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New chiral lithium aluminum hydrides based on biphenyl-2,2′-bisfenchol (BIFOL): structural analyses and enantioselective reductions of aryl alkyl ketones

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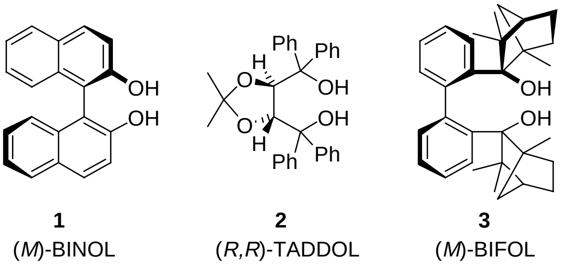
Abstract—A series of new chiral lithium aluminum hydrides based on BIFOL (biphenyl-2,2′-bisfenchol) and various alkyl alcohols (i.e., methanol, *n*-butanol, *tert*-butanol yielding BIFAl-H's) was synthesized and characterized by single crystal X-ray analyses. These investigations point to alkoxide redistribution for BIFAl-H-(O-*t*Bu) (biphenyl-2,2′-bisfenchol aluminum hydride) species. The new BIFAl-H reagents are suitable to reduce aryl alkyl ketones with up to 62% ee. Computational transition structure analyses help to explain the experimentally observed enantioselectivities.

1. Introduction

Lithium aluminum hydride (LAH) represents a powerful reducing agent and is frequently employed in organic synthesis, for example, for conversions of carbonyl functions to alcohols.[1] Appropriate chiral derivates of LAH are widely used as reagents for enantioselective reductions of prochiral ketones.[2] The C_2-symmetric diols BINOL (**1**)[3] and TADDOL (**2**)[4] (Scheme 1) are highly effective for such enantioselective reductions in combination with an alkyl alcohol.[5] The structural characterization of such modified LAH reagents is hence of major interest. Some chiral LAH alkoxides tend to disproportionation and aggravate the syntheses of a well defined reducing species with high enantioselectivity. The use of chelating diols decreases the appearance of multiple LAH species.[5] IR structure analyses of BINOL modified LAH alkoxides by Noyori et al. show that disproportionated LAH species are detectable.[5] Further examinations by Noeth et al. by means of X-ray structure and ^{27}Al NMR analyses show the phenomenon of disproportionation and redistribution of LAH alkoxides.[6]

The chiral chelating diol (*M*)-BIFOL (biphenyl-2,2′-bisfenchol, **3**, Scheme 1), recently developed in our group, exhibits a C_2-axis, which is induced and stabilized by beneficial alignment of the fenchol moieties via hydrogen bonding.[7] As in BINOL (**1**), this flexible biaryl axis can adopt to different metal sizes via rotation around the biaryl axis. Modular aryl fenchols were successfully employed in enantioselective palladium and copper catalyzed C–C-couplings,[8] in organo zinc catalysts[9] and in chiral organo lithium reagents.[10] We here present structural analyses of (*M*)-BIFOL modified lithium aluminum hydrides and their application in enantioselective reductions of aryl alkyl ketones.



Scheme 1. Chiral C_2-symmetric diols for chiral lithium aluminum hydrides.

2. Results and discussion

A series of enantiopure lithium aluminum hydrides, that is, BIFAl-H-(O-R) (**4a**,**b**,**c**), was prepared from $LiAlH_4$, (*M*)-BIFOL and an alkyl alcohol, that is, methanol, *n*-butanol or *tert*-butanol (Scheme 2).

Keywords: Enantioselective reductions; Chiral lithium aluminum hydrides; X-ray structure analyses; Transition structure analyses.

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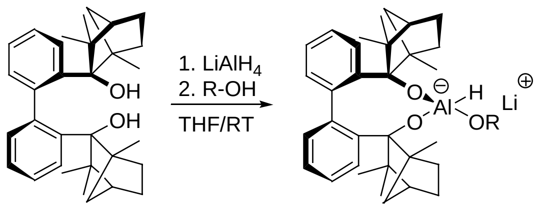
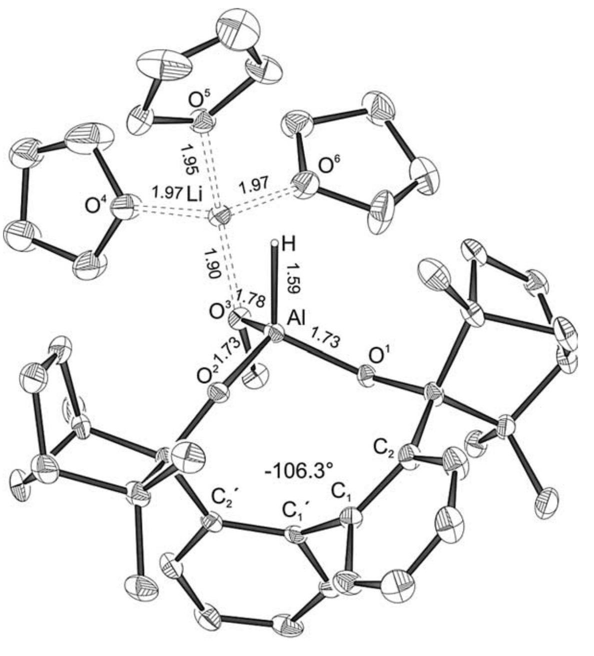


3 (*M*)-BIFOL)

(*M*)-BIFAl-H-(O-R)
4a: R=Me
4b: R=*n*Bu
4c: R=*t*Bu

Scheme 2. Synthesis of chiral, BIFOL-based aluminum hydrides, (*M*)-BIFAl-H-(O-R).

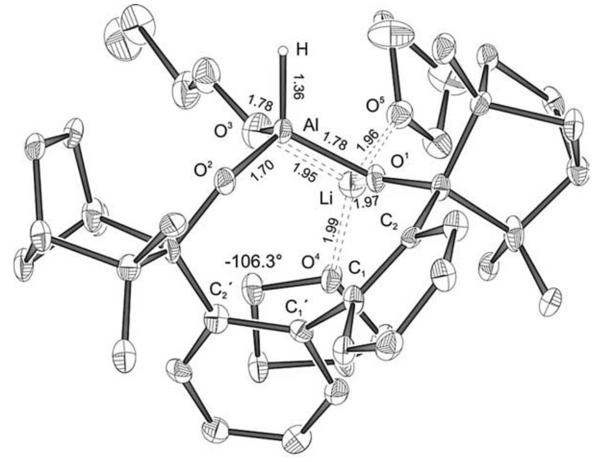
X-ray structures of **4a** and **4b** (Figs. 1 and 2) reveal the formation of the expected reactive hydride species. As observed by the groups of Noyori[5] and Noeth,[6] aging of the reaction solution may give rise to redistribution of hydride components (LiAlH$_{4-n}$(RO)$_n$, Scheme 3). Indeed, the formation of (*M*)-BIFAl-(O-*t*Bu)$_2$ **5** (Fig. 3) from **4c** points to such a redistribution.



4a·3 THF

Figure 1. X-ray crystal structure of **4a**. Hydrogen atoms are omitted except H1. Thermal ellipsoids represent a 20% probability. Selected atom distances (in Å): Al–H1 1.59, Al–O1 1.73, Al–O2 1.73, Al–O3 1.78, Li–O3 1.90, Li–O4 1.97, Li–O5 1.95, Li–O6 1.97. Biaryl angle: C_2–C_1–C_1'–C_2' −106.3°.

Molecular structures of **4a**, **4b** and **5** (Figs. 1–3) show all tetra coordinated lithium and aluminum ions. In the molecular structure of **4a** (Fig. 1) the Li-ion coordinates to three oxygen atoms of three THF ligands with Li–O distances of 1.97 (O4), 1.95 (O5) and 1.97 Å (O6). The Li–O3 distance to the BIFOL ligand is shorter (1.90 Å) than the distances to the solvent THF. The molecular structure of **4b** shows a Li-ion, which is coordinated by two THF molecules with Li–O distances of 1.96 (O3) and 1.99 Å (O5), one oxygen of the BIFOL ligand (2.06 Å) and the *n*-butoxy unit (1.95 Å). In **5** the Li-ion is coordinated by two THF and two oxygen from the *tert*-butanol moieties. The structure of **5** exhibits a shorter Li–O distance to the *tert*-butoxy (1.99 Å (O3), 1.93 Å (O4)) than to the two THF molecules (2.04 Å (O5), 2.05 Å (O6)). All examined BIFAl-H-(O-R) structures crystallize in (*M*) conformations of the chiral biaryl axis. The computed relative energy of the optimized (*M*)-**6-calc** structure is 20.3 kcal/mol lower than its diastereomer (*P*)-**6-calc** (Table 1, Figs. 4 and 5). The dihedral angels of the chiral C_2-axis are very similar (**4a**: −106.3°; **4b**: −106.3°, **5**: −107.4°), which suggest that the influence of the alkyl alcohols are rather small and the steric interactions between the bulky fenchone moieties are high. Hence, the minus biaryl conformations of fenchone moieties in (*M*)-BIFAl-H-(O-R) are more favorable than in the (*P*)-conformations. This parallels the situation in (*M*)-BIFOL, where additional hydrogen bonding contributes to the stabilization of the (*M*)-conformation. Computations and X-ray analyses of BIFAl-H-(O-R) tends to a 100% de of the (*M*) biaryl axis. Similar results were obtained for (*M*)-BIFOL.[7] Enantioselective reduction of aryl alkyl ketones like butyrophenon with (*M*)-BIFAl-H-(O-*n*Bu) yields (*S*)-1-phenylbutane-1-ol in an enantiomeric excess of 62% (Table 2, Scheme 4). Reductions of acetophenon, methylacetophenon and propiophenon result in a range of 3–50% ee.

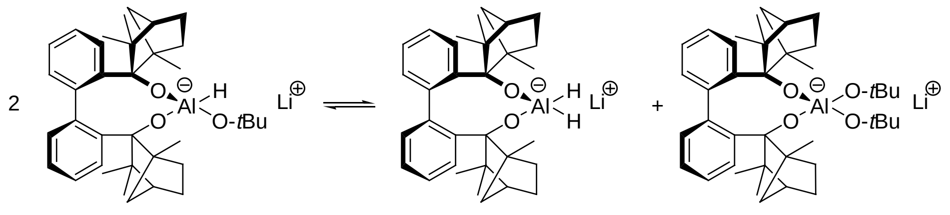


4b·1 THF

Figure 2. X-ray crystal structure of **4b**. Hydrogen atoms are omitted except H1. Thermal ellipsoids represent a 20% probability. Selected atom distances (in Å): Al–H1 1.36, Al–O1 1.78, Al–O2 1.70, Al–O3 1.78, Li–O1 1.97, Li–O3 1.95, Li–O4 1.99, Li–O5 1.96. Biaryl angle: C_2–C_1–C_1'–C_2' −106.3°.

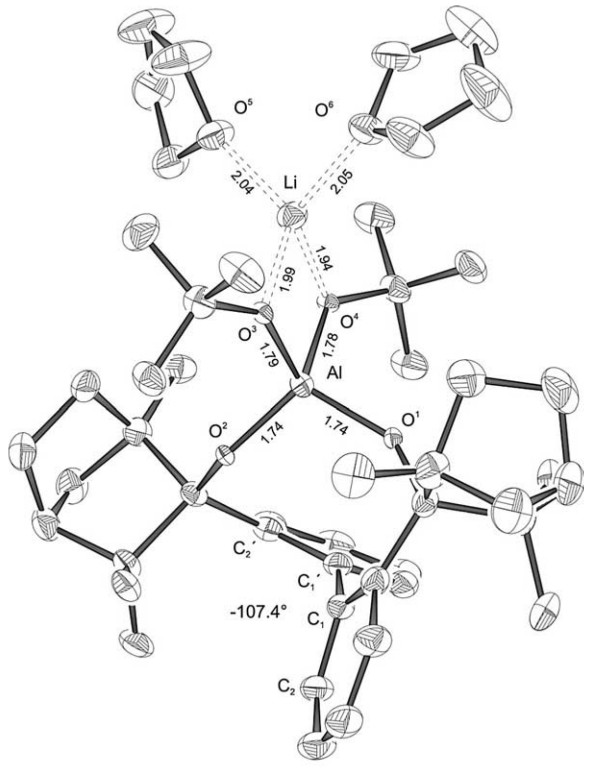
To predict the sense of enantioselectivity for aryl alkyl ketone reductions, Noyori et al. proposed a six-membered transition state model for the reduction of aryl alkyl ketones with (*M*)-BINAl-H-(O-R).[5] Repulsive p–π interactions between the oxygen lone pairs and the delocalized π-system of the phenyl rest favores (*S*)-configuration of the secondary alcohol (Scheme 5).[5]

This qualitative transition state model was adopted for quantitative transition structure computations of the reduction of different prochiral aryl alkyl ketones with (*M*)-BIFAl-H-(O-R). Each reducing agent and the appropriate substrate yielding the highest enantioselectivity were chosen for transition state optimization. In all three cases the



4c **5**

Scheme 3. Redistribution of (*M*)-BIFAl-H-(O-*t*Bu) according to the attempted synthesis of **4c** and the subsequent detection of **5** via X-ray crystal structure analyses.



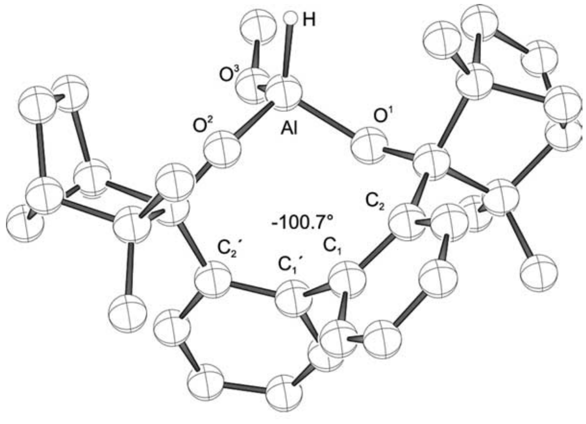
5·2 THF

Figure 3. X-ray crystal structure of **5**. Hydrogen atoms are omitted. Thermal ellipsoids represent a 20% probability. Selected atom distances (in Å): Al–O1 1.74, Al–O2 1.74, Al–O3 1.79, Al–O4 1.78, Li–O3 1.99, Li–O4 1.93, Li–O5 2.04, Li–O6 2.05. Biaryl angle: C_2–C_1–C_1'–C_2' −107.4°.

Table 1. Computed relative energies (E_{rel}, kcal/mol) of (*P*)- and (*M*)-conformations of BIFAl-H-(O-R)[a]

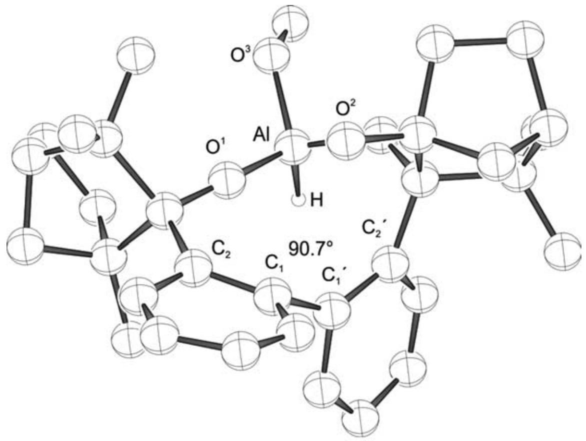
R	(*M*)-BIFAl-H-(O-R)-**calc**	(*P*)-BIFAl-H-(O-R)-**calc**
Me (**6**)	0	25.0
*n*Bu	0	23.4
*t*Bu	0	23.2

[a] MNDO optimized, see Refs. 11–13. Relative energies without ZPE correction.



(*M*)**-6-calc**

Figure 4. MNDO optimized structure of the (*M*)-BIFAL-H-(O-Me) anion. Biaryl angle: C_2–C_1–C_1'–C_2' −100.7°.



(*P*)**-6-calc**

Figure 5. MNDO optimized structure of (*P*)-BIFAL-H (O-Me) anion. Biaryl angle: C_2–C_1–C_1'–C_2' 90.7°.

(*S*)-configuration of the corresponding alcohol is more favorable than (*R*)-configuration (Table 3; Figs. 6 and 7).[11,12,13]

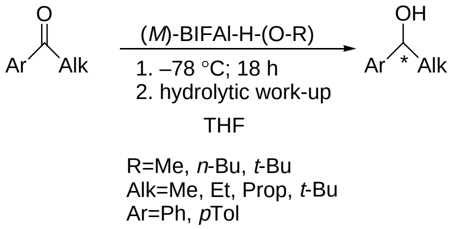
3. Conclusions

The new (*M*)-BIFAl-H-(O-R) reagents are efficiently accessible and suitable for the reduction of aryl alkyl ketones with moderate to fairly good enantioselectivities. X-ray structure analyses and computations reveal only (*M*)-conformations of these BIFOL modified lithium aluminum hydrides. The appearance of BIFAl(O-*t*Bu)$_2$ (**5**) provides evidence for hydride–alkoxide redistributions, according to earlier studies on alkoxide modified lithium aluminum

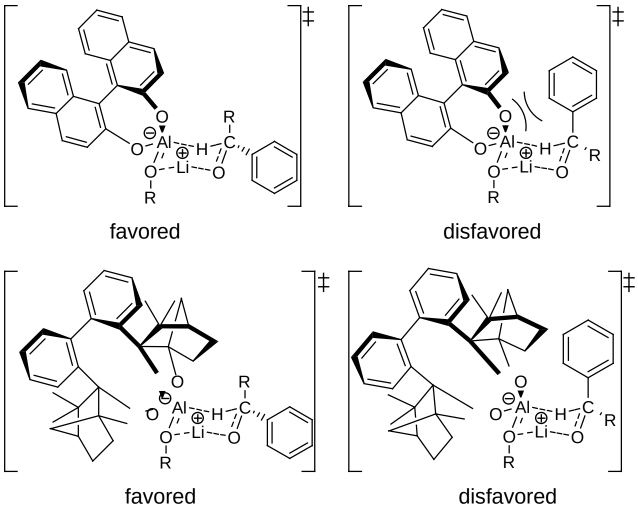
Table 2. Enantioselective reductions of aryl alkyl ketones with BIFAl-H-(O-R) (**4a**,**b**,**c**)[a]

Ketone		(*M*)-**4a**		(*M*)-**4b**		(*M*)-**4c**	
Alk	Ar	conf	ee (%)	conf	ee (%)	conf	ee (%)
Me	Ph	*R*	37	*R*	38	*R*	15
Me	*p*Tol	*S*	22	*S*	39	*S*	38
Et	Ph	*S*	23	*S*	32	*R*	4
Pr	Ph	*R*	24	*S*	62	*R*	17
*t*Bu	Ph	*S*	50	*S*	37	*S*	3

[a] Enantioselectivities were determined by chiral GC (Chiraldex-GTA column). Absolute configurations were determined by POLAR LμP-WR polarimeter. Isolated yields (not optimized) are up to 20%.



Scheme 4. (*M*)-BIFAl-H-(O-R) for enantioselective reductions of prochiral ketones.



Scheme 5. Transition structures of the (*M*)-BINAl-H-(O-R) and (*M*)-BIFAl-H-(O-R) reduction of prochiral aryl alkyl ketones.

Table 3. Computed relative energies (E_{rel}, kcal/mol) and imaginary frequencies (i, cm^{-1}) of six-membered transition structures for alkyl aryl ketone redutions (for **4b** cf. Figs. 6 and 7)[a]

BIFAL-H+alkyl aryl ketones	(*S*) E_{rel}(kcal/mol)	(*R*) E_{rel} (kcal/mol)
4a+*t*Bu, Ph	0 (*i* 846)	1.4 (*i* 807)
4b+Pr, Ph	0 (*i* 716)	0.9 (*i* 439)
4c+Me, *p*Tol	0 (*i* 691)	7.9 (*i* 569)

[a] B3LYP/6-31G*//ONIOM (B3LYP/6-31G* (Al, Li, O, C, H): MNDO), see Refs. 11–13. Relative energies without ZPE correction.

hydride disproportionations. Transition state modeling can reflect some origins of enantioselectivity. Besides their application as hydride transfer reagents, the BIFAl-H species are promising chiral Lewis acids. Such properties are currently under investigation.

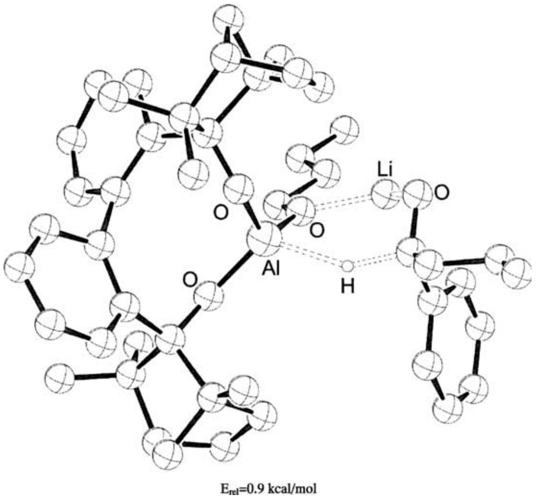


Figure 6. B3LYP/6-31G*//ONIOM (B3LYP/6-31G* (Al, Li, O, C, H): MNDO) optimized transition state leading to (*R*)-1-phenylbutanol (disfavored TS).

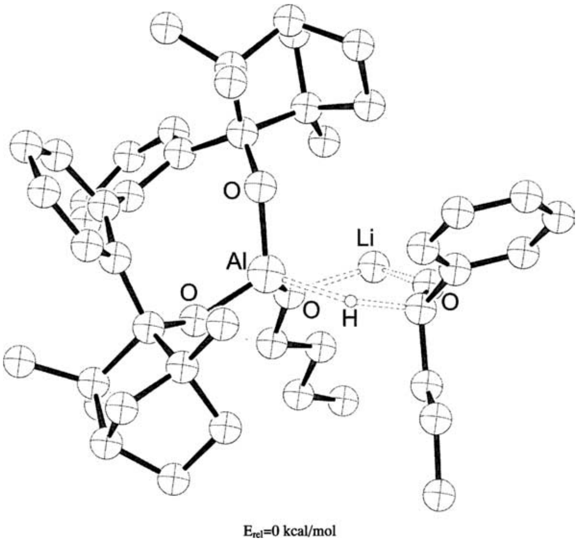


Figure 7. B3LYP/6-31G*//ONIOM (B3LYP/6-31G* (Al, Li, O, C, H): MNDO) optimized transition state leading to (*S*)-1-phenylbutanol (favored TS).

4. Experimental

All reactions and crystallization approaches were carried out under argon atmosphere using long necked Schlenk-tubes dried by heatgun. THF was always freshly distilled over sodium under argon atmosphere before use. Methanol was distilled over magnesium under argon. *n*-Butanol and *tert*-butanol (HPLC-Grade) were used without drying. Lithium aluminum hydride (LAH) was used as a 1 M solution in THF commercially available from Aldrich. Enantiomeric excess of the chiral secondary alcohols were measured on a Hewlett Packard HP 6890 GC (chiral capillary column: Chiraldex-GTA, 30 m, 0.25 mm, 0.25 μm); Absolute configuration of the chiral secondary alcohols were determined by POLAR LμP-WR polarimeter (wavelenght: 589 nm); X-ray analysis were recorded with Nonius Kappa CCD diffractometer (Mo Kα; wavelength $\lambda = 0.71073$ Å).

4.1. Synthesis and crystallization of (*M*)-BIFAl-H-(O-Me) 4a·3THF

(*M*)-BIFOL (1 mmol) was dissolved in 5 ml abs THF in a schlenk-tube and 1.2 equiv of a 1 M solution of lithium aluminum hydride in THF was added under few elusion of hydrogen. The mixture was stirred for 30 min. Then 1 mmol abs methanol was added slowly under a rapid stream of hydrogen gas and stirred again for 30 min. For crystallization the solution was cooled down to 4 °C for 3 days and then cooled down to −28 °C for 5 days. White crystals separated. Yield: 0.26 g (35%). X-ray crystal data of **4a**: $C_{45}H_{68}AlLiO_6$; $M=738.91$; space group orthorhombic, $a=9.9449(8)$ Å, $b=19.389(1)$ Å, $c=22.483(1)$ Å, $\alpha=90$, $\beta=90$, $\gamma=90$; $V=4335.3(6)$ Å^3; $Z=4$; $T=293(2)$ K; $\mu=0.091$ mm^{-1}; reflections total: 24407, unique: 9202, observed: 3695 ($I>2\sigma(I)$); parameters refined: 577; $R1=0.0549$, $wR2=0.1097$; GOF=0.895.

4.2. Synthesis and crystallization of (*M*)-BIFAl-H-(O-*n*Bu) 4b·1THF

(*M*)-BIFOL (1 mmol) was dissolved in 5 ml abs THF in a schlenk-tube and 1.2 equiv of a 1 M solution of lithium aluminum hydride in THF was added under few elusion of hydrogen. The mixture was stirred for 30 min. Then 1 mmol *n*-butanol was added slowly under a rapid stream of hydrogen gas and stirred again for 30 min. For crystallization the solution was cooled down to −28 °C for 3 days. White crystals separated. Yield: 0.10 g (14%). X-ray crystal data of **4b**: $C_{44}H_{66}AlLiO_5$; $M=708.89$; space group monoclinic, $a=9.4880(10)$ Å, $b=19.6400(10)$ Å, $c=11.6700(10)$ Å, $\alpha=90$, $\beta=113.157(5)$, $\gamma=90$; $V=1999.4(3)$ Å^3; $Z=2$; $T=100(2)$ K; $\mu=0.094$ mm^{-1}; reflections total: 5582, unique: 2216, observed: 1485 ($I>2\sigma(I)$); parameters refined: 466; $R1=0.0757$, $wR2=0.1783$; GOF=1.049. All THF were disordered. Only one orientation is shown.

4.3. Synthesis and crystallization of (*M*)-BIFAl-(O-*t*Bu)$_2$ 5·2THF

(*M*)-BIFOL (1 mmol) was dissolved in 3 ml abs THF in a schlenk-tube and 1.2 equiv of a 1 M solution of lithium aluminum hydride in THF was added under few elusion of hydrogen. The mixture was stirred for 30 min. Then 1 mmol *tert*-butanol was added slowly under a rapid stream of hydrogen gas and stirred again for 30 min. For crystallization the solution was cooled down to 4 °C for 3 days and then cooled down to −28 °C for 3 days. White crystals separated. Yield: 0.13 g (17%). X-ray crystal data of **4c**: $C_{48}H_{74}AlLiO_6$; $M=789.99$; space group monocline, $a=10.4959(2)$ Å, $b=19.2992(4)$ Å, $c=11.9120(2)$ Å, $\alpha=90$, $\beta=111.476(1)$, $\gamma=90$; $V=2245.39(7)$ Å^3; $Z=2$; $T=293(2)$ K; $\mu=0.091$ mm^{-1}; reflections total: 18192, unique: 9791, observed: 7781 ($I>2\sigma(I)$); parameters refined: 566; $R1=0.0390$, $wR2=0.1218$; GOF=0.656.

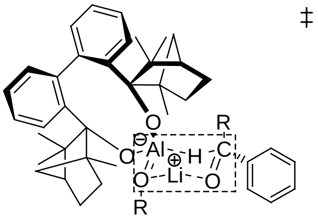
4.4. Enantioselective reduction of the acetophenon, methylacetophenon, propiophenon, butyrophenon, pivalophenon

The respective (*M*)-BIFAl-H-(O-R) reagent was prepared from 2.5 mmol (*M*)-BIFOL and 1 equiv of a 1 M solution of lithium aluminum hydride. After stirring for 30 min, 1 equiv of a primary alkyl alcohol, respectively, methanol, butanol or *tert*-butanol was added slowly under a rapid stream of hydrogen gas. The solution was stirred again for 30 min and cooled down to −78 °C. Then 0.5 equiv of the aryl alkyl ketone was dissolved in 2 ml abs THF was added drop wise. The solution was stirred for 18 h and quenched with 0.5 ml methanol followed by acidic work-up with 2 N HCl and neutral work-up with saturated $NaSO_4$-solution. The secondary alcohol was extracted with diethyl ether. The organic phase was washed with saturated NaCl-solution and dried over $NaSO_4$. The resulting secondary alcohol was distilled and analyzed by chiral GC (Chiraldex-GTA column) and polarimetry.

5. Computational details

All structures were fully optimized and characterized by frequency computations using Gaussian 03[11] with standard basis sets 6-31G*[12] and the B3LYP [13] hybrid-DFT method.

Oniom method is used for transition state computations (Scheme 6).



Scheme 6. B3LYP/6-31G*//ONIOM (B3LYP/6-31G* (Al, Li, O, C, H): MNDO) optimized transition state. B3LYP/6-31G* optimized area is framed.

6. Supplementary material

Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 271631 for compound **4a**; No. 271632 for compound **4b** and No. 271633 for compound **5**. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336 33) or deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk

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