Organocatalytic Stereoisomerization versus Alkene Isomerization: Catalytic Asymmetric Synthesis of 1-Hydroxy-*trans*-2,5-diphenylphospholane 1-Oxide

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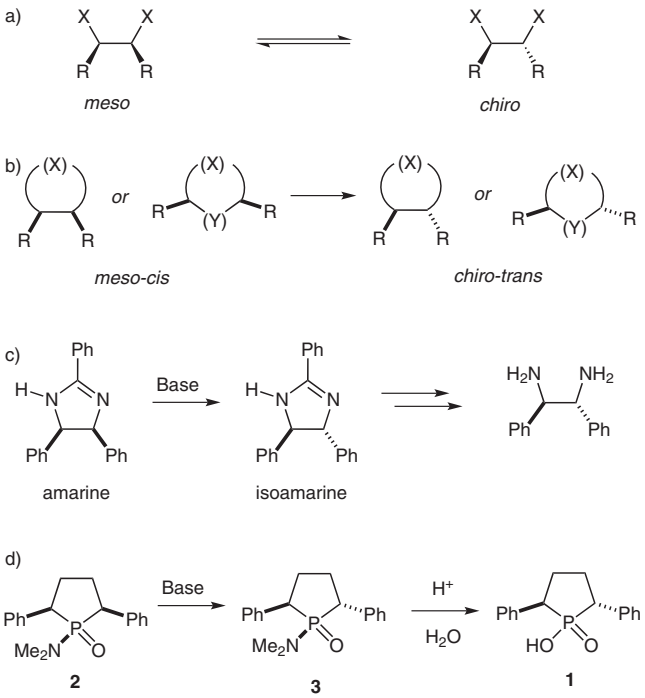
Abstract: The potential for an organocatalytic asymmetric stereoisomerization or alkene isomerization as atom-economic reaction with minimal structural change was investigated. The McCormack cycloaddition of 1,4-diarylbuta-1,3-dienes with (dialkylamino)dichlorophosphane and aluminum trichloride gives *meso*-2,5-diaryl-1-(dialkylamino)-1-oxo-2,5-dihydro-1*H*-phospholes, which were identified as suitable substrates for asymmetric isomerization to (1*R*,5*R*)-2,5-diaryl-1-(dialkylamino)-1-oxo-4,5-dihydro-1*H*-phospholes in the presence of bifunctional organocatalysts (cinchona alkaloids, Takemoto catalyst) in up to 91% ee and quantitative yield. The substrate range and the mechanism of the catalysis were studied. The reaction involves proton abstraction by the base, but a primary deuterium KIE is absent. Enriched (1*R*,5*R*)-1-(diethylamino)-1-oxo-2,5-diphenyl-4,5-dihydro-1*H*-phosphole was hydrolyzed to (5*R*)-1-hydroxy-1-oxo-2,5-diphenyl-4,5-dihydro-1*H*-phosphole, which was hydrogenated diastereoselectively under dissolving metal conditions to give (2*R*,5*R*)-1-hydroxy-1-oxo-2,5-diphenylphospholane (Fiaud's acid) in preference to *meso*-1-hydroxy-1-oxo-2,5-diphenylphospholane. An asymmetric catalytic total synthesis of Fiaud's acid, which is a building block for chiral phospholane synthesis, has been realized in five steps from thiophene, using nickel-catalyzed Wenkert arylation, McCormack cycloaddition, asymmetric dihydro-1*H*-phosphole isomerization, hydrolysis, and diastereoselective hydrogenation.

Key words: asymmetric catalysis, isomerization, heterocycles, phosphorus, stereoselective synthesis

Introduction

Catalytic and stereoselective isomerization reactions with retention of the carbon skeleton[1] are attractive synthetic tools that can increase molecular complexity with full atom economy. Examples include alkene isomerizations,[2] including rearrangements of allyl ethers or amines to enol ethers or enamines, respectively.[3] The rhodium-catalyzed asymmetric isomerization of nerylamine has gained prominence as the key step of an industrial synthesis of (–)-menthol.[3,4] The manner of breaking and making C–H bonds in these reactions is not readily transferred to organocatalysis. Alternatively, several alkene and alkyne isomerizations proceed via carbanions.[5] In principle, such reactions are amenable to asymmetric organocatalysis by chiral organic bases; indeed, the first examples have been reported (*vide infra*).[6] In contrast to double-bond shifts, stereoisomerization reactions proceed with retention of bond connectivity and order. The equilibration of *meso* and *chiro* diastereomers [Scheme 1 (a)] is an example.[7] There is no obvious enthalpic driving force for such *isodesmic* reactions. Equilibrium mixtures of *meso* and *chiro* isomers are obtained, and asymmetric catalysis is hardly feasible in the absence of a driving force.[8] The situation changes, once the groups X are joined to a small cycle [Scheme 1 (b)].



Scheme 1 Examples of hypothetic or established stereoisomerization reactions amenable to asymmetric catalysis

The *meso*/*chiro* transformation becomes a *cis*/*trans* isomerization that profits from releasing the eclipsing strain of the R groups in several ring systems. This principle is seen at work in the base-mediated isomerization of amarine to isoamarine[9] which forms the basis of a stereoselective synthesis of racemic 1,2-diphenylethylenediamine [Scheme 1 (c)].[10] With the aim of developing an asymmetric catalytic stereoisomerization reaction, we planned to study organocatalytic *meso*/*chiro* or *cis*/*trans* isomeriza-

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tions. Model reactions of the type shown in Scheme 1 (b) were defined: *meso*-heterocycles including acceptor groups X/Y should be capable of undergoing chiral base-catalyzed stereoisomerization via deprotonation of acidified α-CH bonds. The attractive reaction shown in Scheme 1 (c) appeared unsuitable due to the limits of the base strength of typical organocatalysts.[11] Through a database search for suitably activated heterocycles, we found Fiaud's synthesis of (±)-1-hydroxy-1-oxo-*trans*-2,5-diphenylphospholane (**1**) using a base-catalyzed isomerization of *meso*-**2** to chiral *trans*-1-amino-1-oxophospholane **3** as the key step [Scheme 1 (d)]. The racemic acid **1** can be resolved by crystallization with quinine.[12] Our attempts to catalyze the transformation of **2** to **3** with chiral bases like the cinchona alkaloids were not successful.[13] As reported in our communication, we next turned to the more activated *meso*-2,5-dihydro-1*H*-phosphole **4**, a precursor of **2**,[12] and found its asymmetric organocatalytic double-bond isomerization to the chiral 4,5-dihydro-1*H*-phosphole **5** [Scheme 2 (a)].[14] Deng and co-workers have recently realized a related asymmetric isomerization of achiral 3-butenolides to enantioenriched 2-butenolides

Biographical Sketches

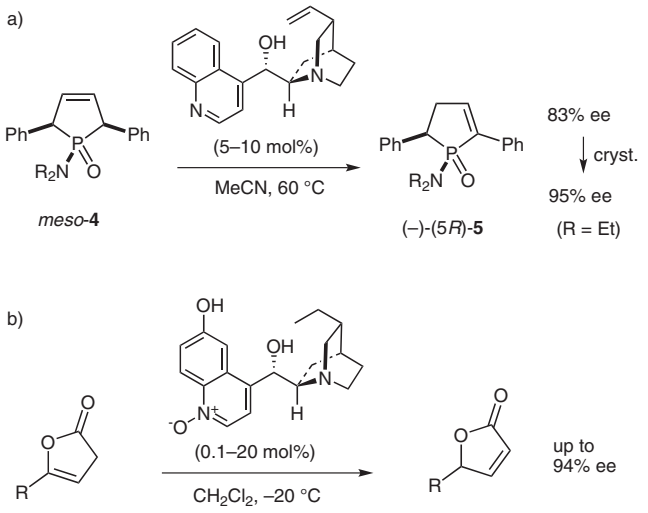
Lukas Hintermann was born in Switzerland in 1972. He studied chemistry at ETH Zurich, obtaining a Ph.D. in 2000 for work on asymmetric catalytic fluorination performed with Antonio Togni. In 2001–2002 he visited the Tokyo Institute of Technology as a JSPS postdoctoral fellow with Keisuke Suzuki. He started independent research at RWTH Aachen University in Germany, hosted by Carsten Bolm and supported by an Emmy Noether program of the DFG. In 2009, he accepted his current professorship at the Technische Universität München (TUM). He is recipient of the medal of the ETH, the Heisenberg fellowship of the DFG, and the Friedrich-Wilhelm-Preis of the RWTH Aachen. His research interests are centered on developing catalytic reactions towards solving specific synthetic problems, and for applications in sustainable organic synthesis.

Marco Schmitz was born in Hamm, Germany, in 1977. He studied chemistry at RWTH Aachen University, Germany, which he concluded with a thesis in technical chemistry with Prof. Marcel Liauw, receiving his diploma in 2004. Starting in 2005, he performed research in the group of Prof. Hintermann on the derivatization of cinchona alkaloids and asymmetric catalytic synthesis of phospholanes, for which he received a Ph.D. degree in 2009. Since 2009, he has been working as Regulatory Affairs Manager in the Novartis/Sandoz-Hexal group at Salutas Pharma GmbH.

Oleg Maltsev was born in Kumertau, Russian Federation, in 1985. He studied chemistry at D. I. Mendeleyev University of Chemical Technology of Russia and N. D. Zelinsky Institute of Organic Chemistry Russian Academy of Sciences, where he earned his Ph.D. in 2011 with work on recoverable chiral ionic liquids as enantioselective organocatalysts with Prof. Sergey G. Zlotin. In 2011, he joined the group of Prof. Hintermann at TUM as HFSP postdoctoral fellow. He is recipient of the Gold Medal of the Russian Academy of Sciences for Best Scientific Works of Young Scientists in Organic Chemistry (2012).

Panče Naumov was born in Macedonia, in 1975. As a scholar of the Japanese Government, he acquired his Ph.D. with Prof. Yuji Ohashi at Tokyo Institute of Technology in 2004. He was a research fellow and a group leader in the National Institute for Materials Science in Japan (2004–2007), and associate professor at Osaka University (2007–2012) where he established new laboratories for solid-state research. In 2012 he took on positions at New York University Abu Dhabi and Kyoto University. His research interests revolve around solid-state and structural chemistry, with focus on photochemistry and reactivity.

[Scheme 2 (b)].[15] Both our and Deng's reaction rely on a prototropic rearrangement, induced by a bifunctional organocatalyst, where the driving force is the generation of a conjugated system.



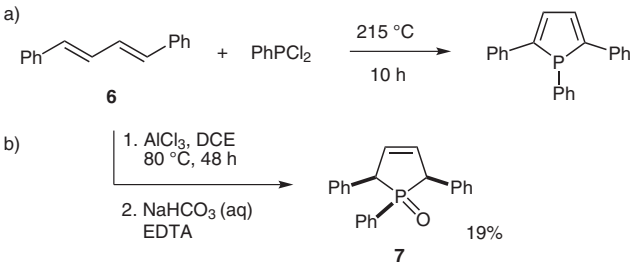
Scheme 2 Examples of organocatalytic, asymmetric double-bond isomerizations. (a) Hintermann et al.[14] (b) Deng et al.[15]

Here we present an extended study of the asymmetric catalytic *meso*-2,5-dihydro-1*H*-phosphole isomerization chemistry, including an extension of the substrate range of asymmetric dihydro-1*H*-phosphole isomerization and the introduction of bifunctional thioureas as suitable catalysts. In addition, deuterium labeling has been used to study the mechanism of the asymmetric reaction. Finally, a stereoselective hydrogenation of (5*R*)-1-hydroxy-1-oxo-2,5-diphenyl-4,5-dihydro-1*H*-phosphole to (2*R*,5*R*)-1-hydroxy-1-oxo-2,5-diphenylphospholane (**1**) was found; incorporating parallel work on Wenkert arylations,[16] we have realized an asymmetric catalytic total synthesis of Fiaud's acid **1** from thiophene in only five steps.

Results and Discussion

Synthesis of New 2,5-Diaryl-2,5-dihydro-1*H*-phospholes by McCormack Cycloaddition

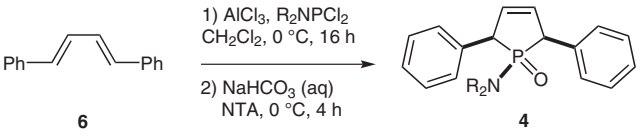
The McCormack cycloaddition[17] of (*E*,*E*)-1,4-diphenylbuta-1,1-diene (**6**) with dichloro(phenyl)phosphane requires high temperatures, producing 1,2,5-triphenyl-1*H*-phosphole [Scheme 3 (a)].[18] Milder reaction conditions were realized by Fiaud and co-workers by choosing the aminophosphenium cycloaddition variant.[19] They reacted diene **6** with $Me_2NPCl_2/AlCl_3$ to obtain **4a** selectively after hydrolytic workup (Table 1, entry 1).[12] We likewise added $AlCl_3$ to the reaction of $PhPCl_2$ with **6** and obtained the desired *meso*-1-oxo-1,2,5-triphenyl-2,5-dihydro-1*H*-phosphole (**7**), though in low, unoptimized yield [Scheme 3 (b)].

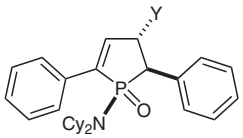


Scheme 3 McCormack cycloaddition of (*E*,*E*)-1,4-diphenylbuta-1,3-diene (**6**) with $PhPCl_2$: (a) a phosphole is obtained under thermal conditions;[18] (b) the use of a Lewis acid allows isolation of *meso*-2,5-dihydro-1*H*-phosphole **7**.

The substrate scope of the aminophosphenium cycloaddition was extended to various R_2NPCl_2[20] (Table 1) or diene structures (Table 2). Either Et_2NPCl_2[20b] (entry 2) or a piperidino derivative (entry 3) gave 1-amino-1-oxo-2,5-dihydro-1*H*-phosphole with yields comparable to those described for Me_2NPCl_2 (entry 1).[12b] The recrystallized or chromatographically purified products were pure *trans*,*trans*-diastereomers, but the crude cycloaddition mixture of **4b** contained the minor *cis*,*cis*-diastereomer[21] in a ratio of *trans*,*trans*/*cis*,*cis* 16:1.

Table 1 McCormack Cycloadditions of 1,4-Diphenylbutadiene

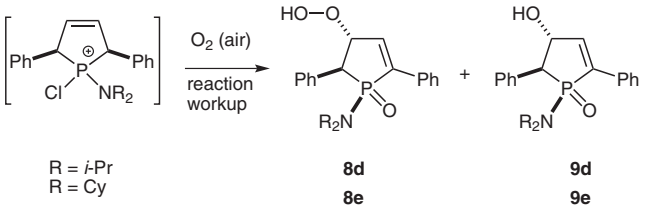


Entry	NR_2	Product	Yield (%)
1	NMe_2	**4a**	74[a]
2	NEt_2	**4b**	83
3	piperidino	**4c**	76
4	N*i*-Pr_2	**4d**	71
5	NCy_2	 **8e** (Y = OOH) **9e** (Y = OH)	57[b]

[a] Data from ref. 12b.
[b] Mixture of **8e**/**9e**, 89:11.

The sterically demanding *i*-Pr_2NPCl_2 gave **4d** reliably only if the reaction and workup were performed under argon (entry 4). When the workup was performed in air, a mixture of the desired **4d** with two unexpected side-products **8d** and **9d** was obtained (Scheme 4). Both **8d** and **9d** are products of a diastereoselective autoxidation; stirring a solution of pure **4d** in CH_2Cl_2 for prolonged times in air only returned **9d**, but no peroxide **8d**. The observed autoxidation to peroxide may have occurred already in the McCormack reaction at the stage of the hydrolytically la-

bile intermediate (Scheme 4), or under the specific conditions of the reaction workup.



Scheme 4 Generation of autoxidation products in the workup of the McCormack cycloadditions with bulky R_2NPCl_2

The structures of both **8d** and **9d** were supported by X-ray diffraction analysis.[22] The crystals of the hydroperoxide **8d** (Figure 1) are twinned, but the apparent twining comes from the two conformations that are present in a 50:50 ratio; crystallographically, **8d** is considered a twin, while chemically it is a racemate.

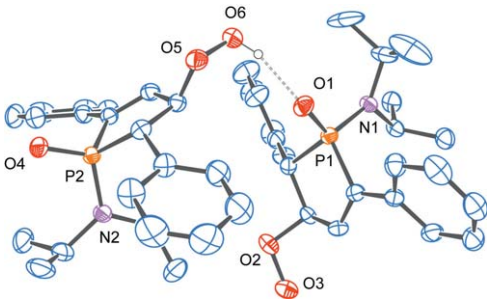


Figure 1 Two molecules in the asymmetric unit of the crystal of the peroxide **8d**; hydrogen atoms are omitted for clarity. The β angle is very close to 90°, and the unit cell emulates orthorhombic symmetry. There are two independent molecules in the asymmetric unit ($Z' = 2$, $Z = 4$).

There are two molecules in the asymmetric unit, where the peroxide hydroxyl group of one molecule is strongly hydrogen bonded to the P=O oxygen of the other, with an O···O distance of 2.652 Å. The P=O group of the first molecule and the peroxide of the second are also hydrogen bonded (O···O = 2.691 Å) to peroxide and P=O groups of adjacent molecules, respectively, thereby extending the packing into infinite linear catemers. The structure of the alcohol **9d**, determined from a racemic twin (Figure 2), contains a single molecule in the asymmetric unit.

Similar to **8d**, the hydroxyl group in **9d** donates a proton (O···O = 2.746 Å) to a P=O group of an adjacent molecule with opposite disposition, but the P=O group also receives a proton from the same molecule, thereby forming centrosymmetric $R^2_2(12)$ dimers. The isopropyl group is disordered even at 120 K. Structurally related 4,5-dihydro-1*H*-phosphol-4-ols have been described.[23,24]

Attempted synthesis of 2,5-dihydro-1*H*-phosphole **4e** from Cy_2NPCl_2 returned mainly hydroperoxide **8e** as mixture with alcohol **9e** (Table 1, entry 5; Scheme 4). The sensitivity towards autoxidation apparently increases with the bulk of the NR_2 group. This could be due to favorable release of strain present in **4** between the NR_2 and *cis*-phenyl groups by generation of the planarized allylic radical in the H-abstraction with oxygen. Spontaneous autoxidation of activated allylic C–H bonds leading to isolation of allylic hydroperoxides or alcohols is well documented.[25]

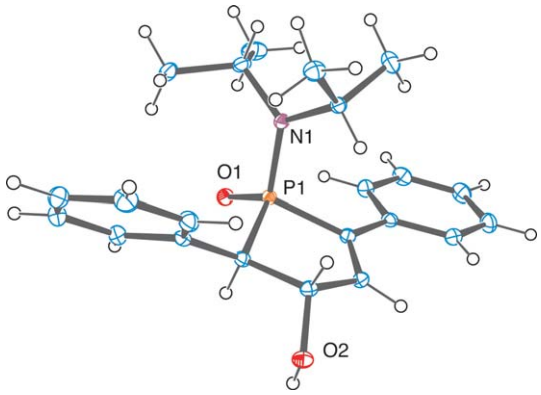
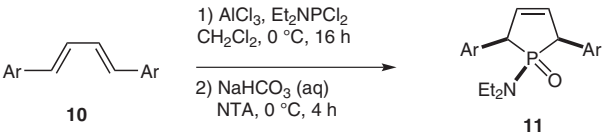


Figure 2 X-ray crystal structure of 4-hydroxy-4,5-dihydro-1*H*-phosphole **9d**, determined from a racemic twin

Variation of the Aryl Groups

The McCormack cycloaddition scope was also extended by varying the aryl groups of the diene component. 1,4-Diarylbuta-1,3-dienes **10** were available by Wenkert arylation of thiophene with ArMgX, according to our optimized protocol.[16,26] Cycloaddition of the dienes with $Et_2NPCl_2/AlCl_3$ proceeds readily if the aryl groups in diene **10** are either devoid of *ortho*-aryl substituents (Table 2, entries 1–3), or only contain a single *ortho* substituent (entries 4 and 5). Cycloaddition of 1,4-bis(1-naphthyl)buta-1,3-diene (**10f**) gave the regular product *trans*,*trans*-**11f** accompanied by the minor *cis*,*cis*-diastereomer (entry 6). The most hindered bis-mesityl diene **10g** gave low yields under standard conditions (entry 7).

Table 2 Synthesis of 1-Amino-2,5-diaryl-1-oxo-2,5-dihydrophospholes



Entry	Ar	Product	Yield (%)
1	4-MeC_6H_4	**11a**	79
2	4-*t*-BuC_6H_4	**11b**	70
3	4-MeO-3,5-*t*-$Bu_2C_6H_2$	**11c**	74
4	2-MeC_6H_4	**11d**	84
5	2-EtC_6H_4	**11e**	63
6	1-naphthyl	**11f** + **11f′**[a]	43 + 7[a]
7	2,4,6-$Me_3C_6H_2$	**11g**	24

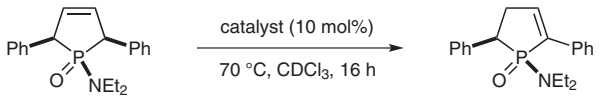
[a] **11f′** is the *cis*,*cis*-diastereomer.

Asymmetric Catalytic Isomerization

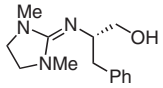
Evaluation of the Reaction Parameters

Addition of an amine base to a solution of *meso*-1-amino-2,5-diaryl-1-oxo-2,5-dihydro-1*H*-phospholes **4** or **11** induces isomerization to the more stable conjugated 4,5-dihydro-1*H*-phospholes **5** or **12**.[14,27] Chiral bases were screened in $CDCl_3$ solution for their efficiency and enantioselectivity in the reaction (Table 3). The use of $CDCl_3$ as solvent allowed for simple ^1H and ^{31}P NMR analysis of the conversion and enantioselectivity, the latter after addition of quinine as chiral shift reagent (*vide infra*).

Table 3 Screening of Chiral Bases in the Isomerization of *meso*-Dihydro-1*H*-phosphole **4b**[a]



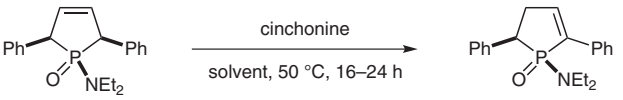
4b **5b**

Entry	Catalyst	Conv.[b] (%)	ee[c] (%)
1[d]	cinchonine	100	54 (5*R*)
2	2′-butylcinchonine	50	39 (5*R*)
3	dihydrocinchonine	94	47 (5*R*)
4	(–)-*N*-methylephedrine	6	33 (5*S*)
5	(*S*)-diphenylprolinol	12	26 (5*R*)
6[e]	$(DHQD)_2Pyr$	9	10 (5*R*)
7	strychnine	10	8 (5*S*)
8[f]	L-proline	78	15 (5*S*)
9[g]		85	49 (5*R*)

[a] All reactions performed at 70 °C with **4b** in $CDCl_3$ (10 L/mol) and 10 mol% of catalyst for 16 h.
[b] Determined by ^1H NMR.
[c] Determined by ^{31}P NMR with quinine.
[d] 20 mol%.
[e] 5 mol%.
[f] 30 mol%.
[g] 50 mol%.

Bifunctional catalysts with a basic site and a hydrogen bond donor group are most successful, e.g. β-amino alcohols (Table 3, entries 1–5) from the cinchona (entries 1–3) or ephedra (entry 4) alkaloid families. Ethers of cinchona alkaloids (entry 6) or other alkaloids lacking a hydrogen bond donor (entry 7) were neither very active nor selective catalysts. Some success was also achieved with an amino acid (entry 8) or a guanidinyl alcohol (entry 9) as bifunctional catalysts, though these leads were not investigated further.

Table 4 Solvent Effect on Asymmetric Olefin Isomerization[a]



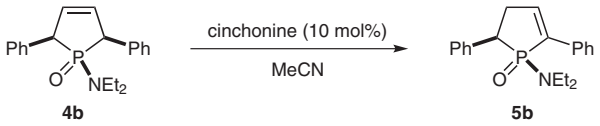
4b **5b**

Entry	Solvent	Cat. (mol%)	Conv. (%)	ee (%)
1	CH_2Cl_2	30	91	64 (5*R*)
2	THF	30	100	55 (5*R*)
3	EtOAc	20	94	62 (5*R*)
4	acetone	20	100	59 (5*R*)
5	*t*-AmOH	20	46	39 (5*R*)
6	toluene	30	98	44 (5*R*)
7	*o*-$C_6H_4Cl_2$	30	100	61 (5*R*)
8	MeCN	30	100	72 (5*R*)
9	MeCN	20	90	74 (5*R*)
10	EtCN	20	100	73 (5*R*)
11	PhCN	20	100	70 (5*R*)
12	DMF	20	100	72 (5*R*)
13	$MeNO_2$	10	89	72 (5*R*)
14	$EtNO_2$	10	97	74 (5*R*)

[a] General: **4b** (0.1 mmol), solvent (1 mL). Conversion and ee determined by ^{31}P NMR with quinine or chiral HPLC.

A screening of solvents was next performed with cinchonine as the most efficient catalyst among the cinchona alkaloids (Table 4). The asymmetric catalysis proceeded readily in polar, nonprotic (entries 1–4), or aromatic solvents (entries 6 and 7), but less successfully in protic solvents (entry 5). However, best results were clearly achieved in dipolar aprotic media including nitriles (entries 8–11), DMF (entry 12), or nitroalkanes (entries 13 and 14). Acetonitrile was chosen as suitable reaction medium that can be recycled by simple vacuum evaporation. Dipolar solvents are suitable media for microwave accelerated reactions,[28] and those were also tested (Table 5). At 50 °C, the thermal reaction requires 16 hours for complete conversion (entry 1), whereas the microwave reaction was stopped after 4 hours, having reached about half conversion (entry 2). The enantioselectivity with either heating modes was almost the same. Reactions at 70 °C were completed in a similar time range (entries 3 and 4). In spite of identical nominal temperature readings, the microwave reaction proceeded faster and with lower enantioselectivity. Presumably, the same nominal temperature readings correspond to a higher internal temperature in case of the microwave heating.[29] Since microwave heating offered no particular advantage, catalyses were henceforth performed under thermal (oil bath) conditions.

Table 5 Comparison of Microwave and Thermal Heating[a]



4b 5b

Entry	Heating	Temp (°C)	Time (h)	Conv.[b] (%)	ee[b] (%)
1	oil bath	50	16	100	78.5 (5*R*)
2	MW	50[c]	4	59	78.1 (5*R*)
3	oil bath	70	5	100	76.7 (5*R*)
4	MW	70[c]	3	100	71.2 (5*R*)

[a] Conditions: MeCN (10 L/mol), cinchonine (10 mol%). Microwave experiments: $p \leq 5$ bar, $P = 300$ W.
[b] Conversion and ee determined by HPLC.
[c] IR temperature measurement.

Asymmetric Isomerization of New *meso*-2,5-Diaryl-2,5-dihydro-1*H*-phospholes

The new *meso*-dihydro-1*H*-phospholes **4** and **11** were catalytically isomerized with cinchonine (Table 6). Compared to **4b** (entries 1 and 2) sterically more demanding NR_2 groups decreased enantioselectivity in the rearrangement (entries 3 and 4).

The presence of *ortho* substituents on the aryl group also lowered enantioselectivity (entries 5–8) and led to slower rearrangements, which was counteracted by increasing the reaction temperature. Generally, substrates with sterically demanding aryl groups require higher reaction temperatures and longer reaction times. The *para*-*tert*-butyl-substituted **11b** (entry 9) and the *meta*/*para*-substituted **11c** (entry 10) gave a reasonably selective rearrangement with similar enantiomeric excesses like the unsubstituted reference substrate **4b**. This indicates that steric bulk in the remote *meta* and *para* positions is better tolerated and sterically does not affect the transition state. The reduced reactivity of these substrates then must be due to a negative electronic effect of electron-donating groups, which would agree with a carbanionic reaction mechanism (*vide infra*). Finally, the 1-oxo-2,5-dihydro-1*H*-phosphole **7** showed great promise by rearranging neatly to **13** with a relatively high enantiomeric excess (entry 11), which shows that the reaction is by no means limited to phosphinic acid amides.

Bifunctional Thioureas as Catalysts

The results obtained so far were promising, but they implied that higher enantioselectivity cannot be achieved with the cinchona alkaloids as catalysts. Being natural products, they lack the structural variability of modular synthetic catalysts. However, the bifunctionality pattern of cinchona alkaloids[30] is also found in fully synthetic chiral organocatalyst families, including Takemoto's thiourea-amines (Table 7).[31] Indeed, the standard Takemoto catalyst (*R*,*R*)-**14a** induced an isomerization at comparable rates to the cinchona alkaloids, but with a higher enantioselectivity (88%) in favor of (5*S*)-**5b** (entry 1). The sense of induction in this case is inverted relative to cinchonine. An advantage of the thiourea-amines is their amenability to structural variation. In a first example, the use of piperidino derivative **14b** (entry 2) gave **5b** with an even higher 91% ee. Mixed results were obtained when applying catalysts **14** to the more difficult substrate **11f** (entries 3 and 4). These first results with structurally variable bifunctional catalysts are promising and imply that additional optimization to find suitable catalyst/substrate matches will be possible.

Mechanism of the Asymmetric Isomerization

The catalyst screening had revealed the importance of a bifunctional activation mode. A strong hydrogen-bonding interaction between the catalyst OH and the substrate/product P=O group can be assumed [Figure 3 (a)]. It is responsible for a very simple determination of the enantiomeric excess of the rearranged 1-oxo-4,5-dihydro-1*H*-phospholes **5**, **12**, and **13**, which consists of recording ^{31}P NMR spectra of the latter in the presence of 1–5 equivalents of quinine in $CDCl_3$ solution [Figure 3 (b)], though for more accurate determinations, chiral HPLC in the normal phase mode was also suitable.[32]

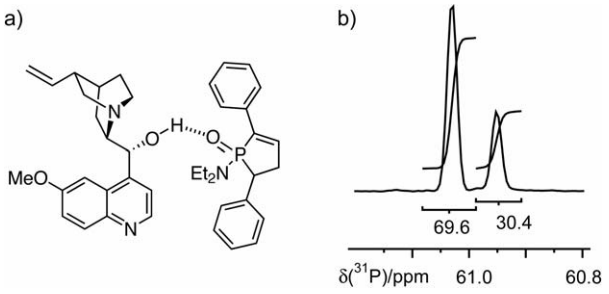
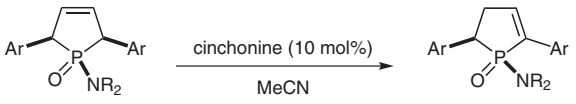


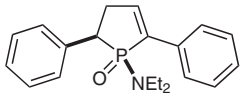
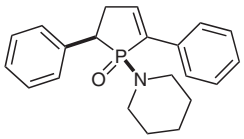
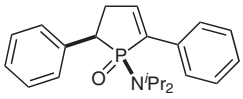
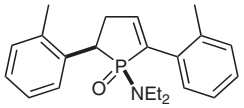
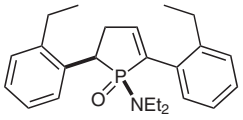
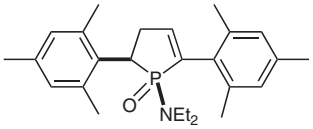
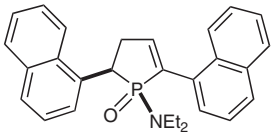
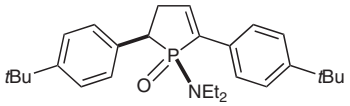
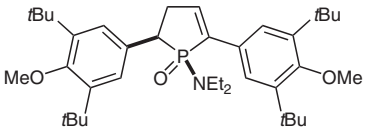
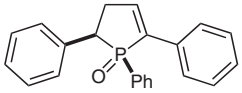
Figure 3 (a) Presumable complexation of 1-oxo-4,5-dihydro-1*H*-phospholes by quinine as hydrogen bond donor; (b) ee determination of 1-amino-1-oxo-4,5-dihydro-1*H*-phospholes by ^{31}P NMR spectroscopy with quinine as chiral shift reagent in $CDCl_3$ [er 69.6:30.4, 39% ee (5*R*)].

Similar enantiomeric excess determinations by NMR have been reported for 1-oxo-dihydro-1*H*-phosphole with chiral amides as H-bond donors.[33] Based on the importance of hydrogen bonding and basicity, we devised a working hypothesis for the mechanism which involved the precomplexation of substrate and catalyst via a hydrogen bond, followed by stereoselective deprotonation of C–H at C2 or C5. In case of rate-limiting deprotonation, a primary deuterium isotope effect might be expected. Thus, placing a deuterium label at C2/5 of **4b** was of greatest interest. Our Wenkert cross-coupling synthesis of 1,4-diarylbuta-1,3-dienes[16] provided a practical access to labeled substrates, as shown in Scheme 5. Thiophene was

Table 6 Catalytic Isomerization of *meso*-2,5-Dihydro-1*H*-phospholes[a]

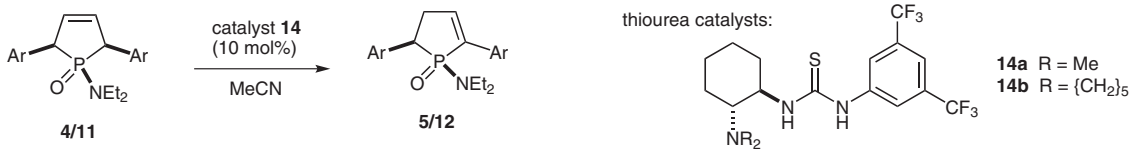


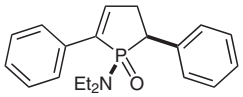
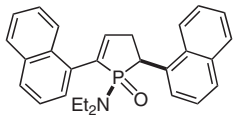
4 *or* **11** **5** *or* **12**

Entry	Product[b]		Temp (°C)	Time (h)	Yield (%)	ee (%)
1		**5b**	50	20	98	79
2[c]		**5b**	50	20	97	78
2a		**5b**	70	5	98	77
3		**5c**	70	16	96	66
4		**5d**	70	16	96	60
5[d]		**12d**	70	220	63	47
6		**12e**	90	180	92	41
7		**12g**	90	220	68	37
8		**12f**	90	170	86	30
9		**12b**	80	100	87	64
10		**12c**	80	100	94	71
11[e]		**13**	50	16	94	77

[a] Conditions: MeCN (10 L/mol); ee determined by ^{31}P NMR with quinine as shift reagent.
[b] The absolute configuration of the excess enantiomer is presumably (5*R*) in all cases by analogy to that of **5b**.
[c] 0.3-mol scale, catalyst (5 mol%).
[d] CH_2Cl_2 (0.3 L/mol) was added for solubility reasons.
[e] Starting material is 1-oxo-2,5-dihydro-1*H*-phosphole **7**.

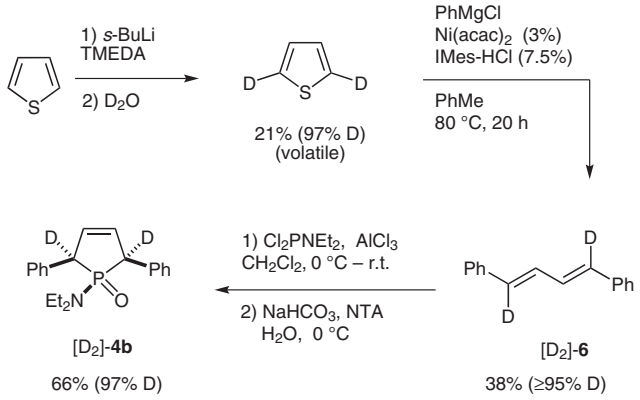
Table 7 Asymmetric Catalytic Rearrangement of *meso*-1-Oxo-2,5-dihydro-1*H*-phospholes with Bifunctional Thiourea Catalysts[a]



Entry	Substrate	Catalyst	Product	Temp (°C)	Time (h)	Conv. (%)	ee (%)
1	**4b**	**14a**	 **5b**	50	20	>99	88 (5*S*)
2	**4b**	**14b**	**5b**	50	16	>99	91 (5*S*)
3	**11f**	**14a**	 **12f**	50	168	7	8 (5*S*)
4	**11f**	**14a**	**12f**	90	144	24	11 (5*S*)
5	**11f**	**14b**	**12f**	90	92	20	66 (5*S*)

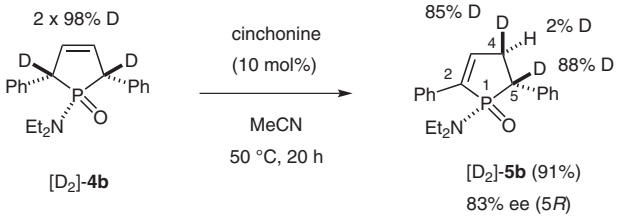
[a] Conditions: MeCN (10 L/mol), catalyst (10 mol%). Conversion and ee determined by chiral HPLC or ^{31}P NMR with quinine.

dilithiated[34] and quenched with D_2O, to give 2,5-[D_2]-thiophene with high deuterium incorporation at C2/5 (Scheme 5). The low chemical yield is due to the volatility of thiophene. Wenkert arylation[16] proceeded as usual to give 1,4-diphenyl-1,4-dideuteriobuta-1,3-diene ([D_2]-**6**) with specific deuterium incorporation. Eventually, McCormack cycloaddition gave the labeled 2,5-dihydro-1*H*-phosphole [D_2]-**4b** (Scheme 5).



Scheme 5 Synthesis of deuterium-labeled dihydro-1*H*-phosphole **4b**

Substrate [D_2]-**4b** was submitted to the catalysis conditions at 50 °C and the rearrangement product isolated (Scheme 6). As expected, the deuterium labels show up at C4 and C5 of **5b**, with a recovery of 85% (H_{Si}, *trans* to Ph) and 2% (H_{Re}) at C4, and a recovery of 88% at C5. Partial loss of the label is readily explained by exchange with the catalyst hydroxy group and residual water in the reaction mixture. The rearrangement is suprafacial, the deuteron ($^2H^+$) being removed from C2 and re-attached to C4 from the same face of the heterocycle. There is no need to postulate a concerted, thermally forbidden mechanism, because face-selectivity can result from binding of the catalyst as proton-shuttle to the substrate via the P=O group (*vide infra*).



Scheme 6 Catalytic isomerization of deuterium-labeled **4b**

The more surprising result concerns the kinetics of the catalytic rearrangement, where the absence of any notable deuterium kinetic isotope effect (KIE) is evident (Figure 4). The kinetic curves of the rearrangement of 2,5-[H_2]-**4b** vs. 2,5-[D_2]-**4b** at 50 °C (Figure 4) or also 70 °C[35] show a close match. There is a small but significant isotope effect on enantioselectivity of the reaction product, both at 50 °C (81% ee vs. 83% ee with deuterated substrate) and 70 °C (76% ee vs. 79% with deuterated substrate).

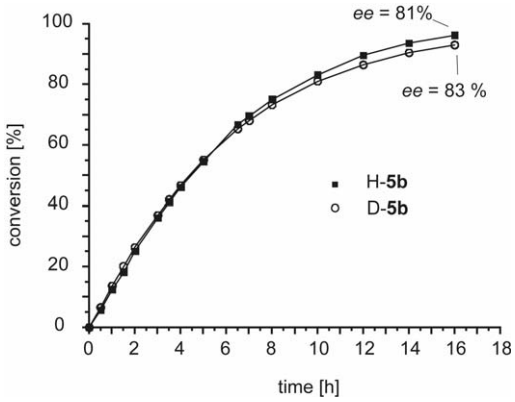
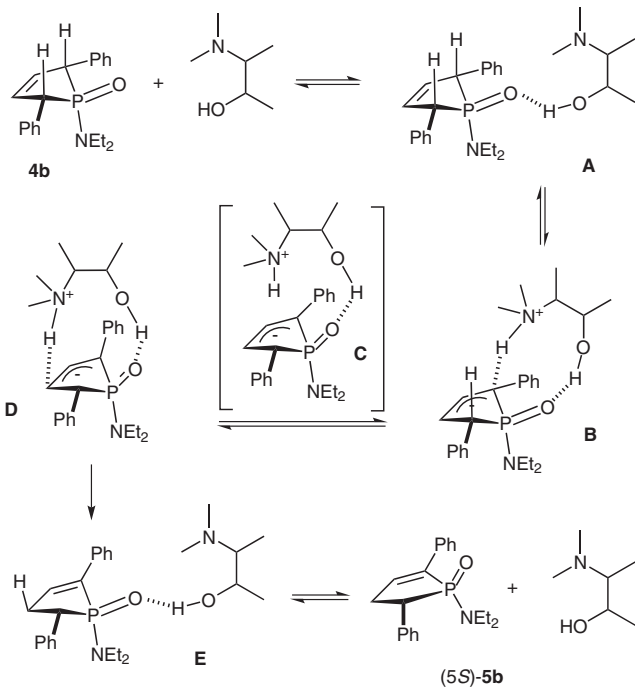


Figure 4 Kinetic reaction progress curve (determined by HPLC) of the catalytic isomerization **4b** → **5b** (10 mol% of cinchonine, 10 L/mol MeCN) recorded with **4b** or 2,5-[D_2]-**4b** at 50 °C. For results at 70 °C, see the Supporting Information.

This clear-cut result was surprising since a primary KIE of up to 6 might have been expected for a rate-limiting deprotonation of H–C2/5,[36] the step which almost certainly initiates the overall prototropic rearrangement. Potential explanations for the absence of a primary KIE have been considered: first, coincidental canceling of two KIEs for the deprotonation (at C2/5) and reprotonation (at C4) step might occur. However, both of those KIEs should be primary, and none is expected to be inverse, excluding this explanation. Thus, the absence of a primary KIE means that initial deprotonation is not rate-limiting. A second explanation then assumes reversible initial deprotonation, followed by a rate-limiting, irreversible conformational change at the stage of the allylic carbanion, followed by fast reprotonation. However, it is not evident what kind of conformational restriction could be responsible for a relatively large energy barrier. The third and in our opinion most probable explanation (cf. Scheme 7) involves a series of ion-pairs as intermediates. We assume fast, reversible initial deprotonation within a hydrogen-bonded adduct **A** to a tight ammonium–carbanion pair **B**, which collapses back to **A** at a comparatively fast rate. The slower, competing dissociation of **A** to **C** (which may be either a high-lying intermediate or a transition state on the way from **B** to **D**) is the rate-limiting as well as enantio-determining step, explaining the absence of a primary KIE (Scheme 7). A similar explanation for the absence of a primary KIE was offered in case of the base-catalyzed hydrogen exchange of tritiated phenylacetylene in water, where, according to Kresge,[37] '*proton transfer is fast, and subsequent separation of the proton transfer products, the acetylide ion and the conjugate acid of the catalyzing base, is slow.*'[37]

Once ion-pair **B** dissociates to **C**, it either returns via **B** to **A** by protonation at C2, or rearranges to the contact ion-pair **D**, followed by a (practically) irreversible protonation at C4 to give adduct **E**. Since the rate-limiting step is dissociation of **B** to **C**, our initial assumption of an enantio-determining selective deprotonation of **4b** at the diastereotopic H–C2/5 positions is not necessarily correct, though



Scheme 7 Suggested mechanism of prototropic rearrangement via fast, reversible initial deprotonation; the catalyst is hydrogen-bonded to the substrate via a hydrogen bond as handle. The pathway to (5*S*)-**5b** is shown.

this step could still proceed enantioselectivity-determining. Another labeling experiment is consistent with this interpretation: a solution of **4b** in [D_4]-MeOH with a drop of triethylamine as catalyst was analyzed by ^{1}H and ^{31}P NMR spectroscopy over several days (Figure 5).

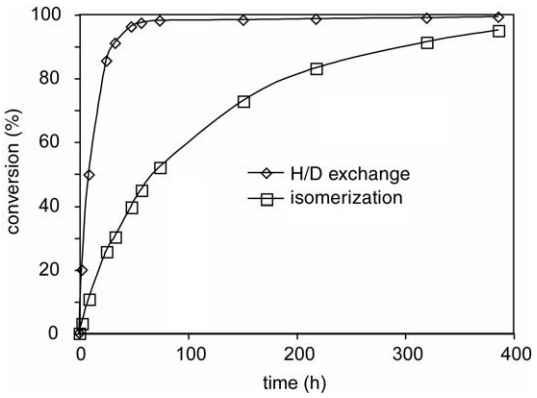
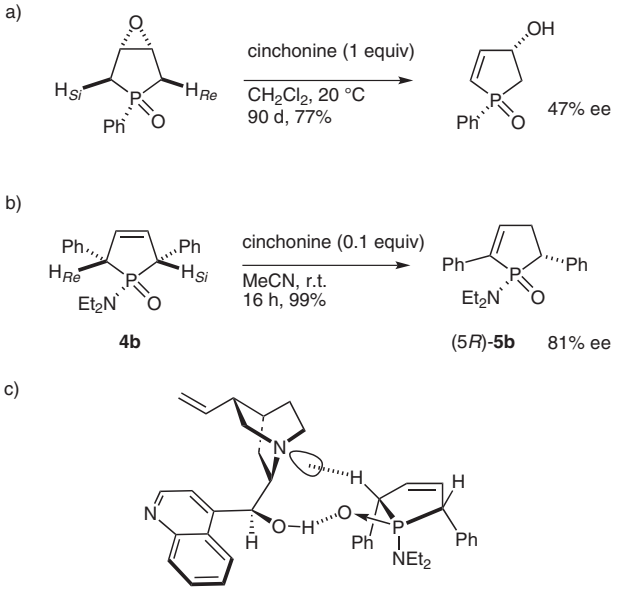


Figure 5 H/D exchange in **4b** and isomerization to **5b** in [D_4]-MeOH at 22 °C with triethylamine (44 mol%); H/D-exchange is given as percentage amount of exchanged hydrogen of H2/5 (two positions) in remaining **4b**. Isomerization is given as percentage conversion to **5b**.

Dihydro-1*H*-phosphole **4b** initially exchanged H for D at C2/5 ca. 7 times faster than it rearranged to **5b**, which supports the assumption of a reversible initial deprotonation to an ion pair. It also suggests that the solvent-separated allylic ion-pair **C** (Scheme 7) will exchange H/D with the solvent, and this exchange is intrinsically favored at C2 by a factor of ca. 14 (twice the relative rate of H/D exchange,

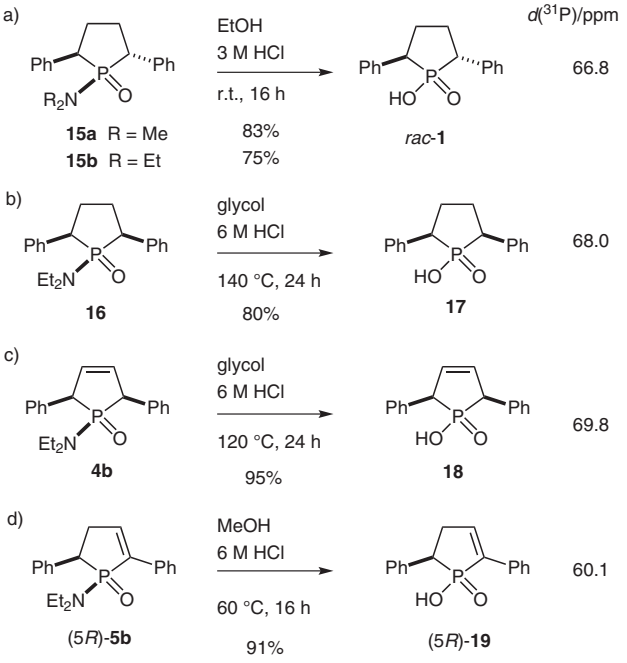
since there are two exchangeable positions) over protonation at C4. This is reminiscent of the kinetically favored protonation of dienolates at C2 over C4,[38] and the preferred deprotonation of 1-oxophospholanes at the C–H bond *cis* to the P=O group.[39] Pakulski et al. have described a reaction related to ours, in which quinidine (or cinchonine) mediated elimination of a *meso*-dihydro-1*H*-phosphole epoxide gave a 4-hydroxy-4,5-dihydro-1*H*-phosphole [Scheme 8 (a)] with the same sense of induction as observed in our catalytic reaction [Scheme 8 (b)].[24] Adaptation of their transition-state model to our reaction is shown in Scheme 8 (c). Even though deprotonation is not rate-limiting in our catalysis, one can assume that the interactions present in Scheme 8 (c) will also be important in the structurally similar ion-pair **C** (Scheme 7), and in the transition state of Pakulski et al., explaining the same sense of induction observed in both reactions.



Scheme 8 Sense of induction in desymmetrization reactions of 1-oxo-2,5-dihydro-1*H*-phospholes: (a) reaction in ref. 24; (b) asymmetric catalytic dihydro-1*H*-phosphole isomerization (this work); (c) adaption of the steric model of Pakulski et al. to the reaction of the current work.[24]

2,5-Diphenylphosphole-Derived Acids

Having found a route to enantioenriched 1-amino-1-oxophospholes, we investigated their hydrolysis to cyclic phosphinic acids in aqueous mineral acid.[19d] The influence of stereochemistry and degree of saturation was analyzed in the 2,5-diphenylphosphole series (Scheme 9). Fiaud had already reported the hydrolysis of racemic *cis*,*trans*-1-amino-1-oxo-2,5-diphenylphospholane **15** to **1** under relatively mild conditions [Scheme 9 (a)].[12] Hydrolysis of the diastereomer *trans*,*trans*-**16**, obtained by hydrogenation of **4b**, to *meso* phosphinic acid **17** required more forcing conditions, presumably because of steric hindrance towards the attack of water [Scheme 9 (b)]. The *meso*-2,5-dihydro-1*H*-phosphole **4b** hydrolyzed to *meso* phosphinic acid **18** under equally forcing conditions, but notably without alkene isomerization [Scheme 9 (c)]. Enantioenriched 1-amino-1-oxo-4,5-dihydro-1*H*-phosphole **5b** was hydrolyzed to cyclic phosphinic acid **19** overnight with relative ease, but under harsher conditions than **15** [Scheme 8 (d)]. The enantiomeric excess of cyclic phosphinic acid **19** was retained in the hydrolysis, as shown by ^{31}P NMR spectroscopy of the product in the presence of quinine as chiral shift reagent. As reported in our communication,[14] phosphinic acid **19** could be fractionally crystallized to ≥95% ee. The enantiopurity of the acid was conveniently analyzed by ^{31}P NMR spectroscopy with quinine as the chiral shift reagent.

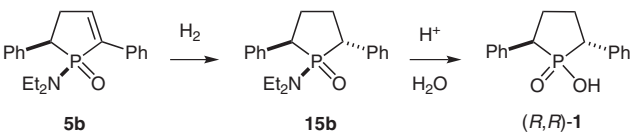


Scheme 9 Conditions for the hydrolysis of 1-amino-1-oxophospholes

The Asymmetric Catalytic Synthesis of Fiaud's Acid

Diastereoselective Reduction of 2,5-Diphenyl-4,5-dihydro-1*H*-phosphole Derivatives

Having developed an asymmetric catalytic access to **5b** and cyclic phosphinic acid **19** from thiophene, we wished to extend this synthetic sequence to an asymmetric total synthesis of Fiaud's acid **1**, which is a useful building block in chiral phosphane ligand synthesis.[40] Diastereoselective hydrogenation of 4,5-dihydro-1*H*-phosphole **5b**, followed by hydrolysis should lead to the desired target (Scheme 10).



Scheme 10 Projected transformation of **5b** to phosphinic acid **1**

However, the conformation of 1-amino-1-oxo-4,5-dihydro-1*H*-phosphole **5b** is not favorable for attack of any hydrogenating reagent from the top-face (*Re*-attack at C2; Figure 6). Instead, favored hydrogenation from the lower face opposing the phenyl and NEt_2 groups should lead to achiral *meso*-1-amino-phospholane **16**.

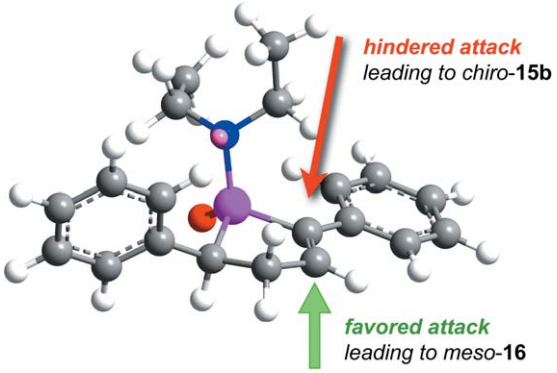
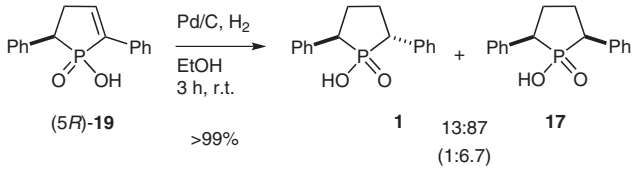


Figure 6 Diastereoselectivity of hydrogenation of **5b**. The modeled (Chem3D, MM2) conformation of (5*S*)-**5b** has the NEt_2 group in an axial position. The (desired) attack from the top face is blocked, instead, attack from the lower face leads to *meso*-**16**.

In agreement with the steric arguments, hydrogenation of **5b** over a palladium catalyst produced almost exclusively *meso*-**16** (Table 8, entry 1). Reagents which hydrogenate via hydride transfer gave mixtures of diastereomers in comparable amounts (entries 2 and 3). Reduction with magnesium in methanol, a reaction proceeding by stepwise transfer of e^- and H^+, inverted the diastereoselectivity (entries 4–6). At ambient temperature the reduction was accompanied by loss of enantiomeric excess, probably due to base-mediated isomerization of side-product *meso*-**16** to give *rac*-**15b**. This side-reaction is suppressed at lower temperatures (entries 5 and 6), where increased diastereoselectivities were also observed.

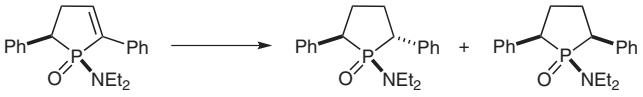
Hydrogenation of cyclic phosphinic acid **19** was also tested and found to show the same global preference for the undesired *meso*-product **17**, but an intrinsically higher selectivity for the desired product (Scheme 11).



Scheme 11 Hydrogenation of cyclic phosphinic acid **19**

Concluding from these experiments, **19** should be the preferred substrate, and a dissolving metal reduction at low temperature should provide the best approach to further direct the diastereoselectivity of the reduction towards the *chiro* product. Sodium in liquid ammonia recommended itself for improved reduction experiments. Phosphinic acid **19** was cleanly and quickly reduced by dissolving metals in liquid ammonia at –78 °C (Table 9). The initially formed carbanionic intermediate was quenched by addition of ammonium chloride at low temperature to prevent base-catalyzed isomerization on warming. The desired 2,5-*trans*-**1** was obtained in excess, and with retention of enantiomeric excess (Table 9). Sodium (entry 1) gave superior results to other metals (entries 2–4). Variation of the acid quencher influenced the diastereoselectivity of the reaction; use of alcohols or water for quenching generated side-products of the Birch type (entries 5–7). Several ammonium salts were good quenchers; interestingly, there was a marked counterion effect of the ammonium salt on the diastereoselectivity of the reduction (entries 1, 8–12).

Table 8 Diastereoselective Hydrogenation of **5b**[a]

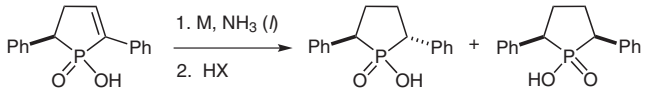


Entry	Reagent	Solvent	Temp (°C)	Time (h)	Ratio **15**/**16**
1	Pd/C, H_2	EtOH	r.t.	4	1:75
2	$NaBH_4$	EtOH	0	3	1:2[b]
3	$NaBH_4/I_2$	THF	0	6	1:1.2[c]
4	Mg	MeOH	r.t.	4	1.21:1[d]
5	Mg	MeOH	0	2	1.3:1
6	Mg	MeOH	–20	15	1.87:1

[a] Reactions were run with enriched (5*R*)-**5b** (81% ee) to ≥99% conversion; **15b** was 81% ee unless otherwise indicated.
[b] 24% conversion.
[c] 43% conversion.
[d] Product was 67% ee.

Finally, the diastereoselective reduction of acid **19** to Fiaud's acid **1** was best performed with sodium in liquid ammonia at –78 °C, followed by quenching of the reaction mixture with ammonium sulfate. The results of Table 9 may be interpreted such that reactions with free NH_4^+ ions give the more stable product **1**, whereas weaker and hindered acids, including strongly ion-paired ammonium salts, produce higher amounts of *meso*-diastereomer. The preferential generation of the thermodynamic stereoisomer in dissolving metal reductions is established[41] and has been attributed to pyramidalization of the carbanion towards the incipient C–H bond of the more stable product diastereomer.[41] In analogy, pyramidalization of the intermediary sp^2-hybridized[42] carbanion **A** (Scheme 12) in direction of the more stable 2,5-*trans* arrangement of phenyl groups could account for the observed results. The ion pairing of an ammonium cation with oxido groups at phosphorus (Scheme 12, **B**/**C**) allows for an assisted proton transfer. Reaction from ion pair **B** to **D** will be faster than from **C** to **E**, because it profits from carbanion pyramidalization, which may conceptually be the same as energetic *product development control* in the reaction to

Table 9 Dissolving Metal Reduction of Dihydro-1*H*-phospholes[a]



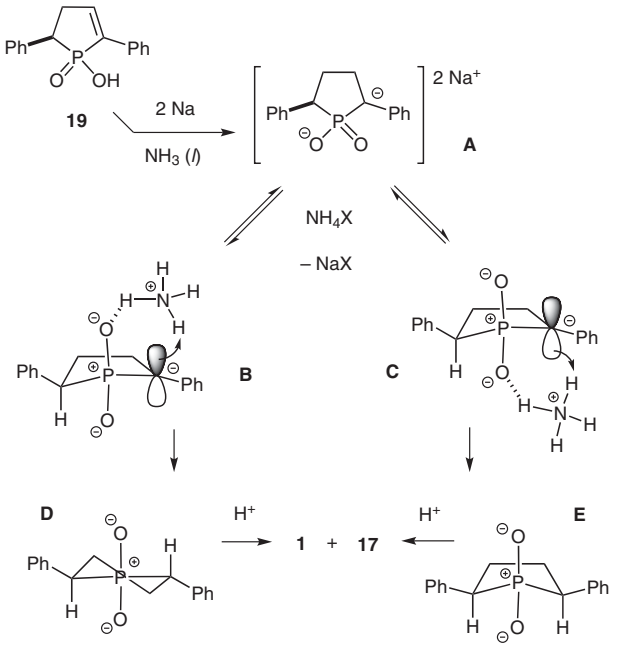
Entry	Metal	Time (h)	Quencher	Ratio **1**/**17**
1	Na	0.1	NH_4Cl	5.6:1
2	Ca	1.5	NH_4Cl	2:1[b]
3[c]	K	0.2	NH_4Cl	4:1
4	Li	0.2	NH_4Cl	2.5:1
5	Na	0.1	H_2O	2.3:1[b]
6	Na	0.2	MeOH	6.7:1[b]
7	Na	0.1	*t*-BuOH	3.2:1[b]
8	Na	0.1	NH_4OAc	2.2:1
9	Na	0.1	NH_4Br	5:1
10	Na	0.1	NH_4NO_3	6:1
11	Na	0.1	NH_4PF_6	4:1
12	Na	0.1	$(NH_4)_2SO_4$	7:1

[a] Reactions performed in liquid NH_3 at –78 °C with excess Na (5–20 equiv). Reactions went to >99% conversion and close to quantitative yield of crude material. Product ee was determined by ^{31}P NMR (*vide infra*); it remained 81 ± 3% in all examples.
[b] Birch reduction side-products were formed.
[c] 90% conversion.

the more stable product. Proton transfer from the lower face will become more favorable for sterically large quencher acids, which prefer attack opposite to the Ph–C5 group. Strongly ion-paired ammonium salts behave like sterically large acids in that respect.

Association of Cyclic Phosphinic Acids Observed by ^{31}P NMR Spectrometry

The ^{31}P NMR spectrum of crude samples of enriched phosphinic acid **1** in $CDCl_3$ solution displayed three peaks instead of the expected two for **1** and **17** (Figure 7). After addition of quinine as chiral shift reagent, the ^{31}P NMR displayed a new set of three peaks in an unchanged ratio. We conclude that either enantiomer of **1** and *meso*-acid **17** display a single ^{31}P NMR peak *in the absence of a chiral shift reagent*;[43] in fact, it is the enriched acid **1** which serves as internal shift reagent. The success of this experiment relies on the use of enriched samples and on the strong hydrogen-bonding interactions of phosphonic acids,[44] which is at the same time sufficiently dynamic to produce time-averaged peaks.



Scheme 12 Dissolving metal reduction of phosphinic acid **19**

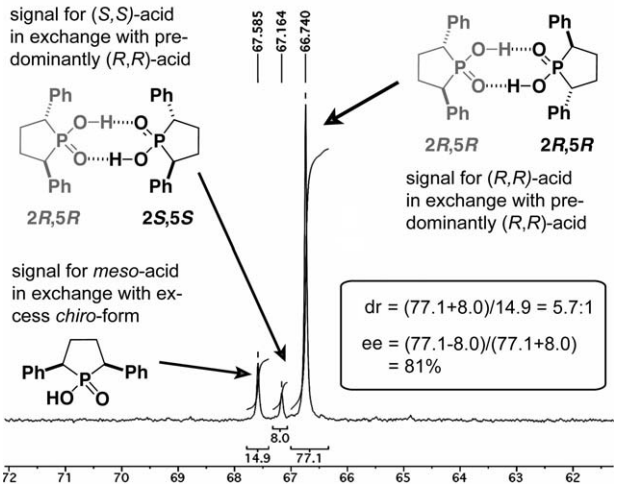
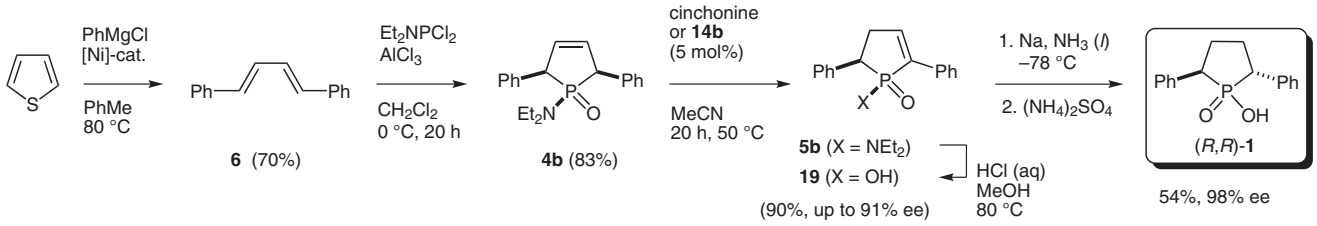


Figure 7 ^{31}P NMR (162 MHz, $CDCl_3$) analysis of the dr (**1**/**17**) and ee of samples of **1** in the absence of chiral additives. Enriched samples of acid **1**, as obtained from dissolving metal reduction of enriched **19** (81% ee), were dissolved in $CDCl_3$.

Asymmetric Catalytic Total Synthesis of 1-Hydroxy-1-oxo-*trans*-2,5-diphenylphospholane

The diastereoselective dissolving metal reduction of **19** provides the missing link to a total synthesis of Fiaud's cyclic phosphinic acid **1** (Scheme 13). The sequence starts from thiophene that is converted into (*E*,*E*)-1,4-diphenylbuta-1,3-diene (**6**) by a modified Wenkert arylation.[16] The McCormack cycloaddition first used by Fiaud stereoselectively gives *meso*-1-amino-1-oxo-2,5-dihydro-1*H*-phosphole **4b**, which is isomerized in an asymmetric organocatalytic process to enantioenriched 1-amino-1-oxo-4,5-dihydro-1*H*-phosphole **5b**, currently in up to 91% ee.



Scheme 13 Overview of the five-step asymmetric catalytic total synthesis of 1-hydroxy-1-oxo-*trans*-2,5-diphenylphospholane

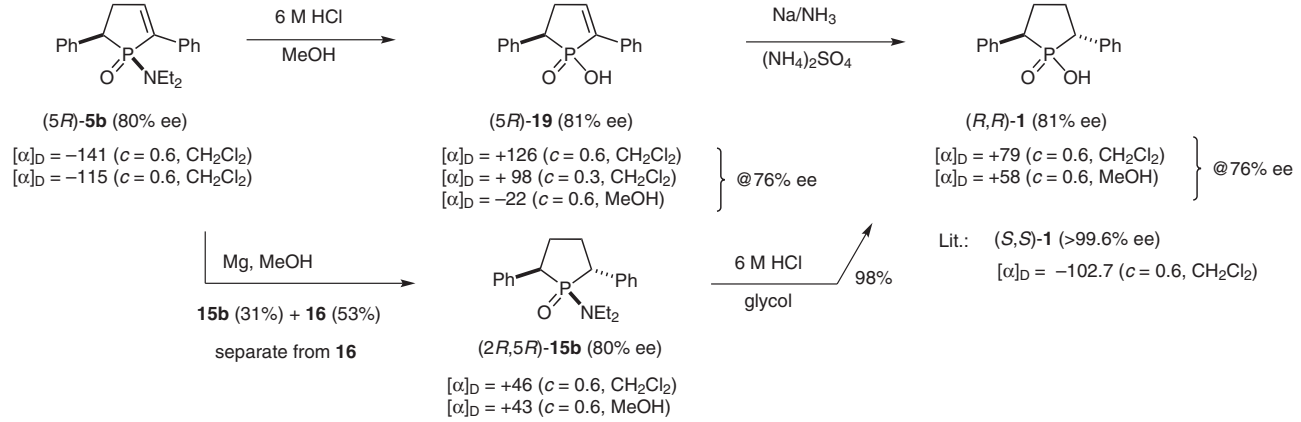
After hydrolysis to phosphinic acid **19**, dissolving metal reduction with diastereoselective protonation gives Fiaud's acid **1**, which is recrystallized to high diastereomeric and enantiopurity. For example, a cinchonine-catalyzed isomerization of **4b** gave **5b** with 80% ee, which was hydrolyzed and reduced without further purification. The crude product **1** (80% ee, dr 6:1) thus obtained was recrystallized from methanol to give pure **1** (>98% ee) in 54% yield.

Structure Correlation Studies

A series of reactions was performed (Scheme 14) to correlate the absolute configuration (of the excess enantiomer) of all our intermediates with Fiaud's acid **1**, whose configuration and optical rotation are known.[12] An enriched sample of 1-amino-1-oxo-4,5-dihydro-1*H*-phosphole (–)-(5*R*)-**5b** as obtained from a cinchonine-catalyzed isomerization of **4b** was hydrolyzed to phosphinic acid **19**. This compound displayed the notable phenomenon of changing the sign of optical rotation in solution, depending on the solvent:[45] in methanol, it was laevorotatory, in dichloromethane dexrotatory.[46] In addition, the magnitude of $[\alpha]_D$ in CH_2Cl_2 was also dependent on sample concentration, pointing to an association equilibrium. A sample of (–)-(5*R*)-**5b** was reduced with magnesium metal in methanol (cf. Table 8, entry 5) and the resulting mixture of (+)-**15b** and *meso*-1-amino-1-oxophospholane **16** separated by chromatography. Either hydrolysis of (+)-(*R*,*R*)-**15b** or dissolving metal reduction of (5*R*)-**19** produced (+)-(*R*,*R*)-**1**,[12b] thereby assuring the absolute configuration assignments of all intermediates (Scheme 14).

Conclusions

The study presented here started from a purely conceptual question: how can we realize an asymmetric organocatalytic stereoisomerization? We chose an approach of isomerizing cyclic *meso* substrates to give the chiral isomers with release of conformational strain, and identified *meso*-1-oxo-2,5-dihydro-1*H*-phosphole described by Fiaud and co-workers[12] as suitable model substrates. The project took a different turn, when *meso*-1-amino-1-oxo-2,5-dihydro-1*H*-phosphole **4b** isomerized (quite predictably, in hindsight) to the conjugated 1-amino-1-oxo-4,5-dihydro-1*H*-phosphole **5b**. This reaction illustrates the utility of asymmetric catalytic isomerizations, and its investigation has exposed us to aspects of phospholane stereochemistry, which have led to new insights. A catalytic asymmetric synthesis of Fiaud's acid **1** by means of an organometallic cross coupling (Wenkert arylation), an asymmetric organocatalysis and a diastereoselective *contrasteric* hydrogenation as key steps has been realized. Practical large-scale applications will profit from further optimization of the catalyst for asymmetric isomerization, and by finding even more selective hydrogenation conditions. The route **6** → **4b** → **5b** → **19** was readily scaled up to 100-gram quantities in each step. The dissolving metal reduction and in particular the acid quench is more problematic, since temperature control is important to achieve high se-



Scheme 14 Structure correlation of intermediates in asymmetric catalytic dihydro-1*H*-phosphole isomerization chemistry with Fiaud's acid **1**

lectivity. The fundaments for asymmetric syntheses of new, more bulky 1-hydroxy-1-oxo-2,5-diarylphospholanes have been laid. Their preparation and use in asymmetric Brønsted acid catalysis is a promising endeavor. We note that the initial quest for an enantioselective catalytic *meso* to *chiro* isomerization [cf. Scheme 1 (a)–(c)] remains an open challenge for new catalytic asymmetric stereoisomerization chemistry.

Reactions with air- and water-sensitive substances were performed in Schlenk glassware under argon. Reaction progress was followed by TLC. Standard workup consisted in quenching with H_2O or aqueous salt solutions, extraction with a suitable solvent, followed by drying of the organic phase ($MgSO_4$). Filtration and evaporation of the filtrate gave crude product that was purified by flash column chromatography (silica gel, 0.040–0.063 mm) with a positive pressure of 0.2 bar.

MeCN: HPLC-grade, used without purification. CH_2Cl_2: distilled over CaH_2. DMF: dry grade, used without purification. Et_2O: predried over KOH, distilled over Na/benzophenone. EtOH: HPLC quality (abs), used without purification. MeOH: HPLC grade, used without purification. THF: predried over KOH, distilled over Na/benzophenone. Toluene: distilled over Na/benzophenone. Solvents for chromatography (EtOAc, CH_2Cl_2, *t*-BuOMe, hexanes) were technical grade and distilled before use. Chemicals were obtained from commercial suppliers and used without further purification. Grignard reagents were prepared according to general procedures and titrated using salicylaldehyde phenylhydrazone indicator.[47] The following compounds were synthesized according to literature procedures: 1,3-dimesitylimidazolium chloride and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride.[48]

Microwave reactions were performed in a microwave reactor with continuous irradiation and adjustable power (0–300 W) to keep the temperature of the reaction vessel at a constant value.

Analytical techniques: Analytical HPLC was performed on chiral columns (250 × 4.6 mm) of the type: Chiralpak OD (10 μm), Chiracel OJ (10 μm). Melting points were measured on a metal heating block with a digital thermometer (thus: corrected values). NMR spectroscopy: Measured at r.t. ^{1}H NMR shifts relative to TMS (δ = 0) or alternatively solvent signals ($CDCl_3$, δ = 7.26; DMSO, δ = 2.50; CD_3OD, δ = 3.34) as internal standards. ^{13}C NMR spectra were referenced to solvent signals ($CDCl_3$, δ = 77.0; DMSO, δ = 39.7, CD_3OD, δ = 49). ^{31}P NMR measured with ^{1}H decoupling. IR spectra: were either measured in KBr pellets, $CHCl_3$ solution, or as a film. Intensities of bands: vs = very strong (0–20%), s = strong (21–40%), m = medium (41–60%), w = weak (61–80%), vw = very weak (81–90%).

Syntheses of *meso*-2,5-Diaryl-2,5-dihydro-1*H*-phospholes

The (dialkylamino)dichlorophosphanes used are known compounds and were prepared from PCl_3 and amine (2 equiv) according to literature procedures.[20a,b,49] 1,4-Diarylbuta-1,3-dienes for this study were prepared as described.[16] 1,4-Diphenylbuta-1,3-diene was also obtained commercially.

(1*s*,2*R*,5*S*)-2,5-Diaryl-1-(dialkylamino)-1-oxo-2,5-dihydro-1*H*-phospholes; General Procedure (GP1)

To a stirred suspension of $AlCl_3$ (1.1 equiv) in anhyd CH_2Cl_2 under argon, a solution of (dialkylamino)dichlorophosphane (1.1 equiv) in CH_2Cl_2 was added dropwise with stirring. The mixture was stirred for 45 min at r.t. to give a greenish solution. After cooling to 0 °C, a precooled solution of 1,4-diarylbuta-1,3-diene (1 equiv) in CH_2Cl_2 was added and the mixture stirred overnight at 0 °C. The red-brown mixture was poured carefully into precooled (0 °C) mixture of nitrilotriacetic acid (NTA) and sat. aq $NaHCO_3$. The two-phase mixture was stirred for 4 h at 0 °C. After filtration through celite, the aqueous phase was decanted off and extracted with CH_2Cl_2 (2 ×). The combined organic phases were washed with sat. $NaHCO_3$, 1 M HCl, and aq NaCl. The solution was dried ($MgSO_4$), filtered, and evaporated to give the crude product. Excess diene was occasionally removed by dissolving the crude in MeOH and filtering off diene. The crude product was purified by crystallization (cold acetone–hexanes, 1:1; by dissolving in acetone, overlayering with hexanes, and storing the mixture at –20 °C in a fridge).

(1*s*,2*R*,5*S*)-1-(Diethylamino)-1-oxo-2,5-diphenyl-2,5-dihydro-1*H*-phosphole (4b)

Synthesis according to GP1:[14] from Et_2NPCl_2 (8.7 g, 0.05 mol, 1.1 equiv), $AlCl_3$ (6.667 g, 0.05 mol, 1.1 equiv) and (*E*,*E*)-1,4-diphenylbuta-1,3-diene (**6**, 9.386 g, 0.046 mol, 1 equiv) in CH_2Cl_2 (120 mL). After crystallization (acetone–hexane, 1:1), **4b** (12.3 g, 83%) was obtained as a white powder that slowly turned yellow on standing in air. The material was stored in a fridge under argon.

Large-scale synthesis: Et_2NPCl_2 (90 g, 0.517 mol) was slowly added to $AlCl_3$ (68.94 g, 0.517 mol) in CH_2Cl_2 (200 mL) at 0 °C with stirring. The mixture was stirred for 45 min at r.t. until the solids had dissolved and then cooled to 0 °C. A chilled solution of (*E*,*E*)-1,4-diphenylbuta-1,3-diene (**6**, 96.96 g, 0.47 mol) in CH_2Cl_2 (700 mL) was slowly added and the mixture stirred for 19 h at 0 °C. The reaction was quenched by slowly transferring into a stirred, ice-cooled mixture of NTA (98.82 g, 0.60 mol) in sat. aq $NaHCO_3$ (1500 mL) and further stirred for 4 h at 0 °C. The organic phase was collected, and the aqueous phase extracted with CH_2Cl_2 (2 ×) The combined organic phases were washed with sat. $NaHCO_3$, aq 2.4 M HCl, and aq NaCl. The solution was dried ($MgSO_4$), filtered, and evaporated to give a crude yellowish product (126.37 g, 83%); ratio of diastereomers 16:1 (^{31}P NMR). Crystallization (acetone–hexane) gave a first crop (86.17 g), and another crystallization of the mother liquors gave a second crop (22.84 g) of pure product (total: 109.01 g, 72%); dr ≥ 50:1.

Mp 160–165 °C; R_f = 0.23 (EtOAc–hexanes 2:1).

IR (KBr): 2978 (s), 1596 (m), 1495 (s), 1380 (s), 1218 (vs), 1027 (vs), 952 cm^{-1} (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.13 (t, *J* = 7.1 Hz, 6 H), 2.42 (ψ-dq, *J* = 9.1, 7.1 Hz, 4 H), 4.33 (dd, *J* = 18.3, 0.7 Hz, 2 H), 6.51 (dd, *J* = 28.8, 0.8 Hz, 2 H), 7.20–7.35 (m, 10 H, aryl).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1 (d, J_{PC} = 2.5 Hz, CH_3), 38.0 (d, J_{PC} = 2.3 Hz, CH_2), 50.1 (d, J_{PC} = 70.5 Hz, CH), 126.6 (d, J_{PC} = 3.8 Hz, CH), 127.3 (d, J_{PC} = 5.7 Hz, CH), 128.5 (d, J_{PC} = 2.5 Hz, CH), 130.8 (d, J_{PC} = 16.6 Hz, CH), 135.7 (d, J_{PC} = 8.3 Hz, C).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 70.8.

MS (ESI): *m*/*z* (%) = 325 (2) M^+, 206 (100), 91 (14).

Anal. Calcd for $C_{20}H_{24}NOP$: C, 73.82; H, 7.43; N, 4.30. Found: C, 73.37; H, 7.36; N, 4.49.

(1*r*,2*R*,5*S*)-1-(Diethylamino)-1-oxo-2,5-diphenyl-2,5-dihydro-1*H*-phosphole

Minor diastereomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (t, *J* = 7.1 Hz, 6 H), 3.11 (ψ-dq, *J* = 10.4, 7.0 Hz, 4 H), 3.90 (dd, *J* = 5.5, 1.1 Hz, 2 H), 6.13 (dd, *J* = 25.6, 1.1 Hz, 2 H), 7.2–7.4 (m, 10 H).

^{31}P NMR (162 MHz, $CDCl_3$): δ = 60.6 (s).

Asymmetric Catalytic Isomerization of *meso*-Dihydro-1*H*-phospholes; General Procedure (GP2)

A solution of the *meso*-2,5-dihydro-1*H*-phosphole **4**, **7**, or **11** (0.10 mmol) and catalyst (5–10 mol%) in MeCN (1–2 mL) was stirred for 16–48 h at 50–70 °C. After completion of the reaction (TLC control, typically EtOAc–hexanes, 2:1) the mixture was cooled and MeCN was removed in vacuo. The residue was dissolved in EtOAc and the solution washed with aq 2 M HCl (2 ×). The organic phase was dried ($MgSO_4$). Filtration and evaporation of the filtrate gave a res-

idue that was either used as received or further purified by flash column chromatography.

Analysis: The enantiomeric excess of the reaction product was determined either by chiral HPLC or by ^{31}P NMR in $CDCl_3$ with addition of quinine (1–5 molar equiv).

Recycling: The evaporated solvent (MeCN) can be directly reused. The catalyst can be precipitated from the aqueous acidic washing phase by addition of excess aq NH_3; it is isolated by filtration, or by extraction with CH_2Cl_2 and evaporation.

Example for a small-scale screening reaction: The catalyst (cinchonine; 2.9 mg, 0.01 mmol) and **4b** (32.5 mg, 0.10 mmol) were stirred in MeCN (2 mL) at 50 °C for 16 h. The solvent was removed in vacuo and the residue taken up in EtOAc (5 mL). After washing with aq 2 M HCl (2 × 1 mL) and H_2O (1 ×), the organic phase was dried ($MgSO_4$), filtered, and evaporated to give **5b** (31.8 mg, 98%) as a slightly yellow solid.

(1*R*,5*R*)-1-(Diethylamino)-1-oxo-2,5-diphenyl-4,5-dihydro-1*H*-phosphole (5b)

Synthesis according to GP2:[14] from **4b** (0.500 g, 1.54 mmol) and cinchonine (0.045g, 0.154 mmol, 10 mol%) in MeCN (30 mL) at 50 °C for 40 h. Evaporation of the solvent gave **5b** (0.49 g, 98%) as a slightly yellow solid; 80% ee (HPLC).

*Large-scale synthesis of **5b***: To a solution of **4b** (97.4 g, 0.30 mol) in MeCN (2.5 L), cinchonine (4.416 g, 0.015 mol, 5 mol%) was added and the mixture stirred for 20 h at 50 °C. The solution was cooled to r.t. and the solvent recycled by evaporation using a rotavapor. The solid residue was dissolved in EtOAc (ca. 2 L), the solution washed with 1 M HCl (2 × 100 mL) and the aqueous phases were retained for catalyst recycling. The EtOAc solution was dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue consisted of **5b** (94.5 g, 97%) as a slightly yellow solid; 78% ee (HPLC).

HPLC (Chiralcel-OJ, *n*-heptane–*i*-PrOH–H_2O,[32] 90:10 + 0.25%; flow = 0.7 mL min^{-1}, λ = 230 nm): t_R = 10.6 [minor, (5*S*)], 12.1 min [major, (5*R*)]; mp 152–155 °C (enriched sample, 80% ee); R_f = 0.3 (EtOAc–hexanes 2:1); $[\alpha]_D$ –141.1 (*c* 0.595, CH_2Cl_2; 80% ee); $[\alpha]_D$ –115.1 (*c* 0.595, MeOH; 80% ee).

IR (KBr): 2973 (s), 2921 (m), 2875 (m), 1597 (s), 1493 (s), 1453 (s), 1376 (s), 1201 (vs), 1023 (vs), 948 (vs), 854 (m), 765 (vs), 697 (vs), 635 (m), 517 (vs), 475 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.54 (t, *J* = 7.1 Hz, 6 H), 2.54–2.91 (m, 4 H, NCH_2Me), 2.98 (ddd, *J* = 18.6, 6.8, 2.8 Hz, 1 H, H4), 3.17 (tdd, *J* = 18.8, 8.5, 3.9 Hz, 1 H, H4), 3.76 (ddd, *J* = 22.6, 8.4, 7.0 Hz, 1 H, H5), 7.14–7.41 (9 H, 8 H_{Arl} + H5), 7.66–7.74 (m, 2 H_{Arl}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6 (d, J_{PC} = 1.9 Hz, CH_3), 32.0 (d, J_{PC} = 14.6 Hz, CH_2), 37.9 (d, J_{PC} = 4.5 Hz, CH_2), 44.9 (d, J_{PC} = 82.1 Hz, CH), 126.6 (CH), 126.6 (d, J_{PC} = 5.2 Hz, CH), 127.7 (d, J_{PC} = 5.0 Hz, CH), 128.2 (CH), 128.5 (d, J_{PC} = 2.5 Hz, CH), 128.6 (CH), 133.7 (d, J_{PC} = 9.4 Hz, C), 136.4 (d, J_{PC} = 5.7 Hz, C), 137.9 (d, J_{PC} = 100.2 Hz, C), 142.8 (d, J_{PC} = 33.1 Hz, CH).

^{31}P NMR (120 MHz, $CDCl_3$): δ = 60.6.

MS (EI, 70 eV): *m*/*z* (%) = 325 (61) M^+, 310 (56), 253 (49), 205 (13), 91 (11), 72 (100).

Anal. Calcd for $C_{20}H_{24}NOP$ + 0.85 H_2O: C, 70.51; H, 7.60; N, 4.11. Found: C, 70.56; H, 7.17; N, 4.11.

Enantiomeric enrichment by crystallization: A sample of **5b** (0.300 g; 80% ee) was dissolved in acetone (20 mL) and the solution overlayered with hexanes (20 mL). After standing for 16 h at –10 °C, the solid (racemate) was filtered off and the filtrate evaporated to leave (1*R*,5*R*)-**5b** (0.213 g, 71%); 95% ee.

Synthesis of 2,5-Diphenyl-1*H*-phosphole-Derived Phosphinic Acids

***meso*-1-Hydroxy-1-oxo-2,5-diphenylphospholane (17)**

A mixture of (1*s*,2*S*,5*R*)-1-(diethylamino)-1-oxo-2,5-diphenylphospholane (**16**)[50] (4.11 g, 12.55 mmol), EtOH (8 mL), H_2O (5 mL) and concd HCl (10 mL, 120 mmol) in a round-bottom flask with a mounted condenser (air cooling) was heated at 120 °C (oil bath) for 20 h; most of the EtOH had evaporated and hydrolysis was incomplete (TLC, EtOAc). Ethylene glycol (6 mL) and concd HCl (2 mL) were added and the mixture refluxed at 140 °C (oil bath) for a further 20 h. The mixture was cooled, diluted with H_2O and extracted with CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (2 ×). The combined organic phases were washed with H_2O (2 ×) and evaporated to dryness. The crystalline residue was redissolved in CH_2Cl_2, diluted with cyclohexane, and slowly evaporated in a rotatory evaporator to give a suspension of crystals. Filtration and washing of the solid with cyclohexane gave a first crop of colorless crystals that was dried in an oven (2.413 g, 71%). The mother liquor and washing phases were combined and crystallized once more (CH_2Cl_2–cyclohexane) to give a second crop (328 mg, 9.5%); total yield: 2.741 g (80%). Note: Non-optimized conditions. The hydrolysis required an elevated temperature (130–140 °C); use of an ethylene glycol–H_2O–concd HCl mixture from the start is recommended.

Mp 207–208 °C (droplet formation and sublimation from 185 °C; compare Lit.[51] 169–171 °C); R_f = <0.1 (EtOAc).

IR (KBr): 3431 (m), 3028 (m), 2946 (m), 2868 (w), 1709 (w), 1597 (m), 1494s, 1449 (m), 1252 (s), 1199 (s), 1075 (m), 1034 (m), 974 (s), 764 (s), 694 (s), 526 (s), 484 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 2.20–2.36 (m, 4 H), 3.09–3.24 (m, 2 H), 7.07–7.21 (m, 10 H), 10.22 (s, 1 OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0 (d, J_{PC} = 14.0 Hz, CH_2), 43.3 (d, J_{PC} = 86.1 Hz, CH), 126.5 (d, J_{PC} = 2.8 Hz, CH), 128.1 (d, J_{PC} = 5.3 Hz, CH), 128.3 (d, J_{PC} = 2.2 Hz, CH), 135.9 (d, J_{PC} = 6.9 Hz, C).

^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 68.0 (s).

MS (EI): *m*/*z* (%) = 272 (100) [M^+], 168 (25), 104 (90).

Anal. Calcd for $C_{16}H_{17}O_2P$ (272.28): C, 70.58; H, 6.29. Found: C, 70.84; H, 6.21.

***meso*-1-Hydroxy-1-oxo-2,5-diphenyl-2,5-dihydro-1*H*-phosphole (18)**

A solution of **4b** (0.260 g, 0.80 mmol) in ethylene glycol (10 mL) and 6 M HCl (10 mL) was heated to 120 °C for 24 h. The cooled mixture was diluted with H_2O and extracted with CH_2Cl_2 (3 ×). The organic phase was washed with a small volume of H_2O and dried ($MgSO_4$). Evaporation gave **18** (0.206 g, 95%) as a white crystalline powder.

Mp 221–223 °C; R_f = 0.24 (EtOAc–MeOH, 3:1).

IR (KBr): 3442 (w), 3030 (m), 1657 (m), 1493 (m), 1218 (vs), 972 (vs), 744 (vs), 696 (vs), 539 (s), 495 cm^{-1} (s).

^1H NMR (300 MHz, $CDCl_3$): δ = 3.87 (d, *J* = 13.3 Hz, 2 H), 6.13 (d, *J* = 29.9 Hz, 2 H), 7.04–7.11 (m, 4 H_{Arl}), 7.19–7.28 (m, 6 H_{Arl}), 7.73 (br s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 47.6 (d, J_{PC} = 84.2 Hz, CH), 126.9 (d, J_{PC} = 3.0 Hz, CH), 128.3 (d, J_{PC} = 5.0 Hz, CH), 128.4 (d, J_{PC} = 2.5 Hz, CH), 131.3 (d, J_{PC} = 18.2 Hz, CH), 134.6 (d, J_{PC} = 8.5 Hz, C).

^{31}P NMR (120 MHz, $CDCl_3$): δ = 69.8.

MS (EI, 70 eV): *m*/*z* (%) = 270 (17) M^+, 206 (100), 191 (14), 104 (21).

Anal. Calcd for $C_{16}H_{15}O_2P$ + 0.2 H_2O: C, 70.17; H, 5.67. Found: C, 70.37; H, 5.52.

(5*R*)-1-Hydroxy-1-oxo-2,5-diphenyl-4,5-dihydro-1*H*-phosphole (19)

Regular-scale synthesis:[14] A sample of **5b** (0.26 g, 0.80 mmol), which had been recrystallized for enantiomeric enrichment, was dissolved in MeOH (10 mL). After the addition of 6 M HCl (10 mL), the mixture was stirred for 16 h at 60 °C. After cooling and dilution with a small volume of H_2O, the mixture was extracted with CH_2Cl_2 (3 ×). The organic phase was washed with a small volume of H_2O, dried ($MgSO_4$), and evaporated to leave **19** (0.197 g, 91%) as a colorless powder; 95% ee (^{31}P NMR).

Large-scale synthesis: To a solution of (5*R*)-**5b** (94.5 g, 0.291 mol; 78% ee) in MeOH (1.6 L), aq 6 M HCl (1.6 L) was added and the mixture heated to 60 °C for 20 h with mechanic stirring. The mixture was cooled and extracted with several portions of CH_2Cl_2. The organic phase was dried ($MgSO_4$). After filtration, the solvents were evaporated in vacuo and the solid residue suspended in a small volume of chilled MeOH. Filtration and drying under high vacuum gave **19** (62.1 g, 79%) as a colorless crystalline material; 77% ee (^{31}P NMR). The enantiomeric excess was determined by ^{31}P NMR of a solution of **19** (5.5 mg) and quinine (37 mg, 5 equiv) in $CDCl_3$ (0.5 mL); $\delta(^{31}P) = 51.14$ (major), 50.79 (minor).

Mp 237–239 °C (77% ee); R_f = 0.26 (EtOAc–MeOH, 3:1); $[\alpha]_D$ +126.4 (*c* 0.595, CH_2Cl_2; 76% ee); $[\alpha]_D$ +98.4 (*c* 0.28, CH_2Cl_2; 76% ee); $[\alpha]_D$ –21.9 (*c* 0.59, MeOH; 76% ee).

IR (KBr): 3439 (w), 3050 (m), 1601 (s), 1494 (s), 1449 (m), 1265 (m), 977 (vs), 755 (vs), 694 (vs), 533 (s), 476 cm^{-1} (m).

^1H NMR (250 MHz, $CDCl_3$): δ = 2.84 (dddd, *J* = 18.6, 6.5, 2.6, 1.1 Hz, 1 H), 3.13 (dddd, *J* = 22.0, 18.5, 8.6, 3.8 Hz, 1 H), 3.46 (ddd, *J* = 18.6, 8.6, 6.6 Hz, 1 H), 7.11 (ddd, *J* = 45.5, 3.7, 2.6 Hz, 1 H), 7.21–7.37 (m, 8 H_{Ph}), 7.51–7.58 (m, 2 H_{Ph}), 10.49 (br s, 1 H).

^1H NMR (300 MHz, CD_3OD): δ = 2.89 (ddd, *J* = 18.7, 6.8, 2.7 Hz, 1 H), 3.20 (dddd, *J* = 21.8, 18.7, 8.7, 3.8 Hz, 1 H), 3.54 (ddd, *J* = 18.4, 8.7, 6.7 Hz, 1 H), 7.19–7.43 (m, 9 H, 8 H_{Arl} + H3), 7.65–7.73 (m, 2 H_{Arl}).

^{13}C NMR (75 MHz, CD_3OD): δ = 35.1 (d, J_{PC} = 17.3 Hz, CH_2), 44.4 (d, J_{PC} = 93.7 Hz, CH), 127.5 (d, J_{PC} = 5.7 Hz, CH), 128.0 (d, J_{PC} = 2.7 Hz, CH), 129.4 (CH), 129.6 (CH), 129.7 (d, J_{PC} = 3.6 Hz, CH), 129.8 (CH), 134.4 (d, J_{PC} = 9.7 Hz, C), 137.4 (d, J_{PC} = 118 Hz, C), 137.6 (d, J_{PC} = 6.1 Hz, C), 143.9 (d, J_{PC} = 35.6 Hz, CH).

^{31}P NMR (101 MHz, $CDCl_3$): δ = 66.39 (s, minor, 12%), 66.28 (s, major, 88%; 76% ee).

^{31}P NMR (120 MHz, CD_3OD): δ = 60.1 (s).

MS (EI, 70 eV): *m*/*z* (%) = 270 (100) M^+, 206 (24), 192 (10), 103 (10), 91 (12).

Anal. Calcd for $C_{16}H_{15}O_2P$ + 0.1 H_2O: C, 70.64; H, 5.63. Found: C, 70.64; H, 5.66.

Diastereoselective Reduction of 4,5-Dihydro-1*H*-phospholes

(2*R*,5*R*)-1-(Diethylamino)-1-oxo-2,5-diphenylphospholane (15b)

Prepared by reduction of (1*R*,5*R*)-**5b** (1.00 g, 3.07 mmol, 81% ee) with Mg powder (1.49 g, 30.7 mmol, 20 equiv) in MeOH (31 mL, 10 mL/mmol): to a solution of **5b** in MeOH at 0 °C, Mg powder was added and the suspension stirred for 7 h at 0 °C. After quenching with a small volume of both 2 M HCl and H_2O, the product was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$), filtered, and evaporated. Separation of the crude by column chromatography (EtOAc) gave **15b** (0.362 g, 36%) as a white solid; 82% ee (^{31}P NMR, HPLC). The *meso*-isomer **16**, which was also formed in this reaction, was not isolated. In a second reaction with (1*R*,5*R*)-**5b** (482 mg, 1.48 mmol) and Mg (>0.72 g) in MeOH (30 mL) at 0 °C, both *meso*-**16** (257 mg, 53%) and (2*R*,5*R*)-**15b** (148.4 mg, 31%) were isolated.

Mp 128–131 °C (82% ee); R_f = 0.26 (EtOAc–hexanes, 2:1); $[\alpha]_D^{25}$ +46.4 (*c* 0.6, CH_2Cl_2; 80% ee); $[\alpha]_D^{25}$ +42.5 (*c* 0.61, MeOH; 80% ee).

IR (KBr): 3427 (vs), 2937 (vs), 1598 (m), 1496 (s), 1382 (s), 1175 (vs), 1027 (vs), 937 (s), 761 (vs), 696 cm^{-1} (vs).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.65 (t, *J* = 7.1 Hz, 6 H), 2.06–2.33 (m, 2 H), 2.38–2.57 (m, 2 H), 2.60–2.85 (m, 4 H), 3.10 (td, *J* = 12.9, 6.8 Hz, 1 H), 3.64 (ddd, *J* = 24.6, 12.7, 7.4 Hz, 1 H), 7.19–7.38 (m, 10 H_{Arl}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (d, J_{PC} = 2.3 Hz, CH_3), 27.9 (d, J_{PC} = 9.0 Hz, CH_2), 30.2 (d, J_{PC} = 11.4 Hz, CH_2), 37.9 (d, J_{PC} = 3.1 Hz, CH_2), 44.3 (d, J_{PC} = 74.9 Hz, CH), 47.7 (d, J_{PC} = 76.5 Hz, CH), 126.3 (d, J_{PC} = 2.6 Hz, CH), 126.6 (d, J_{PC} = 2.3 Hz, CH), 127.4 (d, J_{PC} = 4.9 Hz, CH), 128.3 (d, J_{PC} = 2.2 Hz, CH), 128.4 (d, J_{PC} = 1.8 Hz, CH), 128.9 (d, J_{PC} = 5.0 Hz, CH), 136.5 (d, J_{PC} = 5.1 Hz, C), 137.0 (d, J_{PC} = 4.7 Hz, C).

^{31}P NMR (161 MHz, $CDCl_3$): δ = 59.3.

MS (EI, 70 eV): *m*/*z* (%) = 327 (42) M^+, 312 (30), 206 (15), 120 (14), 104 (100), 91 (15), 72 (88).

Anal. Calcd for $C_{20}H_{26}NOP$: C, 73.37; H, 8.00; N, 4.28. Found: C, 73.16; H, 8.09; N, 4.21.

(2*R*,5*R*)-1-Hydroxy-1-oxo-*trans*-2,5-diphenylphospholane (Fiaud's Acid, 1)

*By Na/NH_3 reduction of **19***: Na (0.17 g, 0.370 mmol, 20 equiv) was dissolved in liquid NH_3 (ca. 50 mL) at –78 °C. A solution of (1*R*,5*R*)-**19** (0.10 g, 0.370 mmol; 81.5% ee) in THF (2 mL) was added and the mixture was stirred for 5 min at –78 °C. The reaction was quenched by addition of solid $(NH_4)_2SO_4$ (1.00 g, 7.57 mmol, 20.5 equiv), causing the blue solution of the mixture to disappear. After warming to r.t. with evaporation of NH_3 into the hood, the residue was suspended in a small volume of 2 M HCl and extracted with CH_2Cl_2. After evaporation of the solvent, a white solid remained (0.0978 g, 98%; ratio **1**/**17** 7.7:1; 82% ee). After crystallization (hot MeOH, ca. 3 mL/mmol), pure product (0.0539 g, 54%) was obtained as colorless solid; ≥ 98% ee.

*By hydrolysis of **15b***: To a solution of (2*R*,5*R*)-1-(diethylamino)-1-oxo-2,5-diphenylphospholane (**15b**, 0.30 g, 0.916 mmol; 81% ee) in MeOH (10 mL), 6 M HCl (10 mL) was added and the mixture stirred for 16 h at 60 °C. The aqueous layer was extracted with CH_2Cl_2 and the organic layer washed with a small volume of H_2O, dried ($MgSO_4$), filtered, and evaporated. The residue (0.225 g, 75%) consisted of a white solid; 81% ee (^{31}P NMR).

Hydrolysis in ethylene glycol: To a sample of (1*R*,5*R*)-**15b** (116 mg, 0.35 mmol) in ethylene glycol (5 mL), aq 6 M HCl (5 mL) was added and the mixture stirred at 90 °C for 12 h. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic phase washed with H_2O (2 × 10 mL), dried ($MgSO_4$), filtered, and evaporated to leave the product (94.2 mg, 98%) as a white solid.

$[\alpha]_D^{24}$ +79.2 (*c* 0.615, CH_2Cl_2; 76% ee); $[\alpha]_D^{24}$ +57.9 (*c* 0.615, MeOH; 76% ee).

^1H NMR (250 MHz, $CDCl_3$): δ = 1.91–2.15 (m, 2 H), 2.19–2.52 (m, 2 H), 3.01–3.26 (m, 2 H), 7.09–7.36 (m, 10 H), 9.54 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4 (d, J_{PC} = 12.2 Hz, CH_2), 45.3 (d, J_{PC} = 88.0 Hz, CH), 126.6 (CH), 128.2 (d, J_{PC} = 5.2 Hz, CH), 128.3 (CH), 135.7 (C).

^{31}P NMR (161 MHz, $CDCl_3$): δ = 66.8 (s).

Analytical data correspond to those reported.[12b]

Analysis of enantiomeric excess by ^{31}P NMR: **1** (4.8 mg, 0.018 mmol) and quinine (33 mg, 0.10 mmol) were dissolved in $CDCl_3$ (0.5 mL). $\delta(^{31}P)$ = 52.07 [minor, (*S*,*S*)-**1**], 51.71 [major, (*R*,*R*)-**1**].

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Supporting Information for this article including experimental procedures, product characterization and copies of NMR spectra is available online at http://www.thieme-connect.com/ejournals/toc/synthesis

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