Cyclopentylphenylmethanol (1a):[8,12] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.34 (m, 5H), 4.40 (d, J = 8.4 Hz, 1H), 2.17–2.27 (m, 1H), 1.85–1.95 (m, 2H), 1.47–1.68 (m, 5H), 1.34–1.42 (m, 1H), 1.11–1.20 (m, 1H). IR (thin film): ν_{max} (cm^{-1}) = 3391, 3029, 1493, 1453, 1025, 762, 701. MS (EI, *m/z*, relative intensity): 176 (M^+, 5), 107 (100). Chiral HPLC, Chiralcel OB-H column (eluent, 2-propanol/hexane 5:95; flow rate: 0.5 mL•min^{-1}; detection: 254 nm light); t_R (*S*) = 11.3 min; t_R (*R*) = 12.2 min. $[\alpha]_D^{20}$ = –42.1°(*c* = 0.70, $CHCl_3$) for a sample with 92% ee. Literature data: $[\alpha]_D^{20}$ = –40.0°(*c* = 0.80, $CHCl_3$) for an (*S*)-product with 78% ee.[12]

(*S*)-Cyclopropylphenylmethanol (2a):[9,10] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21–7.40 (m, 5H), 3.95 (d, J = 8.8 Hz, 1H), 1.98 (s, 1H), 1.15–1.20 (m, 1H), 0.31–0.61 (m, 4H). IR (thin film): ν_{max} (cm^{-1}) = 3362, 3006, 1494, 1453, 1027, 740, 700. MS (EI, *m/z*, relative intensity): 148 (M^+, 2), 120 (100). Chiral HPLC, Chiralcel OD column (eluent, 2-propanol/hexane 5:95; flow rate, 0.5 mL•min^{-1}; detection, 254 nm light); t_R (*R*) = 17.2 min; t_R (*S*) = 20.8 min.[10]

(*S*)-Cyclobutylphenylmethanol (3a):[8,12] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–7.35 (m, 5H), 4.57 (d, J = 8.0 Hz, 1H), 2.61–2.68 (m, 1H), 1.78–2.12 (m, 7H). IR (thin film): ν_{max} (cm^{-1}) = 3391, 3029, 1493, 1453, 1007, 755, 700. MS (EI, *m/z*, relative intensity): 162 (M^+, 7), 107 (100). Chiral HPLC, Chiralcel OB-H column (eluent, 2-propanol/hexane 5:95; flow rate: 0.5 mL•min^{-1}; detection: 254 nm light); t_R (*S*) = 11.7 min; t_R (*R*) = 12.6 min. $[\alpha]_D^{20}$ = –23.5°(*c* = 0.80, $CHCl_3$) for a sample with 75% ee. Literature data: $[\alpha]_D^{24}$ = –35.0°(*c* = 0.80, $CHCl_3$) for an (*S*)-product with 87% ee.[12]

(*S*)-Cyclohexylphenylmethanol (4a):[8,10,12] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26–7.35(m, 5H), 4.36 (d, J = 7.2 Hz, 1H), 0.90–1.77(m, 12H). MS (EI, *m/z*, relative intensity): 190 (M^+, 4), 107 (100). Chiral HPLC, Chiralcel OD-H column (eluent, 2-propanol/hexane 5:95; flow rate: 0.5 mL•min^{-1}; detection: 254 nm light); t_R (*S*) = 17.8 min; t_R (*R*) = 21.1 min. $[\alpha]_D^{20}$ = –16.3° (*c* = 0.30, benzene) for a sample with 99% ee. Literature data: $[\alpha]_D^{22}$ = +26.8 (*c* = 3.29, benzene) for an (*R*)-product with 92% ee.[10]

(–)-(2-Chlorophenyl)cyclopropylmethanol (2b):[23] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17–7.61 (m, 4H), 4.63 (d, J = 7.2 Hz, 1H), 2.50 (s, 1H), 1.20–1.30 (m, 1H), 0.49–0.63 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 130.2, 127.3, 126.5, 125.8, 124.9, 71.5, 15.7. IR (thin film): ν_{max} (cm^{-1}) = 3382, 3009, 1471, 1441, 1026, 752, 703. MS (EI, *m/z*, relative intensity): 182 (M^+, 2), 156 (34), 154 (100). Capillary GC, Chirasil-DEX CB column; 150 °C, isothermal; t_R (minor) = 25.57 min; t_R (major) = 27.40 min. $[\alpha]_D^{20}$ = –7.4° (*c* = 1.00, $CHCl_3$) for a sample with 10% ee.

(+)-3-(Bromophenyl)cyclopropylmethanol (2d):[24] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.44 (m, 2H), 0.62 (m, 2H), 1.17–1.19 (m, 1H), 1.97 (m, 1H), 3.98 (d, J = 8.3 Hz, 1H), 7.23 (dd, J = 16.0, 8.1 Hz, 1H), 7.38 (dd, J = 25.8, 7.7 Hz, 2H), 7.59 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.06, 130.51, 129.93, 129.07, 124.63, 122.47, 77.85, 19.28, 3.63, 3.01. IR (thin film): ν_{max} (cm^{-1}) = 3334, 3006, 1474, 1428, 1033, 784, 695. MS (EI, *m/z*, relative intensity): 228 (M^+, 4), 226 (M^+, 5), 200 (99), 198 (100). Chiral HPLC, Chiralcel OB-H column (eluent, 2:98 2-propanol/hexane; flow rate, 1.0 mL•min^{-1}; detection, 254 nm light); t_R (major) = 12.4 min; t_R (minor) = 14.5 min. $[\alpha]_D^{20}$ = +3.8° (*c* = 0.50, $CHCl_3$) for a 31% ee sample.

(+)-(3-Methoxyphenyl)cyclopropylmethanol (2e):[24] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.38–0.65 (m, 4H), 1.22 (m, 1H), 1.95 (d, J = 3.0 Hz, 1H), 3.82 (s, 3H), 3.99 (m, 1H), 6.83 (dd, J = 8.2, 1.7 Hz, 1H), 7.06–6.95 (m, 2H), 7.27 (dd, J = 10.7, 5.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.64, 145.66, 129.36, 118.42, 112.88, 111.67, 78.38, 55.22, 19.14, 3.60, 2.87. IR (thin film): ν_{max} (cm^{-1}) = 3391, 3005, 1487, 1435, 1040, 744, 699. MS (EI, *m/z*, relative intensity): 178 (M^+, 29), 150 (100). Chiral HPLC, Chiralcel OD-H column (eluent, 2:98 2-propanol/hexane; flow rate, 1.0 mL•min^{-1}; detection, 254 nm light); t_R (minor) = 29.4 min; t_R (major) = 33.5 min. $[\alpha]_D^{20}$ = +2.2° (*c* = 0.50, $CHCl_3$) for a 28% ee sample.

(+)-(4-Chlorophenyl)cyclopropylmethanol (2f):[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.38 (m, 4H), 3.99 (d, J = 8.4 Hz, 1H), 1.99 (s, 1H), 1.15–1.19 (m, 1H), 0.36–0.67 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.4, 133.1, 128.5, 127.4, 77.9, 19.4. R (thin film): ν_{max} (cm^{-1}) = 3364, 3006, 1491, 1430, 1033, 819. MS (EI, *m/z*, relative intensity): 182 (M^+, 20), 153 (33), 151 (100). Capillary GC, Chirasil-DEX CB column; 140 °C, t_R (minor) = 35.26 min; t_R (major) = 36.95 min.[11]

(–)-(2-Chlorophenyl)cyclopentylmethanol (1b):[25] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17–7.53 (m, 4H), 4.99 (d, J = 8.0 Hz, 1H), 1.28–2.36 (m, 10H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 140.7, 131.5, 128.4, 127.4, 127.0, 125.9, 72.9, 45.4, 28.7, 27.9, 24.5. Chiral HPLC, Chiralcel OD-H column (eluent, 2-propanol/hexane 2:98; flow rate: 0.5 mL•min^{-1}; detection: 254 nm light); t_R (minor) = 15.28 min; t_R (major) = 16.98 min. $[\alpha]_D^{20}$ = –12.2° (*c* = 0.42, $CHCl_3$) for a 62% ee sample.

(–)-Cyclopentyl(2-methoxyphenyl)methanol (1c): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20–7.22 (m, 2H), 6.86–6.95 (m, 2H), 4.59 (d, J = 8.5 Hz, 1H), 3.84 (s, 3H), 1.12–2.36 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.0, 132.5, 128.4, 128.2, 120.9, 110.8, 75.6, 55.5, 46.4, 29.8, 25.8. IR (thin film): ν_{max} (cm^{-1}) = 3439, 3050, 1491, 1439, 1030, 754, 704. HRMS (EI) Calcd for $C_{13}H_{18}O_2$ $[M]^+$: 206.1307, Found: 206.1311. Chiral HPLC, Chiralcel OD-H column (eluent, 2-propanol/hexane 5:95; flow

rate: 0.6 mL•min^{-1}; detection: 254 nm light); t_R (major) = 12.56 min; t_R (minor) = 13.89 min. $[\alpha]_D^{20} = -9.8°$ (c = 1.00, $CHCl_3$) for a 55% ee sample.

(–)-(3-Bromophenyl)cyclopentylmethanol (1d): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (s, 1H), 7.18–7.40 (m, 3H), 4.38 (d, J = 8.0 Hz, 1H), 2.10–2.22 (m, 1H), 1.97 (br, 1H), 1.13–1.90 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.0, 130.8, 130.1, 129.8, 125.4, 122.7, 78.6, 47.9, 29.6, 29.5, 25.7, 25.6. IR (thin film): ν_{max} (cm^{-1}) = 3409, 2953, 1488, 1435, 1044, 785, 702. MS (EI, *m/z*, relative intensity): 254 (M^+, 5), 256 (M^+, 5), 185 (100), 187 (98). HRMS (EI) Calcd for $C_{12}H_{15}OBr$ $[M]^+$: 254.0306, Found: 254.0301. Chiral HPLC, Chiralcel OD-H column (eluent, 2-propanol/hexane 2:98; flow rate: 0.5 mL•min^{-1}; detection: 254 nm light); t_R (major) = 12.88 min; t_R (minor) = 16.69 min. $[\alpha]_D^{20} = -22.1°$ (c = 1.00, $CHCl_3$) for a 92% ee sample.

(–)-Cyclopentyl(3-methoxyphenyl)methanol (1e):[8,12] ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.80–7.24 (m, 4H), 4.37 (d, J = 8.0 Hz, 1H), 3.81 (s, 3H), 2.18–2.20 (m, 1H), 1.12–1.90 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 1159.9, 146.4, 129.5, 119.1, 113.2, 112.2, 79.3, 55.4, 47.8, 29.7, 25.7. MS (EI, *m/z*, relative intensity): 206 (M^+, 100). Chiral HPLC, Chiralcel OD-H column (eluent, 2-propanol/hexane 5:95; flow rate: 1.0 mL•min^{-1}; detection: 254 nm light); t_R (major) = 13.30 min; t_R (minor) = 15.33 min. $[\alpha]_D^{20} = -27.2°$ (c = 1.00, $CHCl_3$) for a 91% ee sample.

(–)-Cyclopentyl(4-(trifluoromethyl)phenyl)methanol (1f): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 4.48 (d, J = 8.0 Hz, 1H), 2.05–2.21 (m, 1H), 1.14–1.87 (m, 9H). ^{13}C NMR (100 Hz, $CDCl_3$): δ 148.3, 129.7, 126.7, 125.2, 122.9, 122.8, 78.3, 47.7, 29.3, 29.1, 25.4. IR (thin film): ν_{max} (cm^{-1}) = 3392, 2958, 1454, 1453, 1017, 838. HRMS (EI) Calcd for $C_{13}H_{15}OF_3$ $[M]^+$: 244.1075, Found: 244.1080. Chiral HPLC, Chiralcel AD column (eluent, 2-propanol/hexane 5:95; flow rate: 0.5 mL•min^{-1}; detection: 254 nm light); t_R (minor) = 13.55 min; t_R (major) = 14.62 min. $[\alpha]_D^{20} = -27.5°$ (c = 1.00, $CHCl_3$) for a 91% ee sample.

(–)-Cyclopentyl(*p*-tolyl)methanol (1g):[26] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, J = 10.0 Hz, 2H), 7.15 (d, J = 10.0 Hz, 2H), 4.36 (d, J = 10.5 Hz, 1H), 2.34 (s, 3H), 2.21–2.23 (m, 1H), 1.11–1.82 (m, 10H). ^{13}C NMR (100 Hz, $CDCl_3$): δ 141.5, 137.2, 129.0, 126.4, 79.0, 47.6, 29.6, 29.5, 25.6, 25.4, 21.1. IR (thin film): ν_{max} (cm^{-1}) = 3418, 2955, 1455, 1030, 816, 741. MS (EI, *m/z*, relative intensity): 190 (M^+, 56), 121 (100). Chiral HPLC, Chiralcel OB-H column (eluent, 2-propanol/hexane 2:98; flow rate: 0.5 mL•min^{-1}; detection: 254 nm light); t_R (major) = 15.62 min; t_R (minor) = 18.03 min. $[\alpha]_D^{20} = -31.4°$ (c = 1.00, $CHCl_3$) for a 93% ee sample.

(–)-(2-Chlorophenyl)cyclohexylmethanol (4b):[6b] ^{1}H NMR (400 Hz, $CDCl_3$): δ 7.18–7.51 (m, 4H), 4.91–4.94 (m, 1H), 1.10–1.93 (m, 12H). ^{13}C NMR (100 Hz, $CDCl_3$): δ 140.1, 131.5, 128.3, 127.2, 125.8, 73.9, 42.9, 28.4, 26.8, 25.4, 25.3, 25.0. IR (thin film): ν_{max} (cm^{-1}) = 3373, 3071, 1472, 1449, 1035, 755, 700. MS (EI, *m/z*, relative intensity): 222 ($[M–H]^+$, 16), 141 (30), 139 (100). Chiral HPLC, Chiralcel OD-H column (eluent, 2-propanol/hexane 2:98; flow rate: 0.5 mL•min^{-1}; detection: 254 nm light); t_R (major) = 15.56 min; t_R (minor) = 18.28 min. $[\alpha]_D^{20} = -22.0°$ (c = 1.00, $CHCl_3$) for a 72% ee sample. Literature data: $[\alpha]_D^{20} = -52.4$ (c = 1.80, CHCl3) for a product with 90% ee.[6 b]

(–)-Cyclohexyl(*o*-tolyl)methanol (4c):[25] ^{1}H NMR (400 Hz, $CDCl_3$): δ 7.42 (d, J = 6.0 Hz, 1H), 7.14–7.23 (m, 3H), 4.60 (d, J = 7.0 Hz, 1H), 2.35 (s, 3H), 1.98–2.04 (m, 1H), 1.11–1.78 (m, 11H). ^{13}C NMR (100 Hz, $CDCl_3$): δ 142.0, 135.1, 130.3, 127.0, 126.3, 126.1, 75.1, 44.5, 29.6, 28.6, 26.5, 26.3, 26.1, 19.5. IR (thin film): ν_{max} (cm^{-1}) = 3391, 3023, 1488, 1450, 1051, 756, 729. MS (EI, *m/z*, relative intensity): 204 (M^+, 5), 121 (100). Chiral HPLC, Chiralcel OD-H column (eluent, 2-propanol/hexane 3:97; flow rate: 0.5 mL•min^{-1}; detection: 254 nm light); t_R (major) = 15.53 min; t_R (minor) = 18.71 min. $[\alpha]_D^{20} = -15.5°$ (c = 0.75, $CHCl_3$) for a 57% ee sample.

(–)-(3-Bromophenyl)cyclohexylmethanol (4d): ^{1}H NMR (400 Hz, $CDCl_3$): δ 7.19–7.46 (m, 4H), 4.33 (d, J = 7.2 Hz, 1H), 0.91–2.04 (m, 12H). ^{13}C NMR (100 Hz, $CDCl_3$): δ 145.9, 130.4, 129.7, 129.6, 125.3, 122.4, 78.6, 44.9, 29.2, 28.5, 26.3, 26.0, 25.9. IR (thin film): ν_{max} (cm^{-1}) = 3333, 3061, 1472, 1449, 1023, 783. HRMS (EI) Calcd for $C_{13}H_{17}OBr$ $[M]^+$: 268.0463, Found: 268.0459. Chiral HPLC, Chiralcel OD-H column (eluent, 2-propanol/hexane 2:98; flow rate: 0.5 mL•min^{-1}; detection: 254 nm light); t_R (major) = 21.10 min; t_R (minor) = 30.45 min. $[\alpha]_D^{20} = -13.5°$ (c = 1.00, $CHCl_3$) for a 94% ee sample.

(*S*)-Cyclohexyl(3-methoxyphenyl)methanol (4e):[4b,6b] ^{1}H NMR (400 Hz, $CDCl_3$): δ 7.24–7.28 (m, 1H), 6.81–6.89 (m, 3H), 4.35 (q, J = 3.3 Hz, 1H), 3.83 (s, 3H), 1.97–2.01 (m, 1H), 0.94–1.85 (m, 11H). ^{13}C NMR (100 Hz, $CDCl_3$): δ 158.5, 144.4, 128.1, 118.0, 111.7, 111.1, 78.3, 54.2, 43.9, 28.3, 27.8, 25.4, 25.1, 24.9. IR (thin film): ν_{max} (cm^{-1}) = 3429, 2999, 1487, 1452, 1046, 784, 703. MS (EI, *m/z*, relative intensity): 220 (M^+, 11), 137 (100). Chiral HPLC, Chiralcel OD-H column (eluent, 2-propanol/hexane 5:95; flow rate: 0.7 mL•min^{-1}; detection: 254 nm light); t_R (*S*) = 16.05 min; t_R (*R*) = 27.34 min.

(–)-Cyclohexyl(4-(trifluoromethyl)phenyl)methanol (4f):[6b] ^{1}H NMR (400 Hz, $CDCl_3$): δ 7.58 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 4.44 (d, J = 6.8 Hz, 1H), 2.06 (m, 1H), 0.99–1.90 (m, 11H). ^{13}C NMR (100 Hz, $CDCl_3$): δ 147.5, 126.9, 125.1, 122.9, 78.7, 45.0, 29.2, 28.4, 26.3, 26.0. IR (thin film): ν_{max} (cm^{-1}) = 3366, 2929, 1451, 1418, 1068, 761.MS (EI, *m/z*, relative intensity): 258 (M^+, 2), 175 (100). Chiral HPLC, Chiralcel OD-H column (eluent, 2-propanol/hexane 2:98; flow rate: 0.3 mL•min^{-1}; detection: 254 nm light); t_R (major) = 27.65 min; t_R (minor) = 30.25 min. $[\alpha]_D^{20} = -21.8°$ (c = 1.00, $CHCl_3$) for a 95% ee sample.

(–)-Cyclohexyl(*p*-tolyl)methanol (4g):[27] ^{1}H NMR (500 Hz, $CDCl_3$): δ 7.15–7.21 (m, 4H), 4.33 (d, J = 7.5 Hz, 1H), 2.35 (s, 3 H), 0.90–2.02 (m, 12H). ^{13}C NMR (100 Hz, $CDCl_3$): δ 140.7, 136.9, 128.8, 126.6, 79.2, 44.9, 29.3, 28.9, 26.5, 26.1, 26.0, 21.1. IR (thin film): ν_{max} (cm^{-1}) = 3391, 3021, 1450, 1017, 821. MS (EI, *m/z*, relative intensity): 204 (M^+, 4), 121 (100). Chiral HPLC, Chiralcel OD-H column (eluent, 2-propanol/hexane 3:97; flow rate: 0.5 mL•min^{-1}; detection: 254 nm light); t_R (major) = 24.87 min; t_R (minor) = 31.56 min. $[\alpha]_D^{20} = -29.7°$ (c = 1.00, $CHCl_3$) for a 95% ee sample.

(–)-Cyclohexyl(4-(phenyl)phenyl)methanol (4h):[28] ^{1}H NMR (400 Hz, $CDCl_3$): δ 7.55–7.61 (m, 4H), 7.31–7.46 (m, 5H), 4.42

(d, J = 6.8Hz, 1H), 0.95–2.03 (m, 12H). ^{13}C NMR (100 Hz, $CDCl_3$): δ 142.7, 140.9, 140.3, 128.8, 127.2, 127.1, 127.0, 126.9, 79.2, 45.0, 29.4, 28.9, 26.5, 26.1, 26.0. IR (thin film): ν_{max} (cm^{-1}) = 3406, 3028, 1486, 1449, 1007, 765, 697. MS (EI, *m/z*, relative intensity): 266 (M^+, 4), 183 (100). Chiral HPLC, Chiralcel AD column (eluent, 2-propanol/hexane 10:90; flow rate: 0.5mL•min^{-1}; detection: 254 nm light); t_R (major) = 15.16 min; t_R (minor) = 18.43 min. $[\alpha]_D^{20}$ = –19.4° (c = 1.00, $CHCl_3$) for a 95% ee sample.

(–)-Cyclohexyl(3,5-dimethoxyphenyl)methanol (4i): ^{1}H NMR (400 Hz, $CDCl_3$): δ 6.35–6.46 (m, 3H), 4.27 (d, J =6.8 Hz, 1H), 3.78 (s, 6H), 0.97–2.02 (m, 12H). ^{13}C NMR (100 Hz, $CDCl_3$): δ 160.6, 146.3, 104.6, 99.2, 79.4, 76.8, 55.3, 44.8, 29.4, 28.8, 26.4, 26.1, 26.0. IR (thin film): ν_{max} (cm^{-1}) = 3440, 2999, 1463, 1429, 1026, 732. MS (EI, *m/z*, relative intensity): 250 (M^+, 36), 167 (100). HRMS (EI) Calcd for $C_{15}H_{22}O_3$ $[M]^+$: 250.1569, Found: 250.1566. Chiral HPLC, Chiralcel AD column (eluent, 2-propanol/hexane 10:90; flow rate: 0.5 mL•min^{-1}; detection: 254 nm light); t_R (major) = 20.75 min; t_R (minor) = 26.60 min. $[\alpha]_D^{20}$ = –5.4° (c = 0.33, $CHCl_3$) for a 92% ee sample.

(–)-Cyclohexyl(2-thienyl)methanol (5a):[5c] ^{1}H NMR (400 Hz, $CDCl_3$): δ 6.92–7.25 (m, 3H), 4.62 (d, J = 7.6 Hz, 1H), 0.93–2.07 (m, 12H). ^{13}C NMR (100 Hz, $CDCl_3$): δ 147.6, 126.4, 124.4, 124.3, 75.2, 45.5, 29.3, 28.9, 26.3, 26.0, 25.9. IR (thin film): ν_{max} (cm^{-1}) = 3373, 3051, 1490, 1451, 1135, 741, 698. MS (EI, *m/z*, relative intensity): 196 (M^+, 5), 113 (100). Chiral HPLC, Chiralcel OD-H column (eluent, 2-propanol/hexane 5:95; flow rate: 0.6 mL•min^{-1}; detection: 254 nm light); t_R (major) = 12.75 min; t_R (minor) = 13.58 min.

(–)-Cyclohexyl(3-thienyl)methanol (5b):[29] ^{1}H NMR (500 Hz, $CDCl_3$): δ 7.03–7.30 (m, 3H), 4.47 (q, J = 4.0 Hz, 1H), 1.02–1.96 (m, 12H). ^{13}C NMR (125 Hz, $CDCl_3$): δ 145.2, 125.9, 125.7, 121.2, 75.5, 44.6, 29.2, 28.7, 26.4, 26.1, 26.0. IR (thin film): ν_{max} (cm^{-1}) = 3372, 3105 1449, 1417, 1020, 783, 724. MS (EI): (m/z) (%): 196 (M^+, 9), 113 (100). Chiral HPLC, Chiralcel OD-H column (eluent, 2-propanol/hexane 5:95; flow rate: 0.6 mL•min^{-1}; detection: 254 nm light); t_R (major) = 13.05 min; t_R (minor) = 14.99 min. $[\alpha]_D^{20}$ = –23.6° (c = 1.00, $CHCl_3$) for an 87% ee sample.

(*S*)-Cyclohexyl(2-furyl)methanol (5c):[6b] ^{1}H NMR (400 Hz, $CDCl_3$): δ 7.37 (s, 1H), 6.32 (d, J = 1.6 Hz, 1H), 6.21 (d, J = 1.6 Hz, 1H), 4.36 (d, J = 7.2Hz, 1H), 0.93–2.00 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.9, 26.0, 26.4, 28.9, 29.1, 42.9, 72.7, 106.7, 110.0, 141.8, 156.0. Chiral HPLC, Chiralcel OD-H column (eluent, 2-propanol/hexane 5:95; flow rate: 0.5 mL•min^{-1}; detection: 254 nm light); t_R (*R*)= 10.30 min; t_R (*S*) = 11.07 min.

(+)-Benzo[*b*]2-thienyl(cyclohexyl)methanol (5d):[30] ^{1}H NMR (400 Hz, $CDCl_3$): δ 7.80 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.25–7.35 (m, 2H), 7.15 (s, 1H), 4.68 (d, J = 7.2Hz, 1H), 2.18 (br, 1H), 0.96–2.05 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 139.4, 124.2, 124.1, 123.4, 122.5, 120.9, 75.7, 45.2, 29.3, 28.7, 26.4, 26.0, 25.9. IR (thin film): ν_{max} (cm^{-1}) = 3402, 3058, 1449, 1075, 745, 727. MS (EI): (m/z) (%): 246 (M^+, 11), 163 (100). Chiral HPLC, Chiralcel OD-H column (eluent, 2-propanol/hexane 10:90; flow rate: 0.8 mL•min^{-1}; detection: 254 nm light); t_R (minor)= 10.73 min; t_R (major)= 12.81 min. $[\alpha]_D^{20}$ = +21.4° (c = 1.00, $CHCl_3$) for a 97% ee sample.

(–)-Cyclohexyl(2-pyridyl)methanol (5e):[31] ^{1}H NMR (500 Hz, $CDCl_3$): δ 8.56 (t, J = 3.5 Hz ,1 H), 7.65–7.69 (m, 1H), 7.18–7.21 (m, 1H) 4.53 (s, 1 H), 4.10 (d, J = 6.5 Hz ,1 H), 1.05–1.77 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 147.1, 135.3, 121.2, 120.2, 75.8, 44.0, 28.7, 25.7, 25.4, 25.1. MS (EI): (m/z) (%): 191 (M^+, 2), 108 (100). Chiral HPLC, Chiralcel OD-H column (eluent, 2-propanol/hexane 1:99; flow rate: 1.0 mL•min^{-1}; detection: 254 nm light); t_R (major) = 14.40 min; t_R (minor) = 15.28 min. $[\alpha]_D^{20}$ = –3.7° (c = 0.42, $CHCl_3$) for a 63% ee sample.

(–)-Cyclohexyl(3-pyridyl)methanol (5f):[31] ^{1}H NMR (500 Hz, $CDCl_3$): δ 8.37 (s, 2H), 7.66 (d, J = 9.0 Hz, 1H), 7.25 (s, ,1 H), 4.39 (d, J = 5.0 Hz, 1H), 3.57 (br, 1 H), 0.91–1.96(m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 139.4, 139.3, 134.5, 123.3, 76.7, 76.5, 44.9, 29.1, 28.6, 26.3, 25.9. IR (thin film): ν_{max} (cm^{-1}) = 3227, 2926, 1450, 1426, 1026, 716. MS (EI): (m/z) (%): 191 (M^+, 65), 108 (100). Chiral HPLC, Chiralcel OD-H column (eluent, 2-propanol/hexane 10:90; flow rate: 1.0 mL•min^{-1}; detection: 254 nm light); t_R (major) = 10.83 min; t_R (minor) = 13.34 min. $[\alpha]_D^{20}$ = –15.4° (c = 1.00, $CHCl_3$) for a 62% ee sample.

(–)-Cyclohexyl(4-pyridyl)methanol (5g):[31] ^{1}H NMR (400 Hz, $CDCl_3$): δ 8.53 (d, J = 7.2 Hz, 2H), 7.23 (d, J = 7.2 Hz, 2H), 4.44 (d, J = 6.4 Hz, 1H), 2.37 (br, 1 H), 1.02–1.82 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1, 149.1, 121.8, 77.4, 44.8, 29.3, 27.9, 26.3, 26.1, 26.0. IR (thin film): ν_{max} (cm^{-1}) = 3208, 2927, 1450, 1415, 1039, 737. MS (EI): (m/z) (%): 191 (M^+, 18), 109 (100). Chiral HPLC, Chiralcel OB-H column (eluent, 2-propanol/hexane 10:90; flow rate: 1.0 mL•min^{-1}; detection: 254 nm light); t_R (minor) = 15.56 min; t_R (major) = 22.97 min. $[\alpha]_D^{20}$ = –17.7° (c = 1.00, $CHCl_3$) for a 52% ee sample.

Acknowledgements

We thank the National Natural Science Foundation of China (21172049, 91127010, 21032003, 21072039), the Public Welfare Technology and Application Program of Zhejiang Province (2010C31042) and the Special Funds for Key Innovation Team of Zhejiang Province (2010R50017) for generous financial support of this research.

Notes and references

1 (*a*) *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*, eds. H.-U. Blaser and E. Schmidt, Wiley-VCH: Weinheim, Germany, 2004; (*b*) M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Keβeler, R. Stürmer and T. Zelinski, *Angew. Chem., Int. Ed.*, 2004, **43**, 788–824; (*c*) V. Farina, J. T. Reeves, C. H. Senanayake and J. J. Song, *Chem. Rev.*, 2006, **106**, 2734–2793.

2 M. C. Van Zandt, D. R. Brittelli and B. R. Dixon, PCT Int. Appl. WO 9743239 A1 1997.

3 (*a*) N. Shah and T.-S. Scanlan, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 5199–5203; (*b*) H.-Y. Xiao, D.-R. Wu, M. Malley and T. G. Murali Dhar, *J. Med. Chem.*, 2010, **53**, 1270–1280.

4 F. Schmidt, R. T. Stemmler, J. Rudolph and C. Bolm, *Chem. Soc. Rev.*, 2006, **35**, 454–470.

5 Examples of aryl transfer reactions to cycloalkyl aldehydes include: (*a*) L. Salvi, J. G. Kim and P. J. Walsh, *J. Am. Chem.Soc.*, 2009, **131**, 12483–12493; (*b*) A.-M. DeBerardinis, M. Turlington and L. Pu, *Org.*

Lett., 2008, **10**, 2709–2712; (*c*) A.-M. DeBerardinis, M. Turlington and L. Pu, *J. Org. Chem*., 2010, **75**, 2836–2850.

6 Examples of di(cycloalkyl)zinc addition to aromatic aldehydes include: (*a*) T. Shibata, H. Tabira and K. Soai, *J. Chem. Soc., Perkin Trans. 1*, 1998, 177–178; (*b*) M. Hatano, T. Mizunoa and K. Ishihara, *Chem. Commun.*, 2010, **46**, 5443–5445.

7 For some representative reviews, see: (*a*) R. Noyori and T. Ohkuma, *Angew. Chem., Int. Ed*., 2001, **40**, 40–73; (*b*) H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner and M. Studer, *Adv. Synth. Catal.*, 2003, **345**, 103–151.

8 BINAP = 2,2'-bis(diphenyllphosphino)-1,1'-binaphthyl; H_8-BINAP = 2,2'-bis(diphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl. X. Zhang, H. Kumobayashi and H. Takaya, *Tetrahedron: Asymmetry*, 1994, **5**, 1179–1182.

9 T. Ohkuma, M. Koizumi, H. Doucet, T. Pham, M. Kozawa, K. Murata, E. Katayama, T. Yokozawa, T. Ikariya and R. Noyori, *J. Am. Chem. Soc*., 1998, **120**, 13529–13530.

10 H. Doucet, T. Ohkuma, K. Murata, T. Yokozawa, M. Kozawa, E. Katayama, A. F. England, T. Ikariya and R. Noyori, *Angew. Chem., Int. Ed.*, 1998, **37**, 1703–1707.

11 (*a*) J. Wu, H. Chen, W. H. Kwok, K. H. Lam, Z. Y. Zhou, C. H. Yeung and A. S. C. Chan, *Tetrahedron Lett.*, 2002, **43**, 1539–154; (*b*) J. Wu, J.-X. Ji, R.-W Guo, C.-H. Yeung and A. S. C. Chan, *Chem.–Eur. J.*, 2003, **9**, 2963–2968.

12 D. J. Morris, A. M. Haye and M. Wills, *J. Org. Chem.*, 2006, **71**, 7035–7044..

13 For some recent reviews, see: (*a*) O. Riant, N. Mostefai and J. Courmarcel, *Synthesis*, 2004, 2943–2958; (*b*) S. Rendler and M. Oestreich, *Angew. Chem., Int. Ed.*, 2007, **46**, 498–504; (*c*) S. Díez-González and S. P. Nolan, *Acc. Chem. Res.*, 2008, **41**, 349–358; (*d*) C. Deutsch, N. Krause and B. H. Lipshutz, *Chem. Rev.*, 2008, **108**, 2916–2927; (*e*) B. H. Lipshutz, *Synlett* 2009, 509–524; (*f*) G. A. Carmela, *Mini-Rev. Org. Chem.*, 2009, ***6***, 159–167 and references cited therein.

14 For some selected examples of copper-catalyzed asymmetric hydrosilylation of simple ketones, see: (*a*) H. Brunner and W. Miehling, *J. Organomet. Chem.*, 1984, **275**, C17–C21; (*b*) B. H. Lipshutz, K. Noson and W. Chrisman, *J. Am. Chem. Soc.*, 2001, **123**, 12917–12918; (*c*) S. Sirol, J. Courmarcel, N. Mostefai and O. Riant, *Org. Lett.*, 2001, **3**, 411–4113; (*d*) B. H. Lipshutz, K. Noson, W. Chrisman and A. Lower, *J. Am. Chem. Soc.*, 2003, **125**, 8779–8789; (*e*) D.-W. Lee and J. Yun, *Tetrahedron Lett.*, 2004, **45**, 5415–5417; (*f*) J. Wu, J.-X. Ji and A. S. C. Chan, *Proc. Natl. Acad. Sci. USA*, 2005, **102**, 3570–3575; (*g*) C.-T. Lee and B. H. Lipshutz, *Org. Lett.*, 2008, **10**, 4187–4190; (*h*) K. Junge, B. Wendt, D. Addis, S. Zhou, S. Das and M. Beller, *Chem.–Eur. J.*, 2010, **16**, 68–73; (*i*) W. J. Li and S. X. Qiu, *Adv. Synth. Catal.*, 2010, **352**, 1119–1122.

15 3,5-Xyl-MeO-BIPHEP = (6,6′-Dimethoxybiphenyl-2,2′-diyl)bis[bis-(3,5-dimethylphenyl)phosphine]. R. Schmid, E. A. Broger, M. Cereghetti, Y. Crameri, J. Foricher, M. Lalonde, R. K. Muller, M. Scalone, G. Schoettel and U. Zutter, *Pure Appl. Chem.*, 1996, **68**, 131–138.

16 DTBM-SEGPHOS = (4,4'-bi-1,3-benzodioxol)-5,5'-diylbis(di(3,5-di-tert-4-methoxyphenyl)phosphane). T. Saito, T. Yokozawa, T. Ishizaki, T. Moroi, N. Sayo, T. Miura and H. Kumobayashi, *Adv. Synth. Catal.*, 2001, **343**, 264–267.

17 J. Wu, A. S. C. Chan, *Acc. Chem. Res.* **2006**, *39*, 711–720.

18 (*a*) X.-C. Zhang, Y. Wu, F. Yu, F.-F. Wu, J. Wu and A. S. C. Chan, *Chem. Eur. J.*, 2009, **15**, 5888–5891; (*b*) X.-C. Zhang, F.-F. Wu, S. Li, J.-N, Zhou, J. Wu, N. Li, W. Fang, K. H. Lam and A. S. C. Chan, *Adv. Synth. Catal.*, 2011, **353**, 1457–1462; (*c*) F. Yu, J.-N. Zhou, X.-C. Zhang, Y.-Z. Sui, F.-F. Wu, L.-J. Xie, A. S. C. Chan and J. Wu, *Chem.–Eur. J.* 2011, **17**, 14234–14240. (*d*) Y.-Z. Sui, X.-C. Zhang, J.-W. Wu, S. Li, J.-N. Zhou, M. Li, W. Fang, A. S. C. Chan and J. Wu, *Chem.–Eur. J.* 2012, **18**, 7486–7492.

19 (*a*) F. Yu, X.-C. Zhang, F.-F. Wu, J.-N. Zhou, W. Fang, J. Wu, A. S. C. Chan, *Org. Biomol. Chem.* 2011, **9**, 5652–5654; (*b*) F.-F. Wu, J.-N. Zhou, Q. Fang, Y.-H. Hu, S. Li, X.-C. Zhang, A. S. C. Chan and J. Wu, *Chem. Asian J.*, 2012, *7*, 2527–2530; (*c*) Y. Wu, S.-B. Qi, F.-F. Wu, X.-C. Zhang, M. Li, J. Wu and A. S. C. Chan, *Org. Lett.*, 2011, **13**, 1754–1757.

20 J. Wu, H. Chen, Z.-Y. Zhou, C.-H. Yeung and A. S. C. Chan, *Synlett*, 2001, 1050–1054.

21 L. Zhang and J. Herndon, *Organometallics*, 2004, **23**, 1231–1235.

22 A. Gossauer, F. Nydegger, T. Kiss, R. Sleziak and S.-E. Helen, *J. Am. Chem. Soc.*, 2004, **126**, 1772–1780.

23 Y. Sato, H. Kurihara, K. Kamijo, Y. Onozaki, T. Tsujino, T. Sugimoto, A. Watanabe, M. Mitsuya and H. Komatani, PCT Int. Appl. WO 2006049339, 2006.

24 J.-P. McCormick, A.-S. Fitterman and D.-L. Barton, *J. Org. Chem.*, 1981, **46**, 4708–4712.

25 D. W. Thomas US 3381017, 1968.

26 G.-W. Kabalka and Y.-H. Ju, *Tetrahedron*, 2001, **57**, 1663–1670.

27 J.-P. Guette, *Tetrahedron*, 1979, **35**, 1801–1805.

28 A.-M. DeBerardinis, M.Turlington and L. Pu, *Org. Lett.*, 2008, **10**, 2067–2070.

29 W. H. Baarschers, *Org. Mass Spectrom.*, 1972, **6**, 367–372.

30 B. Yoshihiro, H. Ryoma, T. Ryosuke, PCT Int. Appl. WO 2009110520, 2009.

31 Y. Yamamoto and A. Yanagi, Chem. Pharm. Bull., 1982, **30**, 2003–2010.

