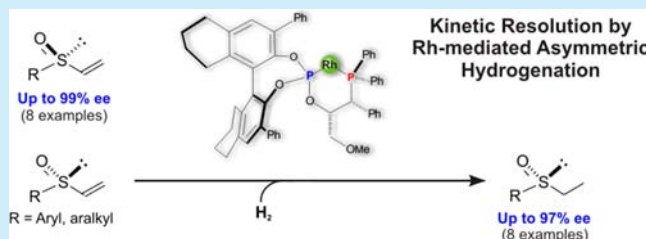


Hydrogenative Kinetic Resolution of Vinyl Sulfoxides

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Supporting Information

ABSTRACT: Enantiopure sulfoxides are valuable precursors of organosulfur compounds with broad application in organic and pharmaceutical chemistry. An unprecedented strategy for obtaining highly enantioenriched sulfoxides based on a hydrogenative kinetic resolution using Rh-complexes of phosphine-phosphite ligands as catalysts is reported. After optimization, highly efficient conditions for the kinetic resolution of racemic sulfoxides have been identified. This methodology has been applied to a set of racemic aralkyl or aryl vinyl sulfoxides and allowed the isolation of both recovered and reduced products in excellent yields and enantioselectivities (up to 99% and 97% ee, respectively; 16 examples).



Optically pure sulfoxides are a valuable family of chiral compounds which have proven to be highly efficient chiral ligands¹ as well as useful intermediates in the synthesis of relevant biologically active compounds.^{1a,2} Among the approaches that asymmetric catalysis offers, kinetic resolution (KR) of racemic sulfoxides³ should be considered an appealing method for the preparation of two optically pure sulfoxides in only one synthetic step, provided that some requisites are fulfilled. First and foremost, it is necessary that efficient enantioselective catalysts working at low catalyst loadings are available and, second, that starting materials and products can be isolated in good yields and enantiomerically enriched forms.⁴

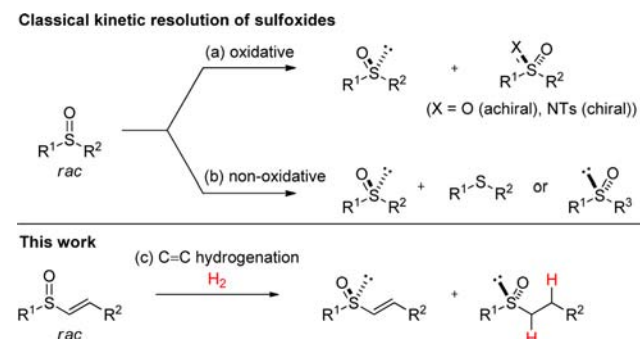
While the reported nonenzymatic KRs on racemic sulfoxides are mainly based on oxidative transformations (Scheme 1a),^{3,5} nonoxidative KRs, including reductive transformations (Scheme 1b), have received much less attention. Moreover, nonoxidative KRs have normally offered unsatisfactory stereoselectivities, with the exception of enzymatic⁶ transformations and hydrogenative dynamic kinetic resolutions (DKR) of allyl

sulfoxides.⁷ There are a few studies reporting reductive KRs of vinyl sulfoxides with optically active reagents;⁸ however, to the best of our knowledge, there are no previous reports on the KR of vinyl sulfoxides via asymmetric hydrogenation.⁹

Our group recently reported the highly enantioselective hydrogenation of a structurally diverse set of substrates mediated by phosphine–phosphite (P–OP)¹⁰ ligands. The high catalytic activities achieved with our ligands prompted us to address the challenge of hydrogenatively resolving racemic vinyl sulfoxides (Scheme 1c), whose resolved products have found broad applicability in catalytic asymmetric synthesis.^{1,2} Herein we describe our results, which include the catalyst optimization studies and the application of the lead catalyst to the highly efficient hydrogenative KR of an array of racemic aralkyl or aryl vinyl sulfoxides. At the onset of our study, we chose phenyl vinyl sulfoxide *rac*-1a as a model substrate. The reaction conditions and the results of this initial screening are summarized in Table 1.

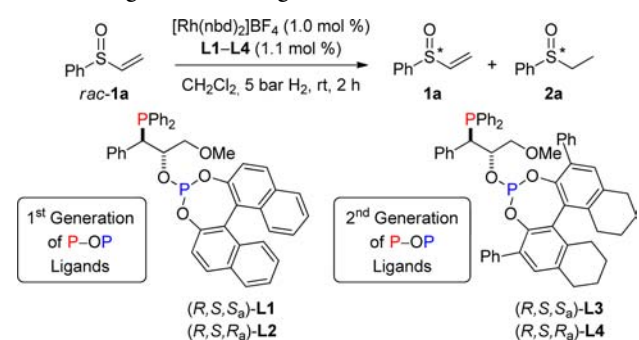
As indicated in Table 1, both activity and selectivity were highly dependent on the P–OP ligand used. Rhodium complexes derived from ligands L1 and L2 afforded the hydrogenated product 2a with 37–73% ee, though conversions were very low and ee values for the recovered starting material 1a poor (see entries 1 and 2 in Table 1). In contrast, rhodium complexes of the new ligands L3 and L4 displayed an opposite trend with high conversions and excellent enantioselectivities for 1a (up to 99% ee) (see entries 3 and 4 in Table 1). Therefore, these results clearly identified L1 and L3 as the optimal ligands for this chemistry with the stereogenic phosphite group being the principal stereochemical director (opposite absolute configurations for sulfoxides 1a and 2a are obtained depending on the configuration of the phosphite

Scheme 1. Kinetic Resolution Strategies for Racemic Sulfoxides



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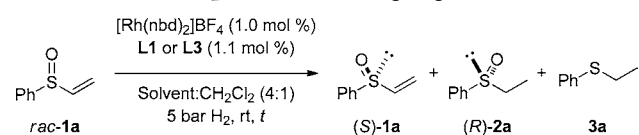
Table 1. Ligand Screening for the KR of *rac*-1a^a

entry	ligand	conv, % ^b	ee of 1a, %; ^c (config.) ^d	ee of 2a, %; ^c (config.) ^d
1	L1	25	22 (S)	73 (R)
2	L2	16	7 (R)	37 (S)
3	L3	79	99 (S)	28 (R)
4	L4	81	85 (R)	20 (S)

^a[Substrate] = 0.2 M. ^bDetermined by ¹H NMR. ^cDetermined by HPLC on chiral stationary phases. ^dThe absolute configuration was assigned by comparison with reported data.

group: compare entries 1 with 2 for L1 and L2, or entries 3 with 4 for L3 and L4 in Table 1, respectively).

Next, we proceeded to optimize the reaction conditions with P-OP ligands L1 and L3 in a range of different solvent mixtures.¹¹ The assayed reaction conditions and results are shown in Table 2. According to these results, a mixture of

Table 2. Solvent Optimization Using Ligands L1 or L3^a

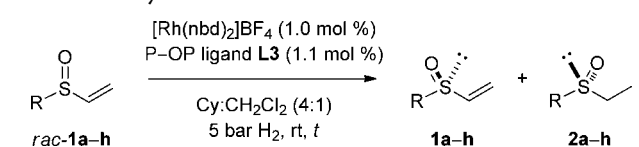
entry	L	solvent	t, h	conv, % ^b	ee of 1a, %; ^c (S) ^d	ee of 2a, %; ^c (R) ^d	ee of 3a, % ^c
1	L1	Cy	2	56	44:34:12	99	80
2	L1	MeOH	2	10	90:6:4	9	73
3	L1	MeTHF ^e	2	44	56:42:2	65	83
4	L1	toluene	2	56	44:52:4	92	76
5	L1	CH ₂ Cl ₂	2	25	75:25:0	22	73
6	L3	Cy	1	54	46:54:0	99	72
7	L3	MeOH	1	79	21:79:0	99	28
8	L3	MeTHF ^e	1	60	40:60:0	99	64
9	L3	toluene	1	58	42:58:0	99	64
10	L3	CH ₂ Cl ₂	1	68	32:68:0	99	45

^aSee footnote a in Table 1. ^bSee footnote b in Table 1. ^cSee footnote c in Table 1. ^dSee footnote d in Table 1. ^eMeTHF ≡ 2-methyl-tetrahydrofuran.

cyclohexane and CH₂Cl₂ was identified as the optimal solvent for *rac*-1a, as it provided the highest ee values for sulfoxides 1a and 2a (see entries 1 and 6 in Table 2). Unfortunately, the rhodium complex derived from ligand L1 led to the formation of significant amounts of ethyl phenyl sulfide 3a as the byproduct arising from the overreduction of the starting material (see entry 1 in Table 2).¹² This phenomenon was also observed for L1 in all the mixtures of solvents tested (see entries 1 to 4 in Table 2). However, we were pleased to find that this side reaction was completely eliminated by using the rhodium complex derived from the P-OP ligand L3.

Moreover, this catalyst provided at 54% conversion the recovered vinyl sulfoxide 1a with perfect enantioselectivity (up to 99% ee in favor of the (S)-enantiomer) and the corresponding hydrogenated product 2a (see entry 6 in Table 2).

With the optimal catalyst in hand, we then attempted to broaden the substrate scope to a set of structurally diverse vinyl sulfoxides (*rac*-1a-h). In order to maximize the yield for both the recovered and hydrogenated products (1a-h and 2a-h, respectively), specific reaction conditions for 1a-h and for 2a-h were investigated.¹³ The results and optimized reaction conditions are listed in Table 3.

Table 3. Substrate Scope of the Hydrogenative KR of Racemic Vinyl Sulfoxides *rac*-1a-h^a

entry	R	t, min	conv, % ^b	product, isol. yield, %; ¹⁴ ee, %; ^c (config.) ^d	s ^e
1 ^f	Ph (<i>rac</i> -1a)	60	54	1a, 74, 99 (S)	30
2		30	44	2a, 62, 86 (R)	35
3	<i>p</i> -Me-Ph (<i>rac</i> -1b)	80	55	1b, 74, 98 (S)	25
4		10	35	2b, 58, 95 (R)	55
5	<i>o</i> -F-Ph (<i>rac</i> -1c)	15	55	1c, 80, 99 (S)	56
6		8	42	2c, 80, 97 (R)	148
7	<i>m</i> -F-Ph (<i>rac</i> -1d)	30	61	1d, 54, 98 (S)	25
8		10	39	2d, 76, 92 (R)	44
9	<i>p</i> -F-Ph (<i>rac</i> -1e)	30	54	1e, 70, 98 (S)	33
10		15	44	2e, 56, 90 (R)	40
11	<i>p</i> -MeO-Ph (<i>rac</i> -1f)	120	64	1f, 64, 99 (S)	26
12		30	39	2f, 76, 88 (R)	29
13	<i>p</i> -NO ₂ -Ph (<i>rac</i> -1g)	25	66	1g, 64, 99 (S)	13
14		10	40	2g, 72, 82 (R)	18
15 ^g	Bn (<i>rac</i> -1h)	240	67	1h, 62, 99 (R) ^h	11
16 ^g		25	33	2h, 56, 80 (S) ^h	13

^aSee footnote a in Table 1. ^bSee footnote b in Table 1. ^cSee footnote c in Table 1. ^dThe absolute configurations of 1a,b and 2a,b,f-h were established by comparison with reported optical rotations. The absolute configurations of 1c-h and 2c-e were tentatively assigned by analogy with the stereochemical outcome of the reactions leading to 1a,b and 2a,b,f-h.¹² ^eThe selectivity factor (s)⁴ was determined by the equations = $k_{rel}(\text{fast/slow}) = \ln[1 - C(1 + ee_2)] / \ln[1 - C(1 - ee_2)]$. ^fThis result has been already shown in Table 2. ^gSolvent ratio used was Cy/CH₂Cl₂ (2.6:1). ^hThe opposite R or S prefixes in 1h and 2h arise from different priorities in the CIP rules.

As illustrated in Table 3, different substitution patterns on the aryl groups of vinyl sulfoxides *rac*-1c-e (*o*-F, *m*-F, and *p*-F substitution, respectively) were well tolerated to furnish sulfoxides 2c-e in 56–80% isolated yield¹⁴ with 90–97% ee, and the recovered vinyl sulfoxides 1c-e in 54–80% isolated yield¹⁴ with very high enantioselectivities (98–99% ee; see entries 5–10 in Table 3). The results obtained for the *ortho*-substituted substrate *rac*-1c were the best among all the substrates assessed (see entries 5 and 6 in Table 3). Plots of ee values of resolved products against conversion displayed that the highest enantioselectivities for such compounds were achieved in the range 40–60% conversion (see Figure 1, which corresponds to the KR of substrate *rac*-1c), demonstrat-

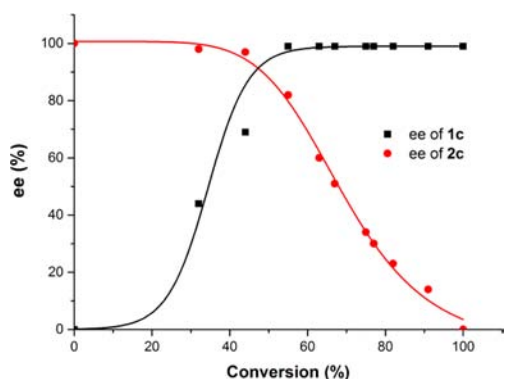


Figure 1. Ee values (%) of 1c and 2c vs conversion (%).

ing the high efficiency of this KR to provide unreacted starting material and hydrogenated product in high yields and ee's.

Electronic effects were also studied by the examination of *para*-substituted substrates *rac*-1b,e,f,g (*p*-Me, *p*-F, *p*-MeO, *p*-NO₂, respectively). Regardless of the electronic nature of the substituent on the aromatic ring, the substrates were hydrogenated leading to both unreacted and reduced sulfoxides with high enantioselectivities (from 82 to 99% ee) in 56–76% isolated yields¹⁴ (see entries 3, 4, and 9–14 in Table 3). However, an electron-withdrawing group at the *para*-position increased the reaction rate (compare entries 9, 10 and 13, 14 with entries 3, 4 and 11, 12 in Table 3). The lead catalytic system was also capable of efficiently resolving benzyl vinyl sulfoxide (*rac*-1h): hydrogenation of *rac*-1h for 4 h provided (*R*)-1h in 62% isolated yield¹⁴ with perfect enantioselectivity (99% ee, see entry 15 in Table 3), while optimal reaction conditions for the hydrogenated product (*S*)-2h led to its isolation in 56% isolated yield¹⁴ and 80% ee (see entry 16 in Table 3). In order to demonstrate the practicality of this KR method, experiments at the mmol scale were performed for racemic substrates *rac*-1a,g to afford products 1a,g and 2a,g with the same efficiency as catalytic experiments.¹²

To shed light on the favored stereodifferentiating routes, we studied the coordination of (*R*)-1g and (*S*)-1g to the [Rh(P–OP)]⁺ complex of the lead ligand (L3). We pursued the *in situ* preparation of [Rh(1g)(L3)]BF₄ by hydrogenation of [Rh-(nbd)(L3)]BF₄ in 1,2-dimethoxyethane followed by the addition of 1.1 equiv of (*R*)-1g or (*S*)-1g. Based on related literature precedents,^{7,9} we hypothesized that the KR proceeds via hydrogenation of the C=C bond with chelating assistance of the oxygen atom of the sulfoxide group. Examination of the NMR data in solution indicated that both (*R*)-1g and (*S*)-1g coordinate to the [Rh(P–OP)]⁺ motif. The coordination of (*S*)-1g led to the formation of a stable complex at rt, as evidenced by the sharpness of the vinylic signals in the ¹H NMR spectrum.¹² The formation of the substrate–catalyst adduct [Rh((*R*)-1g)(L3)]⁺ was evidenced by the appearance of broad vinylic signals in the ¹H NMR spectrum, which sharpened up upon recording the spectra at a lower temperature (253 K). With regard to the geometry of the complexes between (*R*)-1g or (*S*)-1g and the [Rh(P–OP)]⁺ motif, cross-peaks only between the olefinic protons and the phosphino group in heteronuclear ¹H–³¹P correlation experiments were observed.¹² These observations strongly suggest that the C=C bonds of (*R*)-1g and (*S*)-1g are coordinated to the phosphino group in a *cis* fashion, as these data are practically coincident with that reported in the literature for *cis*-

coordinated C=C and phosphorus groups in related rhodium complexes.¹⁵ Furthermore, intense cross-peaks between the olefinic H–C_β proton *trans* to H–C_α and aromatic protons of the diphenylphosphino group in NOESY correlation experiments were observed for bound (*S*)-1g, thus confirming the previous structural assignment.¹² This coordination mode of the C=C double bond places the R group of the sulfoxide in close proximity to the phosphite group, which accounts for this group being the principal stereochemical director in the KR. By comparing the results of these coordination studies and the configuration of the resolved products, a tentative reaction pathway for the stereochemical outcome of the KR is proposed in Figure 2.

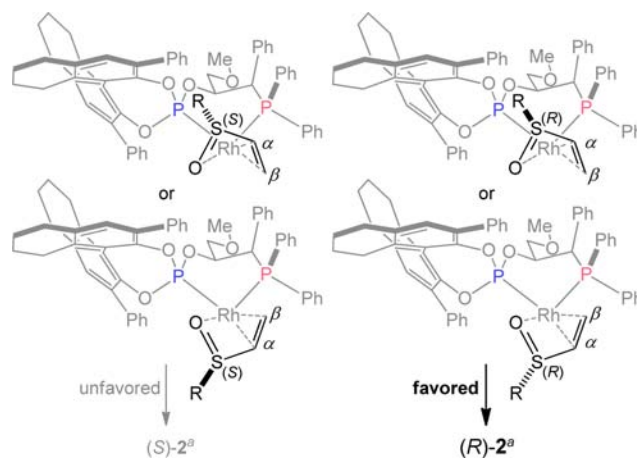


Figure 2. Tentative reaction pathways for the hydrogenative KR of racemic vinyl sulfoxides in the Rh-L3 complexes with the C=C and P (red) groups coordinated in a *cis* fashion (^aR or ^aS configurations of the product have been established assuming the highest CIP's priority for the R group).

In summary, we have developed a highly efficient hydrogenative KR of vinyl sulfoxides mediated by rhodium complexes of P–OP ligand L3, which are responsible for the differentiation of the reaction rates of the two enantiomers of the starting material toward hydrogenation. This KR method is an unprecedented approach for preparing optically active vinyl sulfoxides and their hydrogenated products in notable yields and high enantioselectivities (up to 99% ee). The easy availability of racemic vinyl sulfoxides, together with the excellent catalytic profile of the catalyst derived from L3, makes the herein described synthetic methodology a valuable synthetic entry for chiral sulfoxides. Further studies on the application of this synthetic methodology, together with mechanistic investigations, are underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02139.

Experimental procedures, spectral data, and determination of the enantiomeric excess (PDF)

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Notes

The authors declare no competing financial interest.

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(11) A certain amount of CH₂Cl₂ was kept in order to ensure the complete solubility of both the rhodium precursor and ligand.

(12) See the [Supporting Information](#) for further details.

(13) The reaction conditions were optimized by modifying the reaction times (controlling in this way the value of conversion) in an optimal compromise amongst enantiopurity and amounts of unreacted starting material and product.

(14) Yields are calculated with respect to the 50 mol % amount of starting material that was subjected to KR.

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