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Highly Enantioselective Transfer Hydrogenation of Polar Double Bonds by Macrocyclic Iron(II) / $(NH)_2P_2$ Catalysts

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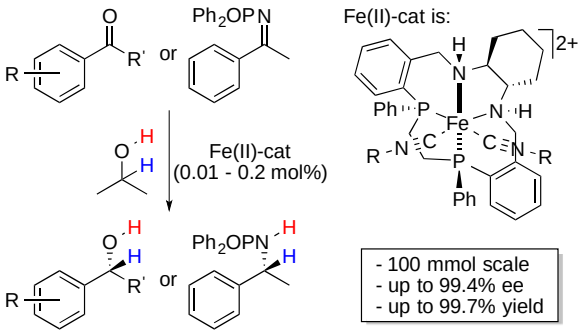


Abstract

We describe herein a new protocol for the synthesis of 2,2'-((1*S*,1'*S*)-ethane-1,2-diylbis(phenylphosphanediyl))dibenzaldehyde ((S_P,S_P)-**5**), which is the key intermediate in the synthesis of macrocyclic iron(II) / $(NH)_2P_2$ catalysts for the highly enantioselective transfer hydrogenation of polar double bonds. The dialdehyde (S_P,S_P)-**5** was obtained as a single diastereoisomer and enantiomer from an optically pure *H*-phosphinate in 33% yield over five steps. It was further converted to afford multi-gram quantities of the macrocyclic iron(II) / $(NH)_2P_2$ complexes, which were tested in the asymmetric transfer hydrogenation of aryl alkyl ketones and imines in 2-propanol on a 100 mmol scale. Ten substrates, including challenging ones such as *tert*-butyl phenyl ketone and industrially relevant molecules such as 3,5-bis(trifluoromethyl)acetophenone, were reduced in high yield (89.0 – 99.7%), excellent enantioselectivity (95.8 – 99.4% ee), and with low catalyst loadings (S / C up to 10 000 / 1).

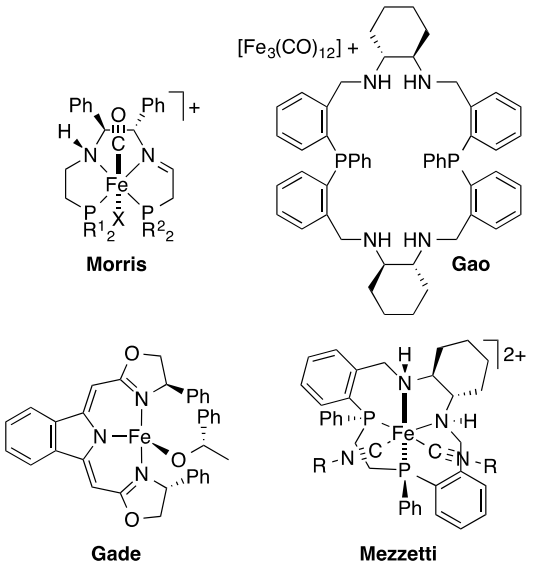
Keywords: iron – macrocycles – asymmetric catalysis – transfer hydrogenation – alcohols

Introduction

Enantiomerically pure alcohols and amines bearing a stereogenic carbon atom in the α-position are present in a variety of pharmaceuticals, agrochemicals as well as flavor and fragrance compounds, and the most straightforward way to prepare them is the asymmetric hydrogenation of prochiral ketones or imines, respectively. In academia, such asymmetric reductions are ubiquitous and a variety of well-defined and highly enantioselective catalysts have been prepared or are even commercially available.[1] However, most of these catalysts are based on ruthenium, iridium, or rhodium, and the high toxicity and costs of these late transition metals has been hindering their implementation in industry.[2] An intriguing alternative to these precious metal catalysts is the use of cheap, abundant and environmentally benign early transition metals, and iron is currently one of the most intensively investigated alternatives.[3]

The iron-catalyzed asymmetric reduction of polar double bonds has been pioneered by Gao,[4] and was further developed by Morris,[5] Beller[6] and Gade.[7] Currently, the most active iron-based system for the asymmetric reduction of aryl alkyl ketones has been developed by Morris, whose third generation Fe(II) / PNNP catalyst achieves outstanding TOFs (up to 200 s^{-1}) and is most efficient under asymmetric transfer hydrogenation (ATH) conditions using 2-propanol as solvent ($R^1 = R^2$ = xylyl, X = Cl, Chart 1).[5g] This catalyst is highly active, but the enantioselectivity is only moderate with most substrates (24 – >99% ee). Higher enantioselectivity was achieved by introducing bulky alkyl phosphines (R^1 = Ph, R^2 = cyclohexyl, X = Br), but at the cost of significantly decreased activity.[5i]

Chart 1. State-of-the-art iron catalysts for the asymmetric reduction of polar bonds.



A highly enantioselective system (generally ≥95% ee) for the asymmetric direct hydrogenation of ketones with H_2 has been developed by Gao using a potentially hexadentate $(NH)_4P_2$ macrocycle in combination with $[Fe_3(CO)_{12}]$, but its activity was modest (TOF up to 40 h^{-1}).[4d] The same catalyst system is also active in the ATH of aryl alkyl ketones, where TOFs of up to 1 940 h^{-1} were achieved without loss of enantioselectivity.[4c] The most selective catalyst (generally ≥98% ee) bearing a tridentate ^{H}boxmi-Ph ligand was recently reported by Gade for the hydrosilylation of ketones, but low temperature (gradient from -78 °C to r.t.) and high catalyst loadings (5 mol%) are necessary.[7,8]

We recently prepared a series of complexes of the type $[Fe(CNR)_2((NH)_2P_2)]^{2+}$, in which a C_2-symmetric macrocycle ($(NH)_2P_2$) carries the chiral information, and isonitriles act as sterically and electronically tunable ancillary ligands.[9-11] These complexes catalyze the ATH of aryl alkyl ketones using 2-propanol as hydrogen donor with high enantioselectivity (generally >95% ee) and activity (TOF up to 1 960 h^{-1}). The macrocyclic complexes are the first iron-based, well-

defined precatalysts that combine high activity with excellent enantioselectivity for a broad range of ketones. Also, the substrate scope includes challenging ketones such as *tert*-butyl phenyl ketone,[12] as well as industrially relevant substrates such as 3,5-bis(trifluoromethyl)aceto-phenone.[13] While these complexes are excellent precatalysts for ATH, their preparation is still challenging as the synthesis of the key intermediate 2,2'-((1*S*,1'*S*)-ethane-1,2-diylbis(phenyl-phosphanediyl))dibenzaldehyde ((S_P,S_p)-**5**) is time-consuming, rather low-yielding (15% over 6 steps),[14] and relies on the use of Jugé's oxazaphospholidine borane,[15] which is prepared using controlled (–)-ephedrine.

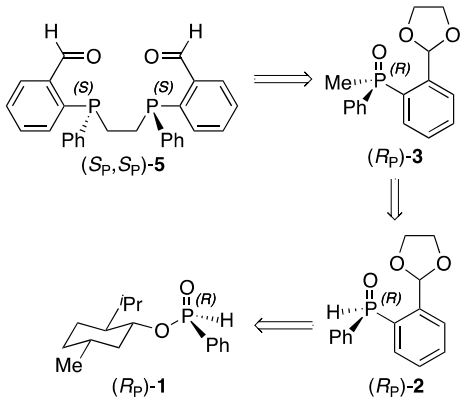
Herein, we report a new synthetic approach to the key dialdehyde (S_P,S_p)-**5** that relies on Han's strategy for the synthesis of enantiomerically enriched secondary phosphine oxides starting from optically pure, ambiphilic *H*-phosphinates.[16,17] This new protocol was used to prepare gram quantities of the previously reported macrocyclic iron(II) / $(NH)_2P_2$ complexes, which allowed us to assay the corresponding bis(isonitrile) complexes in the ATH of ketones and imines on a 100 mmol scale. The results described below confirm the robustness of this new catalyst system and demonstrates its scalability and synthetic utility.

Results and Discussion

General Strategy. The new retrosynthetic approach shown in Scheme 1 indicates that the key dialdehyde (S_P,S_P)-**5** can be obtained by an oxidative coupling / stereoselective reduction / deprotection sequence from enantiomerically pure (*R*)-(2-(1,3-dioxolan-2-yl)phenyl)(methyl)-(phenyl)phosphine oxide ((R_P)-**3**), which in turn is obtained by stereoretentive alkylation of the corresponding secondary phosphine oxide (R_P)-**2**. For the preparation of enantiomerically pure (R_P)-**2,** we chose the method developed by Han,[16,17] which relies on the stereospecific

substitution of secondary *H*-phosphinate (R_P)-**1** with an appropriate organolithium or Grignard reagent.

Scheme 1. Retrosynthetic Analysis of Dialdehyde (S_P,S_P)-**5**

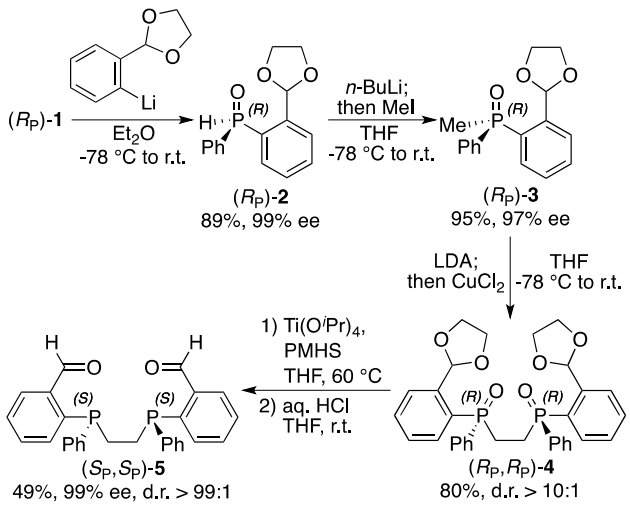


Following Han's procedure, diastereomerically pure (R_P)-(1*R*,2*S*,5*R*)-2-isopropyl-5-methyl-cyclohexyl phenylphosphinate ((R_P)-**1**) was prepared on a >60 g scale in a single step from dichlorophenylphosphine and (–)-menthol, followed by quenching with water and selective crystallization of one diastereoisomer at low temperature.[16]

Synthesis of Dialdehyde (S_P,S_P)-5. Adapting Han's method for the preparation of enantiomerically enriched secondary phosphine oxides,[16a] the (–)-menthyl group in (R_P)-**1** was substituted by (2-(1,3-dioxolan-2-yl)phenyl)lithium (prepared from the corresponding aryl bromide and ^{t}BuLi) at low temperature to give (R_P)-**2** as a single enantiomer and with *inversion* of configuration at phosphorus (Scheme 2).[18] Alkylation of the lithiated secondary phosphine oxide with methyl iodide at low temperature afforded phosphine oxide (R_P)-**3** in high yield and good enantiospecificity (97% ee) with *retention* of configuration at phosphorus. On an 81 mmol scale, (R_P)-**3** was obtained in high yield (85% over two steps) and with good purity (>96% pure

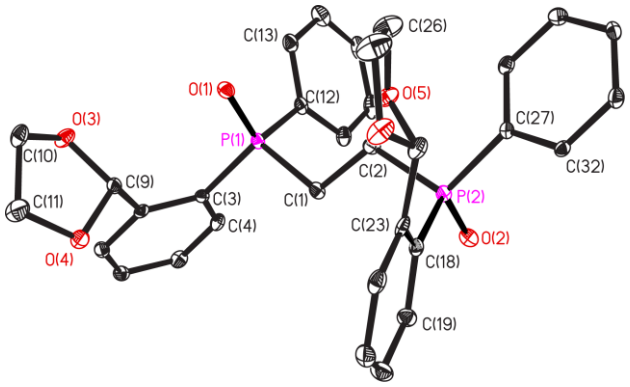
by $^{31}P\{^{1}H\}$ NMR spectroscopy) by simple extraction, thus circumventing the need for flash column chromatography.

Scheme 2. Synthesis of Dialdehyde (S_P,S_P)-**5**



Oxidative coupling of (R_P)-**3** using copper(II) chloride as oxidant after deprotonation of the methyl group with lithium diisopropylamide[19] afforded bisphosphine oxide (R_P,R_P)-**4** in 80% yield on a 59 mmol scale and with a diastereomeric ratio of >10:1. The absolute configuration of (R_P,R_P)-**4** was determined to be (R_P,R_P) by X-ray diffractometry (Figure 1). Attempts to directly couple deprotonated (R_P)-**2** using 1,2-diiodoethane or 1,2-ditosylatoethane only resulted in unidentified side products, and no (R_P,R_P)-**4** was isolated.

Figure 1. ORTEP drawing of (R_P,R_P)-**4** (with ellipsoids at 30% probability)



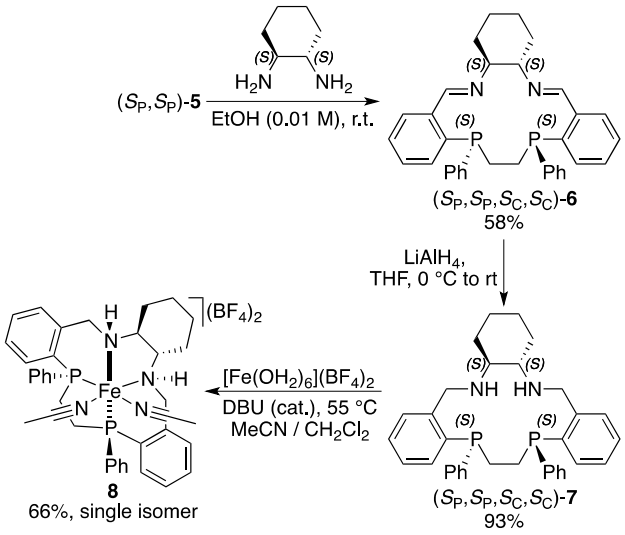
Having installed the skeleton of dialdehyde (S_P,S_P)-**5** in three steps from (R_P)-**1**, the last two steps included the stereospecific reduction of the phosphine oxide to the free phosphine and the deprotection of the aldehyde moiety. While several methods have been described for the stereoselective reduction of tertiary phosphine oxides,[20] the presence of the sensitive acetal groups rendered this reaction a formidable task. Several standard reduction methods (i.e. $HSiCl_3$ / amine,[21] $PhSiH_3$,[22] or $(Et_3O)BF_4$ / $NaBH_4$[23]) gave either low yields or low stereospecificity. Eventually, we found that the inexpensive combination of $Ti(O^iPr)_4$ and PMHS cleanly afforded the desired phosphine with *retention* of configuration at phosphorus.[24] The reduced diphosphine was directly treated with aqueous hydrochloric acid to cleave the acetal groups and give the crude diphosphine (S_P,S_P)-**5** as a ca. 6.4:1 mixture of diastereoisomers. Removal of the minor isomer by crystallization from hot methanol as previously described[14] afforded enantio- and diastereomerically pure (S_P,S_P)-**5** in 49% yield based on (R_P,R_P)-**4** and 5.3 g of pure (S_P,S_P)-**5** were prepared in a single batch. The analytic and spectroscopic data of the resulting product were identical to those of (S_P,S_P)-**5** obtained by the first route.[14]

Diphosphine (S_P,S_P)-**5** is routinely stored in a freezer under argon atmosphere, and no decomposition is observed in the solid state over several months. Prolonged exposure of solutions of (S_P,S_P)-**5** to air leads to oxidation of the phosphine. Concerning the configurational stability at phosphorus, no epimerization was observed in the solid state and in solution at room temperature. However, heating in solution, such as during recrystallization from methanol, should be kept to a minimum to avoid the formation of the *meso* diastereoisomer.

Overall, the synthetic route described herein efficiently affords (S_P,S_P)-**5** in an overall yield of 33% over five steps with a single purification by flash column chromatography and one recrystallization. Furthermore, as (+)-menthol is also commercially available (albeit at a slightly higher price than the (–)-form), both enantiomers of *like*-**5** can be accessed. Compared to the previous synthesis, which afforded dialdehyde (S_P,S_P)-**5** in 15% overall yield after six steps,[14] the present synthetic strategy is shorter, higher yielding, cheaper, and significantly easier to perform as the purifications are less cumbersome and all reaction can be performed on a >20 mmol scale. Also, the substitution of (–)-ephedrine by (–)-menthol is a clear advantage, as access to the former is restricted because of its role in the synthesis of methamphetamine.

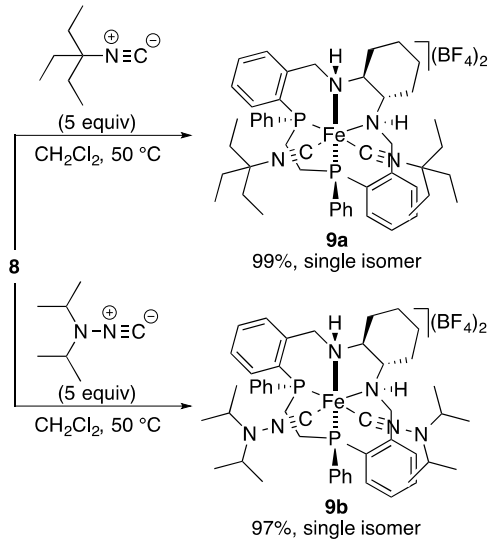
Synthesis of Bis(isonitrile) Complexes. With gram quantities of (S_P,S_P)-**5** in hand, the bis(isonitrile) iron(II) complexes **9a** and **9b** were prepared as previously described (Scheme 3, see Supporting Information for detailed experimental procedures).[9,14] In a first step, dialdehyde (S_P,S_P)-**5** was treated with (1*S*,2*S*)-cyclohexane-1,2-diamine under high-dilution conditions (0.01 M in EtOH) to afford macrocycle (S_P,S_P,S_C,S_C)-**6**, which precipitates from the solution upon concentration and was isolated as a single diastereoisomer in 58% yield on a 10 mmol scale.[14]

Scheme 3. Synthesis of Bis(acetonitrile) Complex **8**



The imine moieties in macrocycle (S_P,S_P,S_C,S_C)-**6** were cleanly reduced with lithium aluminum hydride to afford the corresponding diamino macrocycle (S_P,S_P,S_C,S_C)-**7** in high yield and purity after simple filtration through silica gel.[9] Therefore, the reduced $(NH)_2P_2$ macrocycle (S_P,S_P,S_C,S_C)-**7** was not further purified and treated directly with iron(II) tetrafluoroborate hexahydrate in MeCN / CH_2Cl_2 at 55 °C in the presence of DBU (25 mol%). A catalytic amount of DBU is necessary to isomerize the initial mixture of two Λ-*cis*-β isomers and a *trans* isomer to the thermodynamic isomer Λ-*cis*-β-[Fe(MeCN)$_2$(**7**)](BF$_4$)$_2$ (**8**), which was obtained as a single isomer after crystallization from MeCN / Et_2O (see Supporting Information for detailed experimental procedures).[9] The structure of the bis(acetonitrile) complex **8**, including the absolute configuration of the newly formed stereocenters on the nitrogen atoms, has previously been determined by X-ray diffractometry.[14] This procedure afforded 2.7 g of the bis(acetonitrile) complex **8** as a monomeric, diamagnetic and stable solid in a single reaction highlighting the scalability of this route to such macrocyclic iron(II) / $(NH)_2P_2$ complexes.

Scheme 4. Synthesis of Bis(isonitrile) Complexes **9a** and **9b**



In the last step of the catalyst synthesis, the ancillary acetonitrile ligands in **8** were substituted by bulky isonitriles (Scheme 4, see Supporting Information for detailed experimental procedures). Quantitative substitution of the acetonitrile ligands by the isonitriles was observed within 24 h at 50 °C (as readily monitored by $^{31}P\{^{1}H\}$ NMR spectroscopy), and the bis(isonitrile) derivatives $[Fe(CNR)_2(\mathbf{7})](BF_4)_2$ (R = CEt_3, **9a**; R = N^iPr_2, **9b**) were obtained as single configurational isomers in high yield on a 1.0 g scale. The sterically demanding isonitriles $CNCEt_3$ and CNN^iPr_2 were used as the steric bulk significantly increases the enantioselectivity in the ATH of ketones as previously described.[9] As the isonitrile ligands are introduced in the last step of the catalyst synthesis, the Fe(II) / $(NH)_2P_2$ catalyst system is highly tunable (both electronically and sterically) to give optimal results for specific substrates.

Bis(isonitrile) complexes **9a** and **9b** were routinely stored in a glove box and did not show any sign of decomposition over several months. However, both **9a** and **9b** tolerate exposure to air and moisture, at least for limited periods of time. In control experiments, exposure of these

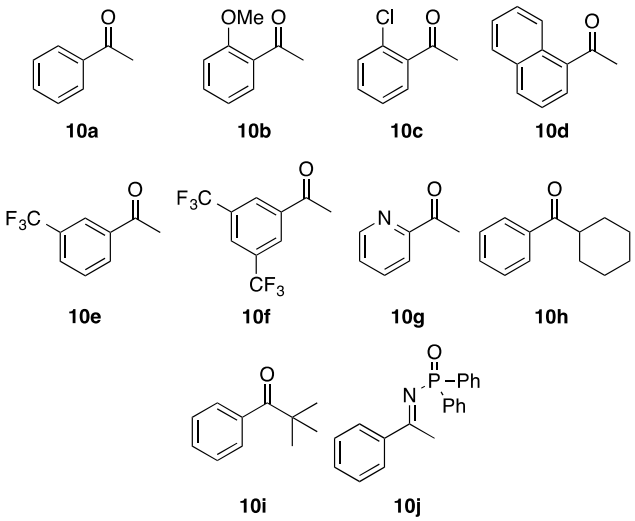
complexes to air both as a solid or in "wet" dichloromethane solutions over several days did not result in any decomposition of the bis(isonitrile) iron(II) complexes as confirmed by ^{1}H NMR and $^{31}P\{^{1}H\}$ NMR spectroscopy.

ATH of Polar Bonds. We have previously reported the ATH of a series of prochiral ketones and imines catalyzed by the macrocyclic bis(isonitrile) Fe(II) / $(NH)_2P_2$ complexes **9a** and **9b** with 2-propanol as hydrogen source.[9] The corresponding alcohols and amines were obtained in high yields (up to 99.9% GC yield) and excellent enantioselectivity (up to 99.3% ee) with relatively low catalyst loading (generally 0.1 mol%) at slightly elevated temperatures (50 and 60 °C for **9a** and **9b**, respectively). The substrate scope included standard aryl alkyl ketones, but also challenging ones such as acyl pyridines, *ortho*-substituted acetophenones, and *tert*-butyl phenyl ketone as well as industrially relevant ones such as 3,5-bis(trifluoromethyl)-acetophenone[13] and 3-trifluoromethylacetophenone.[25] Overall, aryl alkyl ketones were reduced with higher enantioselectivity (generally >95% ee) than dialkyl ketones (up to 24% ee), whereas enones were hydrogenated to allylic alcohols with complete chemoselectivity but moderate enantioselectivity (70% ee).[9] As all reactions were run on relatively small scale (2.5 mmol), we were interested in assaying bis(isonitrile) precatalysts **9a** and **9b** in the asymmetric transfer hydrogenation of prochiral substrates on a larger scale (100 mmol) to highlight the synthetic utility of the catalyst system.

As the ATH of aryl alkyl ketones using 2-propanol as hydrogen source is an equilibrium reaction, and catalysts **9a** and **9b** are inactive in direct hydrogenation, we focus here on substrates for which the equilibrium lies far to the side of the optically active alcohol. This is the case for substrates bearing electron-poor or *ortho*-substituted aromatics or bulky alkyl groups (Chart 2).[9] Nevertheless, the 2-propanol system is in principle not restricted to such substrates,

and strategies to bias the equilibrium towards the formation of the optically active alcohol have been developed. These strategies often rely on the constant removal of the by-product acetone (by distillation)[26] or cycling of the reaction mixture (by complete removal of the solvent and resubjection to reaction conditions).[5h]

Chart 2. Substrates for ATH



For all substrates shown in Chart 2, the ATH reactions were first optimized on a 10 mmol scale before scale-up to 100 mmol. Generally, it was found that an increase of the reaction temperature from 50 to 60 °C for catalyst **9a** (or from 60 °C to 75 °C for catalyst **9b**) increased the activity of the catalyst without erosion of enantioselectivity (Table 1). The optimization of the reaction conditions for each substrate allowed to decrease the catalyst loadings as compared to the reactions on a 2.5 mmol scale, in which 0.1 and 0.4 mol% was used for substrates **10a**-**10g** and **10h**-**10j**, respectively.[9] A further advantage of the increased reaction temperature is the shift of the reaction equilibrium to the product side, which increases the theoretical yield of the optically active alcohol.

Table 1. ATH of substrates **10a**-**10j**[a]

entry	substrate	catalyst	S / C / B[b]	temperature (°C)	time (h)	yield (%)[c]	ee (%)[d]
1	**10a**	**9a**	10 000 / 1 / 25	60	2.0	91.8	96.3
2	**10a**	**9b**	5 000 / 1 / 20	75	3.0	90.7	97.8
3	**10b**	**9a**	2 500 / 1 / 15	60	2.5	98.8	99.4
4	**10c**	**9b**	2 500 / 1 / 15	75	2.0	99.3	97.6
5	**10d**	**9b**	2 500 / 1 / 15	75	1.5	99.3	99.4
6	**10e**	**9a**	1 500 / 1 / 10	60	1.0	99.7	97.1
7	**10f**	**9a**	5 000 / 1 / 20	60	1.5	98.6	99.1
8	**10g**	**9a**	10 000 / 1 / 25	60	1.5	97.1[e]	97.3[e]
9	**10h**	**9b**	2 500 / 1 / 15	75	5.0	89.0	97.7
10	**10i**	**9b**	500 / 1 / 10	75	5.0	97.6	95.8
11	**10j**	**9a**	500 / 1 / 10	75	5.0	94.0[f]	>99.9[f]

[a] Reaction conditions: **10** (100 mmol), 2-propanol (500 mL), sodium *tert*-butoxide as base. [b] S / C / B = substrate / catalyst / base. [c] Yield of isolated product after flash column chromatography. [d] ee was determined by chiral GC or HPLC. [e] Product purified by distillation. [f] Product purified by crystallization (initial ee was 98.4%).

Under optimized conditions, (*R*)-1-phenylethan-1-ol (**11a**) was obtained in 91.8% isolated yield and with 96.3% ee by the ATH of acetophenone (**10a**) within 2.0 h by using 0.01 mol% of the $CNCEt_3$ derivative **9a** as catalyst. Complex **9b**, which bears the *N*-isonitrile CN^iPr_2, was slightly less active and afforded alcohol **11a** in 90.7% isolated yield and with 97.8% ee after 3.0 h with a catalyst loading of 0.02 mol%. For both ATH reactions, the enantioselectivity was identical to that found previously in the hydrogenation with a catalyst loading of 0.1 mol% on a 2.5 mmol scale. It should be noted that, although complexes **9a** and **9b** are stable towards air and

moisture, the ATH reaction solutions are air sensitive. Therefore, the ATH reactions were run under argon atmosphere using degassed and distilled 2-propanol (see Supporting Information for detailed experimental procedures).

The *ortho*-substituted ketones **10b**-**10d** were reduced within 1.5 – 2.5 h using either catalyst **9a** or **9b** with S / C / B = 2 500 / 1 / 15, and the optically active alcohols **11b**-**11d** were obtained in excellent isolated yields (98.8 – 99.3%) and with high enantiopurities (97.6 – 99.4% ee) after flash column chromatography. Trifluoromethyl-substituted substrates **10e** and **10f** were readily reduced with catalyst **9a**, and the corresponding alcohols **11e** and **11f**, which are important synthons for fungicides[25] and NK1-antagonists,[13] were obtained in high isolated yield and with 97.1% and 99.1% ee, respectively. Acyl-substituted heterocycles (i.e. acyl pyridines and thiophenes) were also readily reduced with complex **9a** on 2.5 mmol scale. As an example, we tested the ATH of 2-acetylpyridine (**10g**, 100 mmol) using catalyst **9a** (0.01 mol%). Full conversion to (*R*)-1-(pyridin-2-yl)ethan-1-ol (**11g**) was observed within 1.5 h corresponding to an average TOF of 6 650 h^{-1}, and the pure product was obtained by distillation in 97.1% isolated yield and with 97.3% ee.

The substrate scope is not restricted to aryl methyl ketones, though, and sterically demanding alkyl groups are well tolerated. Although a moderate increase in the catalyst loading (0.04 – 0.2 mol%) is necessary to obtain high conversion, the catalyst loadings are still significantly lower than in the small-scale reactions with the same substrates, where 0.4 mol% of catalyst was used. Cyclohexyl phenyl ketone **10h** was hydrogenated by catalyst **9b** (0.04 mol%) in 89.0% isolated yield and with an impressive 97.7% ee, which shows that the macrocyclic iron(II) / $(NH)_2P_2$ complexes **9** readily differentiate between an alkyl and an aryl group of similar size (Cy vs. Ph). Accordingly, the reduction with catalysts **9** occurs from the *si*-side of the substrate independently

from electronic and steric changes. Along these lines, the very bulky *tert*-butyl phenyl ketone **10i**, which is one of the most challenging substrates for asymmetric hydrogenation,[12] was reduced to give the corresponding alcohol **11i** in 97.6% yield and with high enantioselectivity (95.8% ee) using catalyst **9b**.

Finally, activated imines are also efficiently hydrogenated using bis(isonitrile) complex **9a**. Thus, phosphinyl imine **10j** was reduced using catalyst **9a** (0.2 mol%) to give **11j** with 98.4% ee. As purification of the reduced product by flash column chromatography is difficult due to its high polarity, the crude was crystallized directly from 2-propanol to afford pure **11j** in 94.0% isolated yield as essentially a single enantiomer (>99.9% ee). The phosphinyl group is readily cleaved by ethanolic hydrochloric acid affording chiral amines without loss of enantiopurity,[27] which makes phosphinyl imines efficient precursors to enantiopure primary amines.

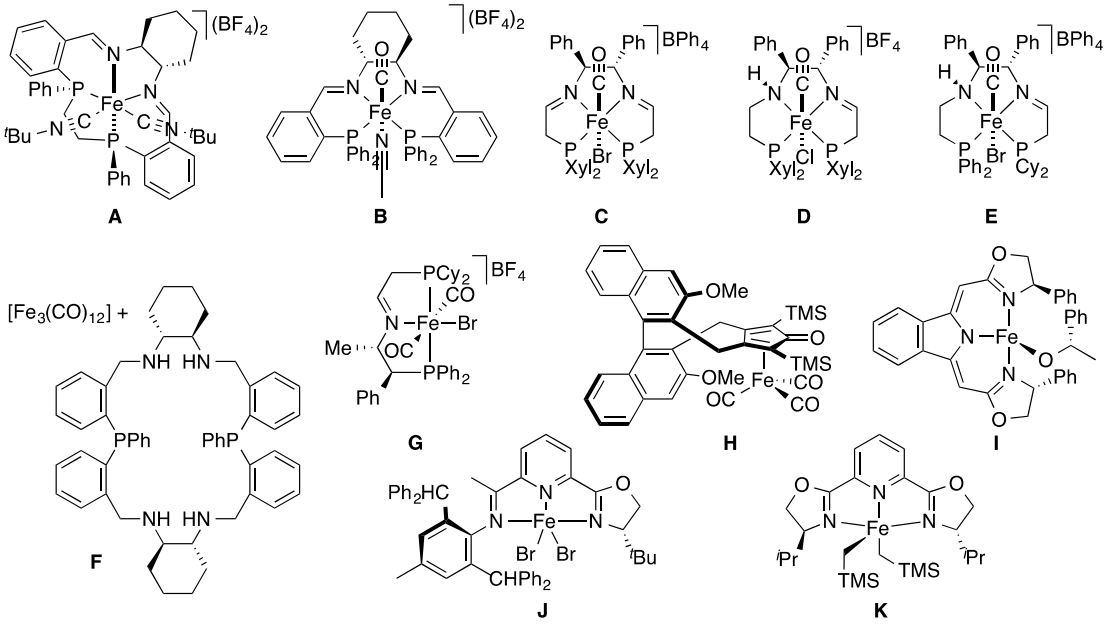
In summary, the ATH of prochiral ketones and imines with the macrocyclic bis(isonitrile) iron(II) complexes **9a** and **9b** is highly efficient and selective. A representative set of aryl alkyl ketones and an activated imine was reduced with low catalyst loadings (0.01 – 0.2 mol%) within short reaction times (1.0 – 5.0 h) on a 100 mmol scale, which highlights the robustness and synthetic utility of the iron(II) / $(NH)_2P_2$ catalyst system.

Comparison with Other Iron-based Catalysts. To gain a full overview on the recent advances in iron-catalyzed asymmetric reductions, we give here a survey of representative iron-based catalysts in the asymmetric reduction of acetophenone **10a** (as standard substrate) in terms of activity, enantioselectivity, and catalyst loading (Table 2). In an analogous comparison, Morris has shown that their second-generation catalyst **C** is considerably more active than most platinum-metal-based ATH catalysts.[5e] As can be seen from Table 2, only few iron catalysts combine high enantioselectivity (>95% ee) with good activity, though. Also taking into account

catalyst loading and reaction temperature, the data in Table 2 show that Morris' third generation complex **D** is by far the most active ATH catalyst, as it achieves 82% conversion within 3 min at room temperature with 0.016 mol% of catalyst.[5g] For comparison, catalysts **9a** and **9b** require 60 – 75 °C and 2 – 3 h to reach 92 % conversion. However, **D** is considerably less enantioselective (90% ee) than **9a** and **9b** (96 and 98% ee, respectively), and the more selective analogue **E** (98% ee) has a similar activity as **9a** and **9b**.[5i] Furthermore, in terms of substrate scope, Morris' third-generation catalysts give high enantioselectivity (>95% ee) only with a few substrates (**10f** for **D**; **10a**, **10f**, and α-chloroacetophenone for **E**).[5g-i]

Besides **9a** and **9b**, Gao's catalyst **F** is the only system that combines good enantioselectivity and high activity for a broad scope of substrates.[4c] Like **9a** and **9b**, **F** is based on macrocyclic ligands, albeit with a much larger ring size, but is considerably less active than **9a** and **9b** under ATH conditions at the same temperature. An advantage of **F** is that it is effective under direct hydrogenation conditions with 50 bar of H_2, which is particularly interesting as the ATH equilibrium is avoided.[4d]

Table 2. Comparison of iron-based catalyst for the reduction of acetophenone **10a**



catalyst	reaction type[a]	S / C	T (°C)	yield (%)	time	ee (%)	ref
9a, base	ATH	10 000	60	92	2 h	96	this work
9b, base	ATH	5 000	75	91	3 h	98	this work
A, base	ATH	100	75	93	15 h	84	10
B, base	ATH	400	22	95	24 min	29	5b
C, base	ATH	1 000	28	94	7 min	90	5e
D, base	ATH	6 121	28	82	3 min	90	5g
E, base	ATH	6 121	28	71	2 h	98	5i
F, base	ATH	2 000	75	89	2 h	97	4c
F, base	AH (50 bar)	500	45	98	12 h	96	4d
G[b], base	AH (5 bar)	1 000	50	99	30 min	80	5j
H[c]	AH (30 bar)	50	70	100	18 h	50	28
I	AHS ($(EtO)_2MeSiH$)	43	-78 to r.t.	94	6 h	98	7
J[d]	AHS (Ph_2SiH_2)	100	25	98	3 h	83	29
K[e]	AHS ($PhSiH_3$)	333	23	99	1 h	54	30

[a] ATH: asymmetric transfer hydrogenation (with 2-propanol); AH: asymmetric hydrogenation (with H_2 under specified pressure); AHS: asymmetric hydrosilylation (with specified silane). [b] Catalyst activated with $LiAlH_4$ and ^{t}AmylOH. [c] Catalyst activated with Me_3NO. [d] Catalyst activated with $NaBHEt_3$. [e] Catalyst activated with $B(C_6F_5)_3$.

Together with Gao's system **F,** Morris' PNP complex **G** is the only highly active catalyst for AH of ketones even at low hydrogen pressure (5 bar), but its enantioselectivity is modest so far (up to 85% ee).[5j] Table 2 also shows that asymmetric hydrosilylation with iron catalysts is not competitive with ATH or AH today.[7,29,30] Overall, we believe that the macrocyclic bis(isonitrile) catalysts **9a** and **9b** are valuable alternatives to the best iron catalyst systems for ATH, particularly as they are broadly applicable and predictably reduce aryl alkyl ketones with high enantioselectivity and activity throughout.

Conclusion

A new synthetic route to macrocyclic iron(II) / $(NH)_2P_2$ complexes is reported, which affords the key synthon (S_P,S_P)-**5** in 33% yield over 5 steps. This new synthetic protocol is shorter, higher yielding and easier to perform compared to the previous route[14] and multigram quantities of the dialdehyde (S_P,S_P)-**5** were prepared in a single batch. Furthermore, the substitution of (–)-ephedrine by (–)-menthol as the chiral auxiliary renders this approach more suitable because (–)-ephedrine is controlled, while menthol is commercially available in the (+)- and (–)-form, thus guaranteeing access to both enantiomers of *like*-**5** (and therefore also to the catalysts **9a** and **9b** in both enantiomeric forms).

The results reported herein show that the bis(isonitrile) complexes **9a** and **9b** bearing *C*-isonitrile $CNCEt_3$ and *N*-isonitrile CNN^iPr_2, respectively, are highly effective and enantioselective catalysts for the ATH of prochiral substrates on a 100 mmol scale. A representative set of aryl alkyl ketones **10a**-**10i** and imine **10j** was hydrogenated in high isolated yield (89.0 – 99.7%), with excellent enantioselectivity (95.8 – 99.4% ee) and low catalyst loadings (0.01 – 0.2 mol%), which highlights the robustness and synthetic utility of the iron(II) / $(NH)_2P_2$ system.

Furthermore, the application of chiral iron complexes to asymmetric reductions on synthetically useful scale shows that the highly desired substitution of precious metal catalyst by cheap and non-toxic 3*d* metals is feasible.

Experimental Section

General Procedures. Reactions with air- or moisture-sensitive materials were carried out under an argon atmosphere using Schlenk techniques. All solvents were distilled from an appropriate drying agent under argon prior to use (Et_2O and THF from Na / benzophenone; hexane from Na / benzophenone / tetraglyme; EtOH from Na / ethyl phthalate; CH_2Cl_2, MeCN, MeOH and 2-propanol from CaH_2). ^1H and ^{13}C positive chemical shifts in ppm are downfield from tetramethylsilane. $^{31}P\{^1H\}$ NMR spectra are referenced to external 85% H_3PO_4. For complexes, $^{13}C\{^{31}P,^1H\}$ were measured with ^{31}P (and ^1H) decoupling to improve the S / N ratio. Mass spectra were measured by the MS service of the Laboratory of Organic Chemistry (ETH Zürich). Elemental analyses were carried out by the Laboratory of Microelemental Analysis (ETH Zürich). Detailed experimental procedures for the preparation of all compounds, and NMR spectra thereof, are given in the Supporting Information.

(*R*)-(2-(1,3-Dioxolan-2-yl)phenyl)phenylphosphine Oxide, (R_P)-2. A pentane solution of *tert*-butyllithium (200 mL, 1.9 M, 380 mmol, 4.2 equiv) was added to 2-(2-bromophenyl)-1,3-dioxolane (28.4 mL, 190 mmol, 2.1 equiv) in Et_2O (570 mL) at -78 °C over 0.5 h. After stirring the resulting solution at 0 °C for 1.5 h, (R_P)-**1** (25.4 g, 90 mmol) in Et_2O (110 mL) was added at -78 °C over 0.5 h, after which the solution was warmed to room temperature overnight. A saturated aqueous NH_4Cl solution (400 mL) was added thereto, and the organic solvent was removed under reduced pressure. The aqueous phase was washed four times with hexane (4 ×

400 mL) and extracted four times with $CHCl_3$ (4 × 400 mL). The combined $CHCl_3$ phases were dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford the product as a slightly yellowish oil (>99% pure by $^{31}P\{^1H\}$ NMR). Yield: 22.1 g (89%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.34 (d, $^1J_{P,H}$ = 502.2 Hz, 1H, P-*H*), 7.86 (ddd, $^3J_{P,H}$ = 15.2 Hz, $^3J_{H,H'}$ = 7.5 Hz, $^4J_{H,H'}$ = 1.5 Hz, 1H, Ar-*H*), 7.73 – 7.63 (m, 3H, Ar-*H*), 7.58 (tt, $^3J_{H,H'}$ = 7.6 Hz, $^4J_{H,H'}$ = 1.6 Hz, 1H, Ar-*H*), 7.55 – 7.42 (m, 4H, Ar-*H*), 6.05 (s, 1H, C*H*$(OCH_2)_2$), 4.00 – 3.89 (m, 4H, CH(OC*H*H)$_2$). $^{31}P\{^1H\}$ NMR (122 MHz, $CDCl_3$): δ 19.0 (s). ^{31}P NMR (122 MHz, $CDCl_3$): δ 19.0 (ddt, $^1J_{P,H}$ = 502.2 Hz, $^3J_{P,H}$ = 15.2, 14.9 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 140.8 (d, $^2J_{P,C}$ = 7.5 Hz, arom.), 132.9 (d, $^2J_{P,C}$ = 10.5 Hz, arom.), 132.5 (d, $^4J_{P,C}$ = 2.7 Hz, arom.), 132.4 (d, $^1J_{P,C}$ = 102.7 Hz, arom.), 132.2 (d, $^4J_{P,C}$ = 2.9 Hz, arom.), 130.8 (d, $^2J_{P,C}$ = 11.4 Hz, arom.), 129.9 (d, $^1J_{P,C}$ = 96.1 Hz, arom.), 129.3 (d, $^3J_{P,C}$ = 12.4 Hz, arom.), 128.7 (d, $^3J_{P,C}$ = 12.9 Hz, arom.), 127.3 (d, $^3J_{P,C}$ = 9.7 Hz, arom.), 101.6 (d, $^3J_{P,C}$ = 4.4 Hz, *C*$H(OCH_2)_2$), 65.1 (CH(O*C*$H_2)_2$), 65.0 (CH(O*C*$H_2)_2$). IR (liquid film, cm^{-1}): 3058 (C-H), 2955 (C-H), 2892 (C-H), 2334 (P=O), 1645, 1591, 1573, 1483, 1474, 1438, 1398, 1347, 1311, 1293, 1177, 1134, 1113, 1096, 1065, 1038, 1023. HRMS (ESI): calcd for $C_{15}H_{16}O_3P$ *m*/*z* = 275.0832, found *m*/*z* = 275.0837 $[M + H]^+$. HPLC: Chiralpak IB-3 (hexane/2-PrOH = 80:20, flow rate 1.0 mL/min, λ = 230 nm), retention times t_R (minor) = 13.5 min, t_R (major) = 19.1 min; 99% ee. $[\alpha]^{20}_D$: +40.5 (*c* 1.0, CH_2Cl_2).

(*R*)-(2-(1,3-Dioxolan-2-yl)phenyl)(methyl)(phenyl)phosphine Oxide, (R_P)-3. A hexane solution of *n*-butyllithium (50.4 mL, 1.6 M, 81 mmol, 1.0 equiv) was added to (R_P)-**2** (22.1 g, 81 mmol) in THF (410 mL) at -78 °C and stirred for 0.5 h. Iodomethane (5.5 mL, 89 mmol, 1.1 equiv) in THF (46 mL) was added over 1.0 h, and the solution was warmed to room temperature over 3 h. The solvent was removed under reduced pressure, water (250 mL) was added to the residue, and the aqueous phase was extracted three times with $CHCl_3$ (3 × 250 mL). The

combined organic phases were dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford the product as a clear oil that solidified upon standing (>96% pure by $^{31}P\{^1H\}$ NMR). Yield: 22.0 g (95%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.83 – 7.78 (m, 1H, Ar-*H*), 7.75 – 7.66 (m, 2H, Ar-*H*), 7.62 – 7.37 (m, 6H, Ar-*H*), 6.41 (s, 1H, C*H*$(OCH_2)_2$), 4.09 – 3.85 (m, 4H, CH(OC*H*H)$_2$), 2.11 (d, $^2J_{P,H}$ = 13.3 Hz, 3H, C*H*$_3$). $^{31}P\{^1H\}$ NMR (122 MHz, $CDCl_3$): δ 27.0 (s). ^{31}P NMR (122 MHz, $CDCl_3$): δ 27.0 (qd, $^2J_{P,H}$ = 13.3 Hz, $^3J_{P,H}$ = 11.6 Hz). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 141.7 (d, $^2J_{P,C}$ = 7.3 Hz, arom.), 134.8 (d, $^1J_{P,C}$ = 101.8 Hz, arom.), 132.5 (d, $^1J_{P,C}$ = 89.6 Hz, arom.), 132.1 (d, $^4J_{P,C}$ = 2.8 Hz, arom.), 132.0 (d, $^2J_{P,C}$ = 10.8 Hz, arom.), 131.8 (d, $^4J_{P,C}$ = 2.7 Hz, arom.), 130.7 (d, $^3J_{P,C}$ = 9.8 Hz, arom.), 128.9 (d, $^3J_{P,C}$ = 7.3 Hz, arom.), 128.7 (d, $^2J_{P,C}$ = 12.0 Hz, arom.), 127.5 (d, $^3J_{P,C}$ = 9.5 Hz, arom.), 100.2 (d, $^3J_{P,C}$ = 4.4 Hz, *C*H$(OCH_2)_2$), 65.4 (2C, CH(O*C*H$_2)_2$), 18.2 (d, $^1J_{P,C}$ = 74.2 Hz, P*C*H$_3$). Melting Point: 108 °C. IR (liquid film, cm^{-1}): 3058 (C-H), 2956 (C-H), 2887 (C-H), 2216 (P=O), 1643, 1591, 1572, 1473, 1437, 1395, 1296, 1177, 1132, 1113, 1091, 1060, 1025. HRMS (ESI): calcd for $C_{16}H_{18}O_3P$ *m*/*z* = 289.0988, found *m*/*z* = 289.0985 $[M + H]^+$. HPLC: Chiralpak ID-3 (hexane/2-PrOH = 90:10, flow rate 1.0 mL/min, λ = 210 nm), retention times t_R (major) = 75.0 min, t_R (minor) = 82.3 min; 97% ee. $[\alpha]^{20}_D$: –16.9 (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{16}H_{17}O_3P$: C, 66.66; H, 5.94. Found: C, 66.48; H, 6.04.

(1*R*,1'*R*)-Ethane-1,2-diylbis((2-(1,3-dioxolan-2-yl)phenyl)(phenyl)phosphine Oxide, (*R*$_P$,*R*$_P$)-4. A hexane solution of *n*-butyllithium (51.6 mL, 1.6 M, 82.6 mmol, 1.4 equiv) was added to diisopropylamine (12.4 mL, 88.5 mmol, 1.5 equiv) in THF (48 mL) at 0 °C. After stirring for 0.5 h, this solution was added to (*R*$_P$)-**3** (17.0 g, 59.0 mmol) in THF (220 mL) at -78 °C over 0.25 h under stirring. After 5 min, copper(II) chloride (13.5 g, 100 mmol, 1.7 equiv) was added, and the solution was warmed to room temperature overnight. The solvent was removed

under reduced pressure, $CHCl_3$ (1000 mL) was added, and the organic phase was washed three times with an aqueous 10% NH_3 solution (3 × 300 mL) and once with water (300 mL). Each aqueous phase was extracted twice with $CHCl_3$ (2 × 100 mL). The combined organic phases were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Flash column chromatography on silica gel (gradient CH_2Cl_2 to MeOH : CH_2Cl_2 = 7 : 93) afforded the product as an off-white solid. Yield: 13.5 g (80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, $^3J_{H,H'}$ = 7.5 Hz, 2H, Ar-*H*), 7.72 – 7.62 (m, 4H, Ar-*H*), 7.61 – 7.35 (m, 12H, Ar-*H*), 6.45 (s, 2H, C*H*($OCH_2)_2$), 4.01 – 3.79 (m, 8H, CH(OC*H*H)$_2$), 2.90 – 2.48 (m, 4H, PC*H*H). ^{31}P{^{1}H} NMR (122 MHz, $CDCl_3$): δ 35.6 (s). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 142.4 (t, $^2J_{P,C}$ = 3.5 Hz, arom.), 133.2 (m, arom.), 132.23 (m, arom.), 132.17 (t, $J_{P,C}$ = 5.4 Hz, arom.), 132.0 (m, arom.), 131.0 (t, $J_{P,C}$ = 4.8 Hz, arom.), 130.6 (t, $^1J_{P,C}$ = 47.3 Hz, arom.), 129.0 (t, $J_{P,C}$ = 5.8 Hz, arom.), 128.7 (t, $J_{P,C}$ = 5.9 Hz, arom.), 127.7 (t, $J_{P,C}$ = 4.8 Hz, arom.), 100.2 (t, $^3J_{P,C}$ = 2.0 Hz, *C*H($OCH_2)_2$), 65.33 (CH(O*C*H$_2)_2$), 65.30 (CH(O*C*H$_2)_2$), 18.2 (t, $^1J_{P,C}$ = 33.8 Hz, P*C*H$_2$). Melting Point: 146 °C. IR (liquid film, cm^{-1}): 3058 (C-H), 3023 (C-H), 2955 (C-H), 2887 (C-H), 2227 (P=O), 1725, 1638, 1596, 1572, 1492, 1473, 1437, 1412, 1396, 1349, 1333, 1312, 1285, 1171, 1132, 1112, 1092, 1061, 1027. HRMS (ESI): calcd for $C_{32}H_{33}O_6P_2$ *m*/*z* = 575.1747, found *m*/*z* = 575.1744 $[M + H]^+$. $[\alpha]^{20}_D$: –5.6 (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{32}H_{32}O_6P_2$: C, 66.90; H, 5.61. Found: C, 66.87; H, 5.59.

2,2'-((1*S*,1'*S*)-Ethane-1,2-diylbis(phenylphosphanediyl))dibenzaldehyde, (S_P,S_P)-5. Titanium(IV) *iso*-propoxide (42.8 mL, 141 mmol, 6.0 equiv) was added dropwise to (R_P,R_P)-**4** (13.5 g, 23.5 mmol) in THF (470 mL) at 60 °C over 0.25 h and stirred for 0.25 h. PMHS (70.2 mL, average M_n = 1700 – 3200, 50 equiv) was added dropwise over 0.75 h, and the solution was stirred overnight at 60 °C. The volatiles were removed under reduced pressure, hexane (350 mL)

was added, and the suspension was stirred at 50 °C for 0.5 h before cooling to -78 °C. The precipitate was filtered over Celite, washed twice with hexane (2 × 15 mL), and dissolved in THF (430 mL). The resulting solution was filtered and 5% aqueous HCl (215 mL) was added thereto. After stirring for 5 h at room temperature, a saturated aqueous $NaHCO_3$ solution (400 mL) was added, and the organic solvent was removed under reduced pressure. The aqueous phase was extracted three times with CH_2Cl_2 (3 × 400 mL), the combined organic phases were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Filtration through silica gel (EtOAc : hexane = 1 : 3) and crystallization from hot MeOH afforded the product as a yellow solid. Yield: 5.28 g (49%). ^{1}H NMR (300 MHz, CD_2Cl_2): δ 10.55 (t, $^4J_{P,H}$ = 2.7 Hz, 2H, O=C*H*), 7.94 – 7.85 (m, 2H, Ar-*H*), 7.55 – 7.45 (m, 4H, Ar-*H*), 7.37 – 7.25 (m, 12H, Ar-*H*), 2.29 – 2.01 (m, 4H, PC*H*H). ^{31}P{^{1}H} NMR (122 MHz, CD_2Cl_2): δ –22.0 (s, (S_P,S_P)-**5**), –22.2 (s, (R_P,S_P)-**5**); dr > 99 : 1. ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2): δ 192.4 (m, *C*HO), 142.6 (m, arom.), 139.5 (m, arom.), 137.9 (m, arom.), 134.1 (arom.), 133.7 (m, arom.), 132.5 (arom.), 131.3 (arom.), 129.6 (arom.), 129.4 (arom.), 129.2 (m, arom.), 24.2 (m, P*C*H$_2$). Melting Point: 128 °C. IR (liquid film, cm^{-1}): 3054 (C-H), 2823 (C-H), 2739 (C-H), 1693 (C=O), 1584, 1561, 1482, 1461, 1433, 1422, 1386, 1294, 1258, 1197, 1163, 1117, 1094. HRMS (ESI): calcd for $C_{28}H_{24}NaO_2P_2$ *m*/*z* = 477.1144, found *m*/*z* = 477.1135 [M + Na]$^+$. $[\alpha]^{20}_D$: +35.6 (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{28}H_{24}O_2P_2$: C, 74.00; H, 5.32. Found: C, 73.73; H, 5.30. Analytical data are in agreement with literature data.[14] For the determination of the enantiomeric purity, the product was converted to (((1*S*,1'*S*)-ethane-1,2-diylbis(phenylphosphanediyl))bis(2,1-phenylene))dimethanol diborane.[14] HPLC: Chiralpak IC-3 (hexane/2-PrOH, 80:20, flow rate 1.0 mL/min, λ = 230 nm), retention times t_R ((R_P,R_P)) = 7.9 min, t_R ((R_P,S_P)) = 8.9 min, t_R ((S_P,S_P)) = 11.0 min; >99% ee.

Representative ATH Reaction: (+)-(*R*)-1-Phenylethan-1-ol, 11a. 2-Propanol (500 mL) was added to **9a** (10.2 mg, 10.0 μmol, 0.01 mol%) and sodium *tert*-butoxide (24.0 mg, 250 μmol, 0.25 mol%) and the yellow solution was stirred for 10 min at 60 °C. Acetophenone (**10a**) (11.7 mL, 100 mmol) was added to the resulting homogeneous solution, and the reaction progress was monitored by gas chromatography. After 2.0 h, the solvent was removed under reduced pressure. Flash column chromatography on silica gel (gradient Et_2O : pentane = 1 : 9 to 3 : 2) afforded the product as a clear liquid. Yield: 11.22 g (91.8%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 – 7.27 (m, 5H, Ar-*H*), 4.92 (d, $^3J_{H,H'}$ = 6.4 Hz, 1H, C*H*OH), 2.10 (br s, 1H, O*H*), 1.53 (d, $^3J_{H,H'}$ = 6.4 Hz, 1H, CH_3). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 145.9 (arom.), 128.6 (arom.), 127.5 (arom.), 125.5 (arom.), 70.5 (*C*HOH), 25.3 (*C*H_3). IR (liquid film, cm^{-1}): 3338 (O-H), 3085 (C-H), 3062 (C-H), 3029 (C-H), 2972 (C-H), 2926 (C-H), 2872 (C-H), 1602, 1493, 1450, 1407, 1368, 1327, 1283, 1261, 1203, 1177, 1156, 1098, 1075, 1028, 1009. HRMS (EI): calcd for $C_8H_{10}O$ *m*/*z* = 122.0727, found *m*/*z* = 122.0727 $[M]^+$. GC: β-DEX column, 100 °C isotherm, retention times t_R (major) = 22.2 min, t_R (minor) = 24.1 min; 96.3% ee. $[\alpha]^{20}_D$: +61.3 (*c* 1.0, $CHCl_3$). Analytical data are in agreement with literature data.[9]

ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures and characterization of all products.

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Notes

The authors declare no competing financial interest.

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