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Enantioselective Synthesis of Phospholenes *via* Asymmetric Organocatalytic Alkene Isomerization

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Abstract: An asymmetric synthesis of the 2,5-diphenylphosphol-2-ene fragment (≥95% *ee*) has been realized *via* enantioselective *Cinchona*-alkaloid catalyzed double bond isomerization of a *meso*-2,5-diphenylphosphol-3-ene amide to a 2,5-diphenylphosphol-2-ene amide (up to 83% *ee*), followed by enantiomeric enrichment to ≥95% *ee* by crystallization. The 2,5-diphenylphosphol-2-ene amide (a cyclic phosphinic acid amide) was hydrolyzed to the 2,5-diphenylphosphol-2-ene acid (a cyclic phosphinic acid) with retention of configuration at C-5.

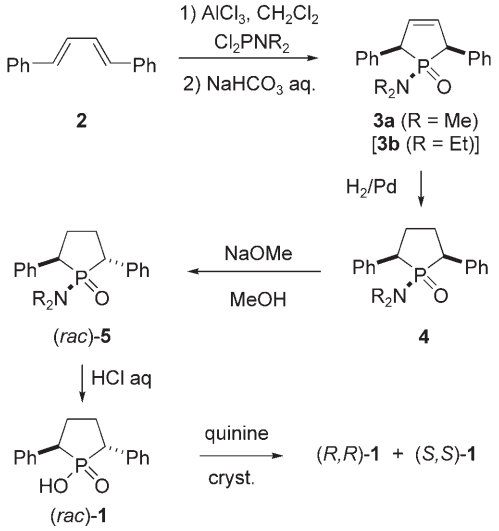
Keywords: alkaloids; alkenes; asymmetric catalysis; *Cinchona* alkaloids; isomerization; phosphorus heterocycles

Enantiopure phospholanes are building blocks in the synthesis of chiral 2,5-dialkylphospholane ligands that find widespread use in asymmetric transition metal-catalyzed hydrogenation and other reactions.[1] Limitations in synthetic methodology had prevented the access to 2,5-diarylphospholanes, until Fiaud and coworkers presented a synthesis and resolution of *rac*-2,5-diphenylphospholanic acid (±)-**1**[2,3] *via* the McCormack reaction of 1,4-diphenyl-1,3-butadiene (**2**) (Scheme 1).[4] The resolved acid **1** is the starting material for the synthesis of a number of 2,5-diphenylphospholane ligands that have already proved successful in various transition metal-catalyzed asymmetric reactions and other applications.[3,5,6]

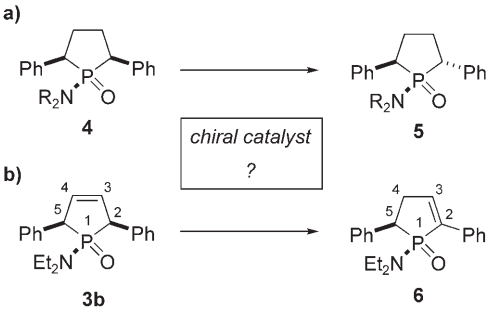
The procedure of Scheme 1 requires stoichiometric quantities of chiral resolving agents and obviously yields a maximum of 50% for each enantiomer of **1**. An attempt to convert this route to an enantioselective synthesis *via* sparteine/*sec*-BuLi deprotonation/reprotonation of *meso*-1,2,5-triphenylphospholane oxide suffered from low yields or selectivities,[7] even though a corresponding α-alkylation via deprotonation with chiral lithium amides and an electrophilic quench was possible.[8]

We now present a *catalytic asymmetric* synthesis of phospholenes that relies on the new concept of organocatalytic enantioselective double-bond isomerization.[9] This chemistry represents another extension of organocatalysis towards a reaction type that has previously been associated with the field of metal catalysis.[10,11] For realizing an efficient asymmetric synthesis of phospholane acid **1**, the catalytic asymmetric isomerization of *meso*-phospholane **4** to enriched *cis*,*trans*-phospholane **5** is a very desirable reaction, since it would convert the existing efficient synthetic sequence[3] into an asymmetric catalytic one (Scheme 2, **a**).

Initial experiments showed that such a process is difficult to realize because it requires strongly basic reaction conditions that are difficult to achieve with usual types of chiral base catalysts.[12] On the other hand, the *meso*-phospholene **3**, which is the initial



Scheme 1. Fiaud's route (R = Me) to 2,5-diphenylphospholanic acid **1**.[3]



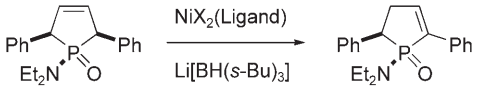
Scheme 2. Desirable desymmetrization reactions of *meso*-phosphacycles. **a)** *cis-trans* isomerization of a *trans-trans-meso*-phospholane. **b)** Isomerization of a *meso*-3-phospholene to a chiral 2-phospholene.

product of the McCormack reaction in the Fiaud sequence (Scheme 1),[3] bears activated allylic C–H bonds that should be more susceptible to catalytic transformations. In fact, we find that the 3-phospholene amide **3b** undergoes an irreversible double-bond shift to the conjugated chiral 2-phospholenamide **6** (Scheme 2. **b**).[13] This alkene isomerization is catalyzed either by transition metal complexes or Brønsted bases (*vide infra*). In a first set of experiments, **3b** was submitted to the action of hydride-activated complexes NiX_2(Me-DuPHOS) (Table 1, entries 1 and 2) that have already been used as catalysts in asymmetric olefin isomerization by Frauenrath and co-workers.[14] No enantioselectivity was observed in the isomerization to **6** for either the chloride- or iodide-containing catalyst, but when the corresponding hydride activated complexes NiX_2(JOSIPHOS)[15] were used, inductions of up to 38% *ee* were achieved (Table 1, entries 3–7).

In the course of these experiments, we noted that an excess of the hydride activator induced an unfavourable background reaction, which we ascribed to simple base catalysis. In fact, the isomerization of **3b** to **6** was also catalyzed by the amidine base DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) (Table 2, entry 1). This observation led to the development of an *organocatalytic enantioselective double-bond shift* for the desymmetrization of phospholene **3b**. A screening of chiral amine bases revealed that amino alcohols and, among them particularly the *Cinchona* alkaloids (Figure 1) were suitable catalysts for the desired asymmetric catalysis (Table 2, entries 2–8). For convenience, initial experiments were carried out in an NMR tube in $CDCl_3$. The conversion was readily observed by NMR spectroscopy. Even more conveniently, the addition of an excess of quinine to the catalysis mixture (irrespective of the initial catalyst) gave two distinct ^{31}P NMR resonances for the enantiomers of **6**; thus, the quinine served as a chiral shift reagent (Figure 2, *left*).[16,17] Presumably, the alkaloid forms diastereomeric complexes *via* hydrogen bonding of its alcoholic hydroxy proton to the P=O double bond (Figure 2, *right*). Purified samples of **6** were also readily analyzed by chiral HPLC.[18]

An initial screening of catalysts in $CDCl_3$ solution (Table 2, entries 2–8) led to identification of cinchonine (CN) as the most selective catalyst. In a second step, several reaction media were tested (entries 9–13). Dipolar aprotic solvents gave the best results both in terms of selectivity and activity, and acetonitrile was favoured due to its volatility. The *Cinchona* alkaloids were more selective catalysts in this solvent (entries 14–17). Additional studies of the reaction conditions included variations of the catalyst loading, the temperature and the substrate dilution (Table 3). Catalyst loadings of 10% were efficient, and even loadings of 5% gave satisfactory results (entries 5, 9, 11, 13, 16). The substrate concentration was set to

Table 1. Transition metal-catalyzed asymmetric isomerization of **3b** to **6**.[a]

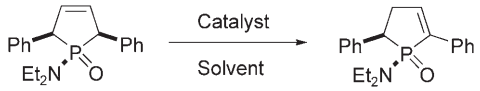


3b **6**

Entry	Ligand[b]	X	Solvent	*T* [°C]	Time [h]	Conversion [%][c]	*ee* [%][c]	
1	(*S*,*S*)-Me-DuPHOS	Cl	THF	r.t.	30	33	0	-
2	(*S*,*S*)-Me-DuPHOS	I	PhMe	r.t.	5	88	0	-
3	(1*R*,S_P)-JOSIPHOS	Cl	THF	50	5	29	19	(2*R*)
4	(1*R*,S_P)-JOSIPHOS	Cl	THF	50	50	58	12	(2*R*)
5	(1*R*,S_P)-JOSIPHOS	Cl	THF	0	5	54	38	(2*R*)
6	(1*R*,S_P)-JOSIPHOS	I	THF	50	20	>99	0	-
7	(1*R*,S_P)-JOSIPHOS	I	THF	0	51	98	0	-

[a] *Conditions:* 0.1 mmol **3b**, 5 mol% of catalyst, 1 mL solvent. The Ni complex was activated with a co-catalytic (5 mol%) amount of LiBH(*s*-Bu)$_3$ solution prior to substrate addition.
[b] See Figure 1 for ligand structures.
[c] Conversion and *ee* (±1%) determined by HPLC (Supporting Information).

Table 2. Amine-catalyzed asymmetric isomerization of **3b** to **6**.[a]



Entry	Catalyst[b]	[mol%]	Solvent	T [°C]	Time [h]	Conversion [%][c]	*ee* [%][d]	
1	DBU	100	$CDCl_3$	55	16	90		
2	QN	30	$CDCl_3$	50	16	35	16	(5*S*)
3	QD	30	$CDCl_3$	50	16	47	31	(5*R*)
4	CN	30	$CDCl_3$	50	16	76	59	(5*R*)
5	CD	30	$CDCl_3$	50	16	49	39	(5*S*)
6	(−)-NME	10	$CDCl_3$	70	16	6	33	(5*S*)
7	(2*S*)-DPP	10	$CDCl_3$	70	16	12	26	(5*R*)
8	L-proline	30	CD_3CN	70	18	78	15	(5*S*)
9	CN	30	PhMe	50	24	98	44	(5*R*)
10	CN	30	PhCl	50	24	>99	53	(5*R*)
11	CN	30	MeCN	50	24	>99	72	(5*R*)
12	CN	30	THF	50	24	>99	50	(5*R*)
13	CN	20	DMF	50	24	>99	72	(5*R*)
14	QN	10	MeCN	50	16	81	30	(5*S*)
15	QD	10	MeCN	50	16	91	40	(5*R*)
16	CN	10	MeCN	50	16	98	71	(5*R*)
17	CD	10	MeCN	50	16	79	62	(5*S*)

[a] Conditions: 0.1 mmol of **3b**, 1 mL solvent ($c = 0.1$ M).
[b] CN = cinchonine; CD = cinchonidine; QN = quinine; QD = quinidine; NME = *N*-methylephedrine; DPP = diphenylprolinol; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.
[c] The conversion was determined by ^{1}H NMR.
[d] The *ee* was determined by ^{31}P NMR in $CDCl_3$ with quinine as chiral shift reagent (accuracy ±5%).

0.1 M, since this assures dissolution of the alkaloid catalyst; further dilution had no marked beneficial effect. It was possible to replace part of the acetonitrile by dichloromethane to assure dissolution of the catalyst in smaller reaction volumes, without loss of selectivity (entry 3). The enantioselectivity of the reaction was not markedly lowered upon increasing the reaction temperature to as high as 90 °C (entries 8–16), but the reaction time was considerably reduced. Under optimized conditions, the pseudo-enantiomeric catalyst cinchonidine (CD) gave (1*S*,5*S*)-**6** in similar enantioselectivity (entry 7).

A set of robust reaction conditions emerged from this screening (MeCN, 0.05–0.10 M, 5–10 mol% of cinchonine, 50 °C) that regularly gave the product (1*R*,5*R*)-**6** in an enantiomeric excess of 82–83% on preparative scale (5 g). After evaporation of the solvent, the reaction product was separated from the catalyst by a simple acid wash, with no additional purifi-

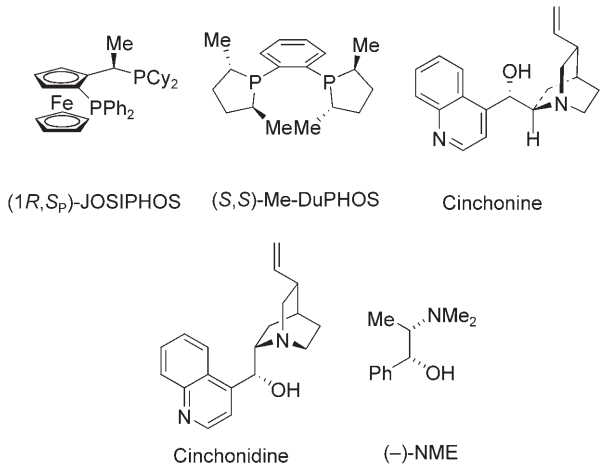


Figure 1. Catalysts and ligands tested in the catalytic isomerization reaction of **3b** to **6**.

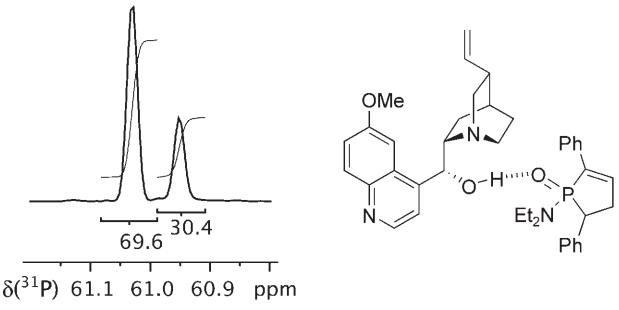
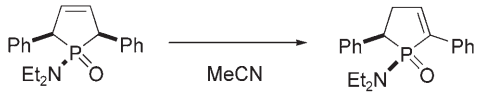


Figure 2. *Left: In situ* enantiomer analytics of **6** by ^{31}P NMR spectroscopy ($CDCl_3$) with quinine in $CDCl_3$ [*er* = 69.6:30.4, *ee* = 39% (2*R*)]. *Right:* Proposed complexation of quinine to phospholene **6**.

Table 3. *Chincona* alkaloid-catalyzed isomerization of **3b** to **6** in MeCN: temperature and concentration effects.[a]

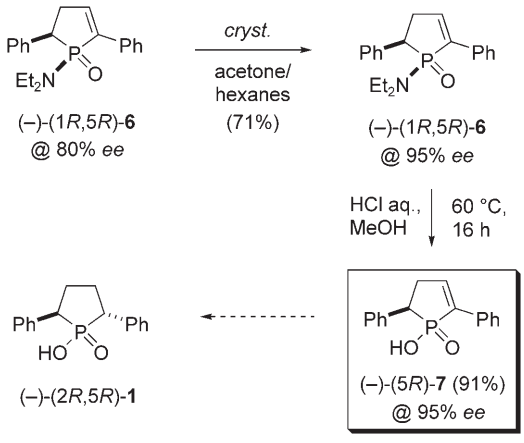


3b **6**

Entry	Catalyst	[mol%]	Dilution [L·mol^{-1}]	T [°C][b]	Time [h]	Conversion [%][c]	*ee* [%][c]	
1	CN	10	10	50	16	>99	79	(5*R*)
2	CN	10	20	50	16	>99	80	(5*R*)
2a	CN	10	20	50	16	>99	83[d]	(5*R*)
3[e]	CN	10	10+1.6[e]	50	16	>99	80	(5*R*)
4[f]	CN	10	10	50	4	59	78	(5*R*)
5	CN	5	20	50	22	>99	78	(5*R*)
7	**CD**	10	10	50	40	>99	72	(5*S*)
8	CN	10	10	60	7.5	>99	78	(5*R*)
9	CN	5	10	60	16	>99	76	(5*R*)
10	CN	10	10	70	5	>99	77	(5*R*)
11	CN	5	10	70	6	>99	75	(5*R*)
12	CN	10	10	80	3	>99	75	(5*R*)
13	CN	5	10	80	4	>99	74	(5*R*)
14	CN	10	10	90	1.5	>99	73	(5*R*)
15	CN	10	20	90	3	>99	75	(5*R*)
16	CN	5	20	90	3.5	>99	74	(5*R*)

[a] *Conditions:* 0.1 mmol substrate in MeCN; closed vessels under argon.
[b] Temperature of the oil bath. Reactions at 80 or 90 °C may build up pressure.
[c] Conversion and *ee* determined by chiral HPLC (accuracy ±1%), see Supporting Information.
[d] Large scale reaction (5 g of **3b**).
[e] Reaction in a mixed solvent MeCN/dichloromethane.
[f] Reaction with microwave heating.

cation needed. Both the acetonitrile solvent and the catalyst are readily recycled.[19] Importantly, the enantiomeric excess of the phospholenamide **6** was increased to ≥95% by a single crystallization from acetone and hexanes (Scheme 3). Acidic hydrolysis of **6** gave the new 2-phospholenic acid **7**. We are currently investigating uses of acid **7** as a chiral Brønsted acid catalyst[11] and as a synthetic precursor of phospholane ligands; in this connection, the stereoselective hydrogenation to Fiaud's cyclic phosphinic acid **1** will be of particular interest.[20]



Scheme 3. Conversion of amide **6** to acid **7**. Optical rotation signs refer to both CH_2Cl_2 and MeOH solution.

In conclusion, we have presented both a metal-catalyzed and a superior organocatalytic asymmetric double-bond isomerization of achiral *meso*-3-phospholene **3b** to the chiral 2-phospholene **6** with high enantioselectivity. This new asymmetric catalytic process opens the way to a catalytic enantioselective synthesis of 2,5-diarylphospholane building blocks for applications as catalysts, chiral auxiliaries or ligands in transition metal catalysis.

Experimental Section

Typical Procedure

To a solution of *meso*-phospholene **3b** (5.00 g, 15.35 mmol) in acetonitrile (300 mL) at 50 °C, cinchonine (0.452 g, 1.535 mmol, 10 mol%) was added and the mixture stirred for 22 h at 50 °C. The solvent was evaporated at room temperature, and the residue taken up in EtOAc (200 mL). After washing with aqueous HCl (2 M; 2×30 mL) and water (50 mL), the organic phase was dried over $MgSO_4$, filtered, and the solvent evaporated to leave (1*R*,5*R*)-**6** as slightly yellow solid; yield: 4.89 g (98%); *ee* 83% (HPLC).

Crystallization: A sample of **6** (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*)-**6**; yield: 0.213 g (71%); *ee* 95% (HPLC).

Supporting Information

Experimental procedures, characterization data and NMR spectra of compounds **3b**, **6**, **7**. Conditions for chiral HPLC and NMR analyses are given as Supporting Information.

Acknowledgements

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[2] Acid **1** is a cyclic dialkylphosphinic acid, which is called here "phospholanic acid"; according to systematic nomenclature, **1** is 1-hydroxy-1*r*-oxo-2*c*,5*t*-diphenylphospholane.

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[10] Metal-catalyzed asymmetric double bond isomerization reactions: see ref.[14] and a) G. Fu, in: *Modern Rhodium-Catalyzed Organic Reactions*, (Ed.: P. A. Evans) Wiley-VCH, Weinheim, **2005**; b) S. Akutagawa, *Topics in Catalysis* **1997**, *4*, 271; c) S. Otsuka, K. Tani, *Synthesis* **1991**, 665.

[11] Other reactions that have been typically associated with metal catalysis include the hydrogenation of imines or conjugated alkenes with Hantzsch ester in the presence of chiral Brønsted acids, see, e.g.: a) M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781 and subsequent works; b) S. Hoffmann, A. Seayad, B. List, *Angew. Chem.* **2005**, *117*, 7590; *Angew. Chem. Int. Ed.* **2005**, *44*, 7424 and subsequent works; c) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84 and subsequent works.

[12] The isomerization of **4** to **5** requires 5 equivalents of NaOMe (2 M in MeOH; 1 h, r.t.) or catalytic amounts of methyllithium in THF (16 h, r.t.), see ref.[3]

[13] In a variation of the Fiaud synthesis (ref.[3]), we installed the *N*,*N*-diethylamino group at phosphorus (**3b** instead of **3a**). The chemistry shown in Scheme 1 proceeds analogously for either *N*,*N*-dimethylamino and -diethylamino derivatives. See the Supporting Information for a detailed procedure of the McCormack cycloaddition leading to **3b**.

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[17] Due to systematic errors, the *ee* values obtained by the NMR method (Table 2) are low by several % points relative to the more accurate HPLC values. This was of no great concern in the course of initial catalysis optimization.

[18] For specific HPLC conditions, see the Supporting Information. For a discussion of the peculiar necessity to add traces of water to the HPLC eluent, see: L. Hintermann, *J. Org. Chem.* **2007**, *72*, 9790.

[19] The reaction solvent is simply recycled by evaporation from the reaction mixture. The alkaloid catalyst is recycled from the water phase of the acid wash by precipitation with aqueous ammonia.

[20] For the sake of stereochemical correlation, (5*R*)-**6** has been converted to acid (2*R*,5*R*)-**1** by a) hydrogenation (Pd/H_2) and b) hydrolysis (HCl aq./MeOH), albeit with as yet low levels of diastereoselectivity.

