Stereoselective Catalytic Synthesis of *P*-Stereogenic Oxides via Hydrogenative Kinetic Resolution
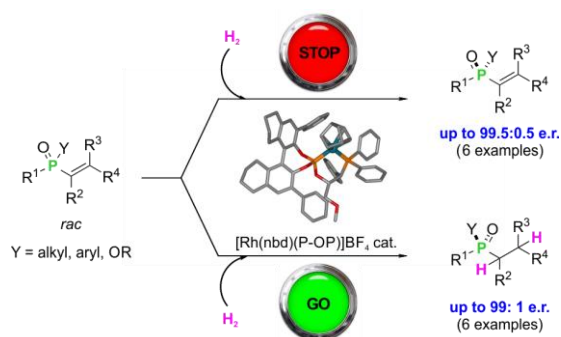
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Supporting Information Placeholder

ABSTRACT: A highly stereoselective catalytic method for the preparation of structurally diverse *P*-stereogenic oxides has been developed. The approach relies on the ability of rhodium complexes derived from an enantiopure P−OP ligand to kinetically resolve racemic α,β-unsaturated phosphane oxides by hydrogenation of the C=C motif and formation of highly enantioenriched (or even enantiopure) *P*-stereogenic oxides. The practicality of the methodology has been demonstrated by the preparation of potentially functional *P*-chiral molecules for catalytic enantioselective synthesis.

The catalytic stereoselective preparation of enantiopure *P*-stereogenic compounds has been pursued by synthetic chemists due to the use of these motifs in biological systems,[1] as enantiopure synthetic drugs[1] and enantioselective catalytic systems.[2] The preparation of such compounds in an enantiomerically pure form mostly relies on classical approaches such as resolution processes[2] or the use of stoichiometric amounts of chiral auxiliaries.[2] Regarding the preparation of *P*-stereogenic oxides using catalytic methods, only two approaches have been reported, with the first relying on the arylation (Scheme 1a.1)[3] of secondary phosphane oxides (SPOs) and the second on desymmetrization strategies. Methods to desymmetrize[4] encompass ring-closing metathesis,[5] hydroetherification,[6] [2+2+2] cycloaddition,[7] C–H functionalization,[8] oxidation,[9] allylic alkylation,[10] and conjugate addition[11] reactions (Scheme 1a.2). To conclude this succinct overview on the reported catalytic synthetic methods for the preparation of optically active *P*-stereogenic oxides, we highlight that the use of reductive transformations for their preparation is underdeveloped.

Our research group has recently reported the use of rhodium complexes derived from phosphine-phosphite (P–OP)[12] ligand **L**[13] for the kinetic resolution of racemic mixtures of unsubstituted vinyl sulfoxides using hydrogen.[14] Specifically, our group described the efficient preparation and isolation of an array of *S*-stereogenic sulfoxides derived from such process in

a highly enantioenriched form.[14] In a kinetic resolution,[15] success relies on there being distinct reaction rates for the reaction between the two enantiomers of the starting material with the reagent (the highest relative ratio of rate constants, or selectivity factor *s*, of the two enantiomers of the vinyl sulfoxides with dihydrogen was found to be 148[14]).
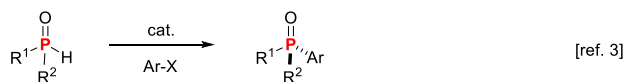
Given our ongoing interest in developing catalytic stereoselective tools for underdeveloped transformations, and encouraged by the precise stereocontrol exhibited in the hydrogenative kinetic resolution of unsubstituted vinyl sulfoxides, we turned our attention to expanding the scope of the reaction to α,β-unsaturated *P*-containing oxides (Scheme 1b), which seemed to us to be ripe with potential for this chemistry. Thus, we report herein the development of an efficient, and catalytic stereoselective method based on a kinetic resolution of racemic α,β- unsaturated phosphorus derivatives by hydrogenation. We also describe how our method complements already existing catalytic methods by giving access to *P*-stereogenic synthetic building blocks as potentially functional molecules for catalytic enantioselective synthesis.

At the onset of our studies, we proceeded to explore the hydrogenative kinetic resolution of methyl(phenyl)(vinyl)-phosphane oxide *rac*-**1a** to assess the potential of P–OP ligand **L** in this chemistry. Standard catalyst screening conditions
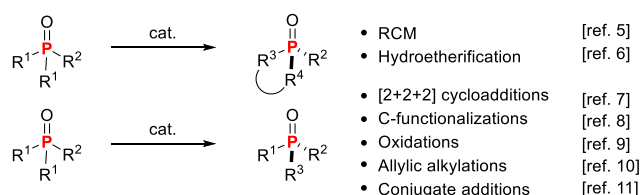
Scheme 1. (a) Reported Catalytic Methods Towards Optically Active *P*-Stereogenic Oxides; (b) Present Work on Rh-Catalyzed Hydrogenative KR of α,β-Unsaturated *P*-Containing Substrates

Table 1. Initial Screening on Rh-Catalyzed Hydrogenative KR of Racemic *P*-Stereogenic *rac*-1a[a]

entry	reaction conditions	conv. (%)[b]	e.r. **1a**[c] (conf.)[d]	e.r. **2a**[c] (conf.)[d]
1	Cy:DCM (4:1), 1 h	51	81:19 (S)	77.5:22.5 (R)
2	PhMe:DCM (4:1), 1 h	51	78.5:21.5 (S)	76:24 (R)
3	MeTHF[e]:DCM (4:1), 1 h	45	76.5:23.5 (S)	85:15 (R)
4	DCM, 0.75 h	60	95.5:4.5 (S)	72.5:27.5 (R)
5	MeOH, 1 h	>99	—[f]	rac

[a] Reaction conditions are indicated in the scheme on Table 1. [b] Conversions were determined by ^{1}H NMR. [c] Enantiomeric ratios were determined by HPLC on chiral stationary phases. [d] Absolute configurations of products **1a** and **2a** were established by comparison with reported optical rotations for compounds **1a** and **2a**.[16] [e] MeTHF = 2-Methyltetrahydrofuran. [f] Not detected in the reaction mixture.
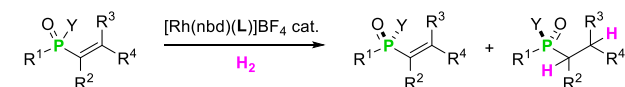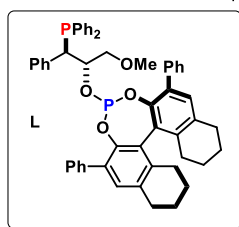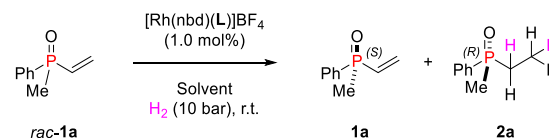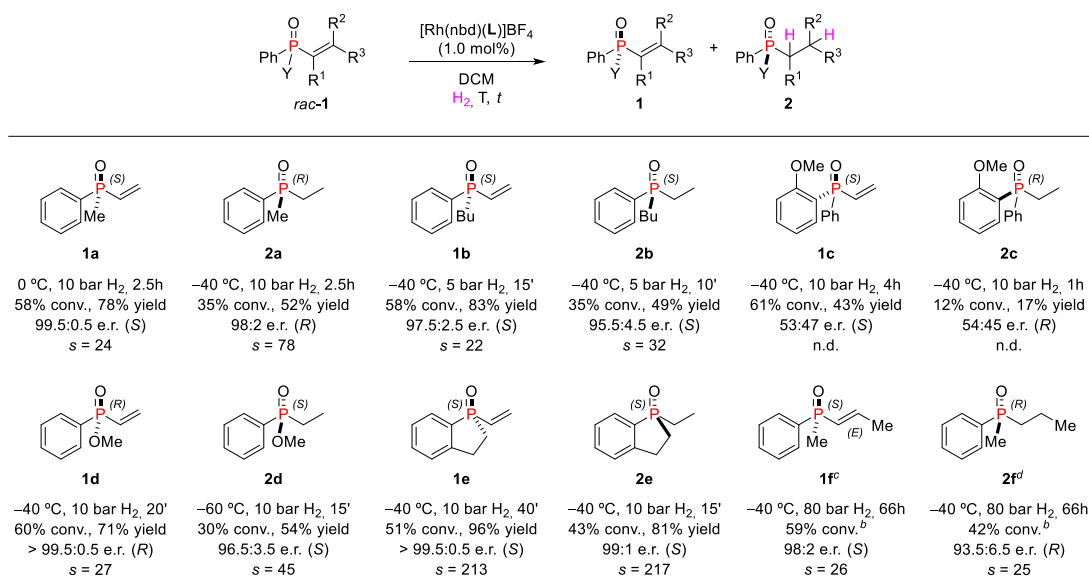
(1.0 mol% rhodium pre-catalyst, 10 bar H₂, room temperature, 1 h reaction time) in different solvents were used in this study, whose results are summarized in Table 1. Pronounced solvent effects were observed, with conversions varying with the polarity of the solvent. The hydrogenation proceeded to 45−60% conversion in DCM as (co)-solvent, whilst full conversion was observed for the reaction in methanol (entries 1−4 compared with entry 5 of Table 1). As expected, e.r. of the unreacted starting material increased with conversion (95.5:4.5 e.r. at 60% conv., entry 4 in Table 1), whilst that of the hydrogenated product was higher at lower conversions (85:15 e.r. at 45% conv., entry 3 in Table 1).

In order to maximize the yield and enantiomeric ratios for both the unreacted and hydrogenated products ((*S*)-**1a** and (*R*)-**2a**, respectively), specific reaction conditions for both products were investigated. Unreacted starting material (*S*)-**1a** was isolated with high yield and very high enantiomeric ratio (99.5:0.5 e.r.) when the kinetic resolution was performed in DCM at 0 ºC under 10 bar H₂ (Scheme 2). Alternatively, hydrogenated product (*R*)-**2a** was isolated in acceptable yield and high enantiomeric ratio (98:2 e.r.) by performing the hydrogenation under the same conditions but lowering the temperature at −40 ºC.

Having demonstrated that highly stereoselective kinetic resolutions of α,β-unsaturated *P*-containing oxides were feasible, we then attempted to broaden the substrate scope to a set of structurally diverse α,β-unsaturated *P*-containing oxides *rac*-**1b**−**1f**. The results and the optimal reaction conditions for unreacted starting materials and hydrogenation products are shown in Scheme 2. Increasing the chain length of the Y substituent at the *P*-atom barely influenced the outcome of the reaction with isolated yields and enantiomeric ratios remaining high both for compound (*S*)-**1b** and (*S*)-**2b** (97.5:2.5 e.r. and 95.5:4.5 e.r., respectively, see Scheme 2). Interestingly, when the alkyl group in *rac*-**1a** was replaced by an aryl motif of similar size as in *rac*-**1c**, the stereoselectivity of the kinetic resolution was almost lost. The catalytic system also tolerated α,β-unsaturated phosphinate *rac*-**1d** (Scheme 2). Unreacted starting material (*R*)-**1d** was isolated in high yield and excellent enantiomeric ratio (> 99.5:0.5 e.r) and hydrogenated product (*S*)-**2d** was also isolated in satisfactory yield and high enantiomeric ratio (up to 96.5:3.5 e.r.). Compounds (*R*)-**1d** and (*S*)-**2d** are configurationally stable, as no racemization took place after standing two months at room temperature.

Phosholane 1-oxide derivatives (*S*)-**1e** and (*S*)-**2e** could also be prepared by kinetic resolution of compound *rac*-**1e**. Both target products were isolated in high isolated yields. Regarding the stereoselectivity of the kinetic resolution, both reaction products were obtained in very high enantiomeric ratios, with compound (*S*)-**2e** being isolated in an excellent 99:1 e.r. and the highest selectivity factor of the whole study (*s* = 217). Finally, Me-substituted α,β-unsaturated phosphane oxide *rac*-**1f** was also studied. In contrast to substrates unsubstituted at the C=C motif, these compounds were less reactive towards

Scheme 2. Rh-Mediated Hydrogenative KR of a Set of Structurally Diverse α,β-Unsaturated *P*-Containing Oxides[a]

[Rh(nbd)(**L**)]BF$_4$ (1.0 mol%)

DCM, H$_2$, T, *t*

rac-**1** → **1** + **2**

1a
0 °C, 10 bar H$_2$, 2.5h
58% conv., 78% yield
99.5:0.5 e.r. (*S*)
s = 24

2a
−40 °C, 10 bar H$_2$, 2.5h
35% conv., 52% yield
98:2 e.r. (*R*)
s = 78

1b
−40 °C, 5 bar H$_2$, 15'
58% conv., 83% yield
97.5:2.5 e.r. (*S*)
s = 22

2b
−40 °C, 5 bar H$_2$, 10'
35% conv., 49% yield
95.5:4.5 e.r. (*S*)
s = 32

1c
−40 °C, 10 bar H$_2$, 4h
61% conv., 43% yield
53:47 e.r. (*S*)
n.d.

2c
−40 °C, 10 bar H$_2$, 1h
12% conv., 17% yield
54:45 e.r. (*R*)
n.d.

1d
−40 °C, 10 bar H$_2$, 20'
60% conv., 71% yield
> 99.5:0.5 e.r. (*R*)
s = 27

2d
−60 °C, 10 bar H$_2$, 15'
30% conv., 54% yield
96.5:3.5 e.r. (*S*)
s = 45

1e
−40 °C, 10 bar H$_2$, 40'
51% conv., 96% yield
> 99.5:0.5 e.r. (*S*)
s = 213

2e
−40 °C, 10 bar H$_2$, 15'
43% conv., 81% yield
99:1 e.r. (*S*)
s = 217

1f[c]
−40 °C, 80 bar H$_2$, 66h
59% conv.[b]
98:2 e.r. (*S*)
s = 26

2f[d]
−40 °C, 80 bar H$_2$, 66h
42% conv.[b]
93.5:6.5 e.r. (*R*)
s = 25

[a] [Substrate] = 0.2 M. Conversions were determined by ^{1}H NMR. Yields refer to isolated ones and were calculated with respect to the 50 mol% amount of starting material that was subjected to KR. Enantiomeric ratios were determined by HPLC on chiral stationary phases. Absolute configurations of products **1a,d** and **2a,d** were established by comparison with reported optical rotations for compounds **1a,d** and **2a,d**. Absolute configurations of products **1b** and **2b** were tentatively assigned by analogy with the results for **1a** and **2a**. The absolute configuration of product **1e** was unambiguously assigned by anomalous X-ray single crystal diffraction of its derivative (*S*,*S*)-**3** and, consequently, that of **2e** was also unambiguously assigned. The selectivity factor (*s*) was calculated with the equation: $s = \ln[1-C(1+ee_2)]/\ln[1-C(1-ee_2)]$, where C = ee$_1$/(ee$_1$+ee$_2$), ee$_1$ = ee of **1** and ee$_2$ = ee of **2**.[15] [b] Reaction products could not be separated by standard column chromatography. The KR was carried out in MeOH as solvent. [c] [Rh(nbd)(**L**)]BF$_4$ (5.0 mol%) and MeOH as solvent. [d] [Rh(nbd)(**L**)]BF$_4$ (2.5 mol%) and MeOH as solvent.

hydrogenation. After some experimentation, efficient kinetic resolution conditions involving higher pressure (80 bar) and the use of MeOH as solvent were identified. Under these conditions, unreacted starting material (*S*)-**1f** and hydrogenated product (*R*)-**2f** were obtained in high enantiomeric ratios (98:2 and 93.5:6.5 e.r., respectively).

To demonstrate the utility of the products obtained from the kinetic resolution process, we devised further transformations of the resulting *P*-stereogenic oxides (see Scheme 3). We envisaged that a dimerization reaction of vinyl-substituted phosphane oxides **1** *via* olefin metathesis would pave the way to interesting *P*-stereogenic bidentate derivatives. To demonstrate the viability of this idea, we chose vinyl-substituted compound (*S*)-**1e**, as it was obtained with one of the highest selectivity factors. Dimerization of (*S*)-**1e** *via* olefin metathesis towards the *E*-derivative (*S*,*S*)-**3** was achieved using 5 mol% of Grela's ruthenium catalyst.[17] The *S* configurations at the phosphorus atoms were established by anomalous X-ray diffraction studies (Figure 1).[16] Further hydrogenation of the homocoupling product (*S*,*S*)-**3** with Pd/C led to enantiopure *P*-stereogenic diphosphane dioxide (*S*,*S*)-**4**. This enantiopure bidentate phosphorus derivative incorporates phospholane units in its structure and holds promise as efficient ligand in enantioselective catalysis,[9] given its structural similarities with highly efficient ligands that contain two phospholane (1-oxide) units linked by a 1,2-ethanediyl motif.[18]

As previously indicated, cationic rhodium complexes of P–OP ligand **L** catalyze highly stereoselective hydrogenative kinetic resolutions of racemic mixtures of α,β-unsaturated P=O-derivatives towards unreacted starting materials (selec-

tivity factors up to 213) and hydrogenated compounds (selectivity factors up to 217). The stereochemical outcome of the studied kinetic resolutions has been summarized in Scheme 4: enantiomers of the starting material with a *S* configuration at the phosphorus atom remain unreacted as they are less prone to hydrogenation under the effects of rhodium catalyst derived from **L**.

Scheme 3. Further Transformations of (*S*)-1e

(*S*)-**1e** → (5.0 mol%), DCM, 45 °C, 96h → (*S*,*S*)-**3**
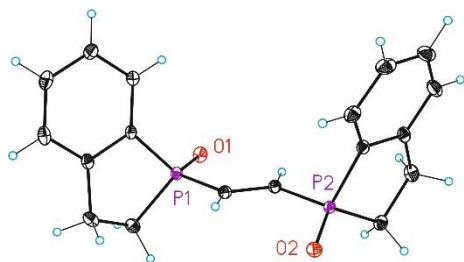34% yield

H$_2$, Pd/C, MeOH

(*S*,*S*)-**4**
80% yield
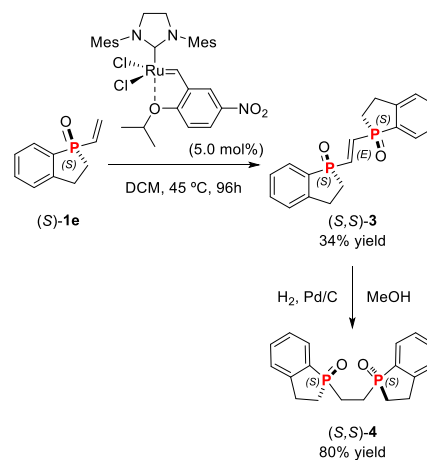
Figure 1. ORTEP drawing (thermal ellipsoids drawn at a 50 % probability level) showing the structure and the absolute configuration of product (*S*,*S*)-**3**

Regarding hydrogenated products, enantiomers of the starting material with a *R* configuration at the phosphorus atom are those being hydrogenated (Scheme 4, changes in the indicated configuration at the phosphorus atoms in **1d**, **2b**, **2d**, and **2e** are due to an inversion in the CIP priority rules indicated in this scheme).

Scheme 4. Stereochemical Outcome of the KRs
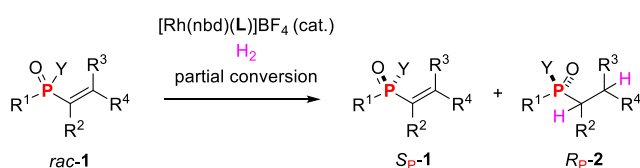
CIP priorities for phosphorus derivatives: P > R^1 > C=C or C**H**–C**H** > Y

In summary, we have developed a highly stereoselective catalytic kinetic resolution of racemic mixtures of α,β-unsaturated P=O-derivatives allowing the efficient preparation of an array of structurally diverse *P*-stereogenic oxides through one hydrogenation step. The catalyst derived from P–OP ligand **L** tolerated different substitution patterns at the phosphorus atoms (alkyl, aryl or methoxy groups), as well as at the C=C motif (alkyl at the β-positions of the alkene group) and led to the unreacted and hydrogenated enantiomers of the starting material with high selectivity factors (up to *ca.* 220). The applicability of this synthetic methodology has been further expanded through the preparation of enantioenriched *P*-stereogenic products, which could easily undergo subsequent derivatization to useful molecules, which have potential as both ligands or catalysts in enantioselective transformations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/XXXXXXXXXX..

Experimental details, catalytic results and spectroscopic and crystallographic data (PDF)
X-ray data for compound (*S*,*S*)-**3** (CIF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

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