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Exploiting Substrate Diversity for Preparing Synthetically Valuable Sulfoxides *via* Asymmetric Hydrogenative Kinetic Resolutions

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Abstract: A detailed study is disclosed on the Rh-mediated hydrogenative kinetic resolution of α,β-unsaturated sulfoxides with alkyl and aryl substituents at the α-, *E*- and *Z*-positions of the double bond. This stereoselective catalytic methodology has allowed for the preparation of highly enantioenriched (or even enantiopure) alkyl and aryl substituted (un)saturated sulfoxides *via* a simple and efficient synthetic operation. Moreover, the application of the hydrogenative KR to the preparation of valuable optically active sulfoxide-containing building blocks or biologically active intermediates is described.

Introduction

The catalytic stereoselective synthesis of enantiopure sulfoxides has attracted the interest of the synthetic community due to the broad applicability of enantiopure sulfoxides in asymmetric synthesis (as chiral auxiliaries or ligands).[1] Apart from their usefulness in asymmetric synthesis, and also due to the crucial role of sulfur in living systems,[2] sulfoxide groups can be found in a myriad of bioactive compounds that naturally participate in the metabolism (*e.g.*, mustard oils[2] or L-methionine *S*-oxides[3]; see Figure 1) or in a broad array of enantiopure synthetic drugs (*e.g.*, the hydroxyamic acids[4] and sulfinyl propanamines[5] indicated in Figure 1).

Regarding the preparation of optically active *S*-stereogenic sulfoxides *via* catalytic methods, the most common strategy involves the direct oxidation of thioethers using metal complexes or biocatalysts (see Scheme 1a).[6] More recently, efficient strategies for the preparation of optically active sulfoxides based on kinetic resolutions using an oxidant have also been reported (see Scheme 1b).[6a,7] (Dynamic) kinetic resolutions relying on a hydrolytic step,[8] a Mislow-Evans rearrangement coupled with the hydrogenation of an allyl group,[9] or a C–H olefination of diaryl compounds[10] efficiently lead to optically active sulfoxides

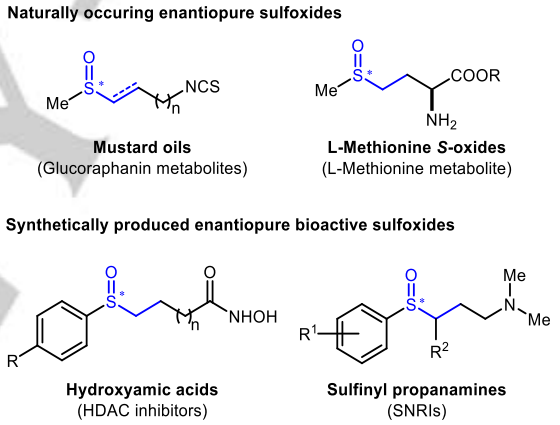
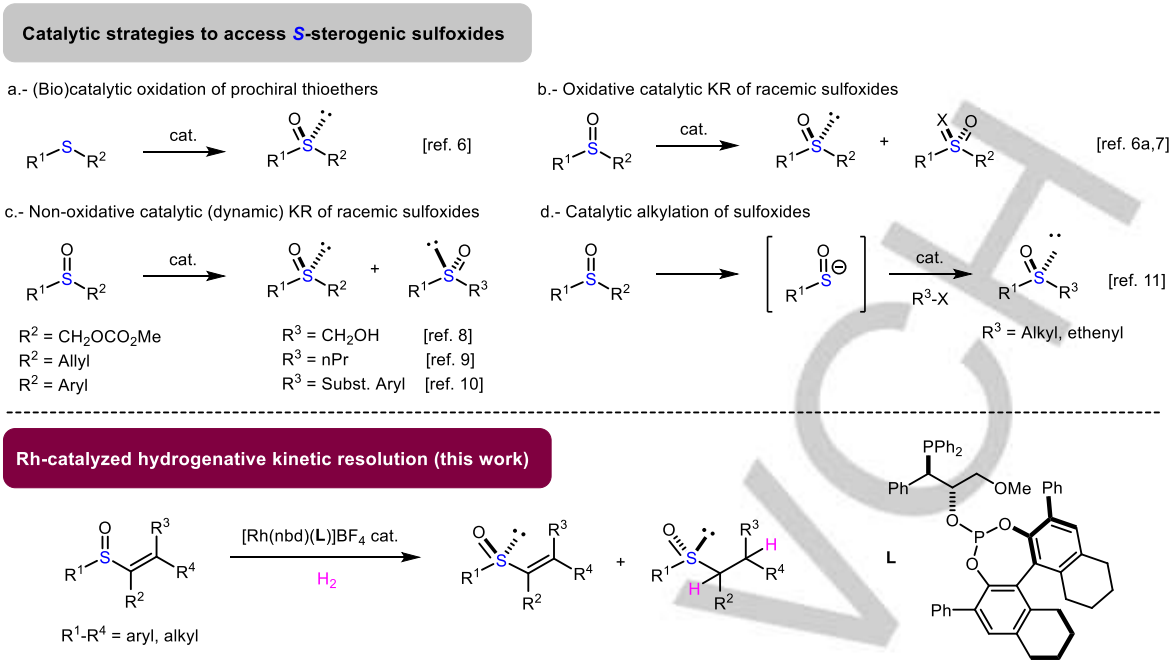


Figure 1. Selected examples of naturally occurring or synthetically produced biologically active sulfoxides.[2-5]

(see Scheme 1c). Finally, elegant methodologies based on C–S bond forming reactions onto *in situ*-generated sulfenate anions have also been reported (see Scheme 1d).[11]

We recently reported efficient catalytic tools for the preparation of highly enantioenriched unsubstituted vinyl and ethyl sulfoxides through a hydrogenative kinetic resolution (KR) catalyzed by a Rh complex derived from a phosphine-phosphite[12] ligand.[13] The success of this KR methodology is based on the complexation of the starting substrates on the rhodium catalyst (coordination of the C=C double bond with chelating assistance of the oxygen of the sulfoxide group) and differentiation of the reaction rates of the two enantiomers of the substrate towards hydrogenation of the alkenyl group.[13]

Given our ongoing interest in developing highly stereoselective catalytic tools,[14], and encouraged by the precise stereocontrol exhibited in the hydrogenative kinetic resolution of unsubstituted



Scheme 1. Reported catalytic methods towards optically active *S*- stereogenic sulfoxides and present work on Rh-catalyzed hydrogenative KR of α,β-unsaturated sulfoxides.

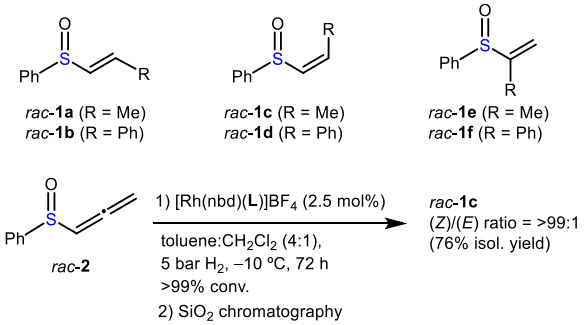
vinyl sulfoxides,[13] we studied herein the effects of precisely positioning alkyl or aryl substituents at the α-, *E*- and *Z*-positions of the double bond in the (stereo)chemical outcome of the reactions (Scheme 1). The selective synthesis of some of the racemic starting α,β-unsaturated sulfoxides constituted a challenging task. In this manuscript, we also detail interesting synthetic protocols for their preparation that can be useful for the synthetic community. Lastly, to demonstrate the synthetic utility of hydrogenative kinetic resolutions, we report herein the application of this method for the catalytic enantioselective synthesis of intermediates of selected biologically active relevant enantiopure sulfoxides.

Results and Discussion

As previously mentioned, the initial set of substrates in our studies to explore the effects of structural complexity on the stereochemical outcome of the reaction encompassed racemic alkyl and aryl substituted α,β-unsaturated sulfoxides at the α-, *E*- and *Z*-positions (sulfoxides *rac*-**1a–f** in Scheme 2). *trans*-Substituted α,β-unsaturated sulfoxides *rac*-**1a,b** were prepared straightforwardly following a Horner-Wittig protocol.[15] While *cis*-phenyl derivative *rac*-**1d** was easily prepared following a reported procedure,[16] we developed an efficient synthesis for the methyl substituted analogue (*rac*-**1c**) by the chemoselective hydrogenation of allenyl sulfoxide *rac*-**2** (see Scheme 2). After some experimentation, we identified selective hydrogenation conditions towards *rac*-**1c** (2.5 mol% of [Rh(nbd)(**L**)]BF_4, 5 bar of H_2 and –10 ºC). Experiments led to full conversion and under the developed reaction conditions, we observed that the addition of hydrogen occurred exclusively at the allene C_β–C_γ-position with complete (*Z*)-selectivity.[17] It is worth mentioning that the preparation of sufficient amounts of *rac*-**1c** following other synthetic protocols[18] remained elusive in our hands. However, we efficiently performed the hydrogenation of allenyl sulfoxide *rac*-**2** at the mmol scale[19] and we were able to include sulfoxide *rac*-**1c** as a substrate in our studies (Scheme 2). Lastly, α-substituted α,β-unsaturated sulfoxides *rac*-**1e,f** were conveniently prepared by reaction of the required organo-magnesium reagent with methyl benzenesulfinate after adapting a previously reported synthetic procedure for analogous chemistry.[20]

With the array of structurally diverse α,β-unsaturated sulfoxides in hand (*rac*-**1a–f**), we then turned our attention to the assessment of the catalytic activity of our highest performing Rh-catalysts (*i.e.* those incorporating ligand **L**;[13] see Scheme 1) in hydrogenative kinetic resolutions (HKR) of the selected sulfoxides *rac*-**1a–f**.

The presence of substituents at the vinyl moiety of these substrates translated into lower hydrogenation rates than those observed for sulfoxides containing the unsubstituted vinyl group.[13] After some experimentation, efficient kinetic resolution conditions (5 mol% of [Rh(nbd)(**L**)]BF_4 as precatalyst and $PhCH_3$ and CH_2Cl_2 (4:1 v/v) as solvents) were identified and the H_2



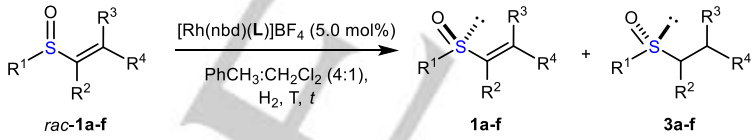
Scheme 2. Initial set of substrates (*rac*-**1a–f**) and preparation of *rac*-**1c** by selective hydrogenation of racemic allenyl-substituted sulfoxide *rac*-**2**.

pressure and reaction temperature and time were specifically optimized for both recovered and hydrogenated products (Scheme 3).

In general terms, efficient and selective catalytic conditions were identified for all substrates, with the exception of compound *rac*-**1b** (efficient kinetic resolution conditions remained elusive for this substrate, as low enantioselectivities were observed under all reaction conditions assayed, Scheme 3). Having mentioned this exception, it should be noted that the presence of methyl or phenyl substituents at the vinyl moiety (substrates *rac*-**1a** and *rac*-**1c–f**) was well tolerated and that enantioselectivities ranging from 62 to 99% *ee* and from 56 to 93% *ee* for recovered and hydrogenated products were observed, respectively (Scheme 3).[21] As evidenced by the results, high selectivity factors (*s* = 58 and *s* = 25, Scheme 3) were observed in the kinetic resolution of (*E*)-Me-substituted substrate *rac*-**1a**. These selectivity factors translated into high enantioselectivities for the recovered and hydrogenated products (99% and 91% *ee* for **1a** and **3a**, respectively; see Scheme 3). A lower selectivity factor was observed for the analogous α,β-unsaturated sulfoxide with the methyl group in the (*Z*)-position (*rac*-**1c**; *s* = 8, Scheme 3). Despite the low selectivity factor in the kinetic resolution of *rac*-**1c**, optically pure starting material **1c** could be obtained at 92% of conversion (99% *ee* for **1c**, Scheme 3). Although the enantioselectivity of the hydrogenated product from *rac*-**1c** could not be further improved, this result was no drawback for obtaining this product in high enantioselectivity with our method, as it can also be obtained by hydrogenatively resolving substrate *rac*-**1a** (Scheme 3) instead of *rac*-**1c**. Regarding the kinetic resolutions of (*Z*)- and (*E*)-2-phenylethenyl substituted sulfoxides *rac*-**1b** and *rac*-**1d**, those transformations proceeded with lower selectivity factors than those observed for the methyl substituted analogues *rac*-**1a** and *rac*-**1c** (compare data in Scheme 3). Moreover, moderate values of enantioselectivity were obtained for the aryl-substituted recovered and hydrogenated sulfoxides **1d** and **3d** (up to 62% ee, see Scheme 3).

The hydrogenative kinetic resolution of α,β-unsaturated sulfoxides bearing substituents at the α-position (*rac*-**1e,f**) proceeded with higher selectivity and under milder reaction conditions than those of the substrates with substituents at the β-position (*rac*-**1a–d**; compare data in Scheme 3). Substrates *rac*-**1e,f** provided the best results of the whole series (Scheme 3), with high to excellent *ee* values for the recovered starting material (99% *ee* both for **1e** and **1f**; Scheme 3) and for the hydrogenated products (89 and 93% *ee* for **3e** and **3f**, respectively; Scheme 3). Slightly beneficial effects on the enantioselectivity were observed for the phenyl substituted substrate (*rac*-**1f**) with selectivity values as high as *s* = 154 and *s* = 62 for **1f** and **3f**, respectively. Most remarkably, the hydrogenation of *rac*-**1f** took place with perfect diastereoselectivity, leading to the exclusive formation of the *anti*-diastereoisomer *anti*-**3f** (*dr* of *anti*-**3f**:*syn*-**3f** ≥ 99:1; see Scheme 3).[26]

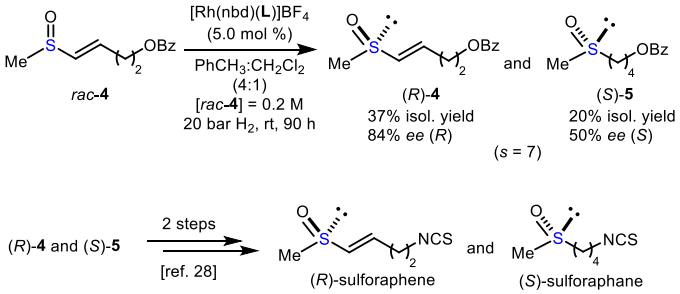
Having expanded the use of hydrogenative KR on a set of substituted α,β-unsaturated sulfoxides, the practicality of this methodology was further demonstrated by preparing a number of advanced synthetic intermediates of biologically active molecules containing sulfoxide groups: (*R*)-sulforaphene,[22] (*S*)-sulforaphane[23] and a histone deacetylase (HDAC) inhibitor[24] (see Scheme 4 and Scheme 5). To this end, the strategically devised starting materials *rac*-**4** and *rac*-**6** were easily prepared using the above-mentioned procedures.[15]



1a[f]	**3a**[f,g]	**1b**[f,h]	**1c**[f]	**1d**[f]
0 ºC, 10 bar H_2, 66h	–10 ºC, 10 bar H_2, 20h	r.t., 5 bar H_2, 48h	r.t., 8 bar H_2, 70h	r.t., 20 bar H_2, 90h
61% conv.[b], 99% *ee*[c] (*S*)[d]	25% conv.[b], 91% ee[c] (*R*)[d]	53% conv., *rac*[c]	92% conv.[b], 99% *ee*[c] (*S*)[d]	75% conv.[b], 62% *ee*[c] (*S*)[d]
s^e = 58	s^e = 25		s^e = 8	s^e = 3
3d[f]	**1e**	**3e**	**1f**	**3f**
0 ºC, 40 bar H_2, 48h	r.t., 5 bar H_2, 48h	–10 ºC, 10 bar H_2, 72h	r.t., 5 bar H_2, 24h	r.t., 5 bar H_2, 3.5h
24% conv.[b], 56% *ee*[c] (*R*)[d]	90% conv., 20% yield[i]	21% conv., 32% yield[i]	54% conv., 76% yield[i]	42% conv., 49% yield[i]
s^e = 4	99% *ee*[c] (*S*)[d], s^e = 10	89% *ee*[c] (*R*)[d], s^e = 21	99% *ee*[c] (*R*)[d], s^e = 154	≥ 99: 1 *dr*[c,j], 93% *ee*[c] (R_S,R_C)[d]
				s^e = 62

[a] [Substrate] = 0.2 M. [b] Determined by ^{1}H NMR. [c] Determined by HPLC on chiral stationary phases. [d] The absolute configurations of products **1e,f** and **3e,f** were determined by comparison with reported optical rotations for **3e,f**.[19] The absolute configuration of products **1a–d** and **3a–d** were tentatively assigned by analogy with the results for **3e,f**. [e] The selectivity factor (*s*) was calculated with the equation: $s = \ln[1-C(1+ee_3)]/\ln[1-C(1-ee_3)]$ where $C = ee_1/(ee_1+ee_3)$.[7a] [f] Reaction products could not be separated by standard column chromatography. [g] Solvent mixture = Cyclohexane:CH_2Cl_2 (4:1 v/v). [h] 5% of isomerized product **1a** was detected in the reaction crude, as determined by NMR.[19] [i] Isolated yields.[25] [j] *dr* ratio of *anti*-**3f**:*syn*-**3f** ≥ 99:1, as determined by ^{1}H NMR.[26]

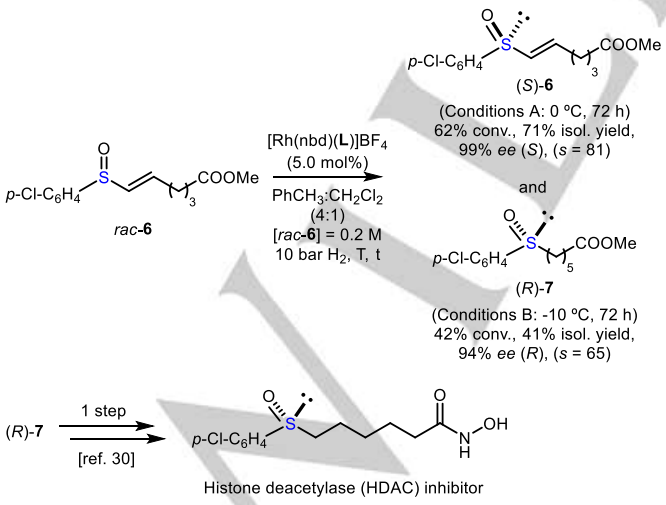
Scheme 3. Kinetic resolution of sulfoxides **1a–f**[a]



Scheme 4. Preparation of advanced synthetic intermediates of (*R*)-sulforaphene and (*S*)-sulforaphane.

Resolution of sulfoxide *rac*-**4** furnished unreacted starting material (*R*)-**4** with notable enantioselectivities (84% *ee*; see Scheme 4), whilst the hydrogenated product (*S*)-**5** could only be obtained with moderate enantioselectivity (50% *ee*; Scheme 4). The resulting products are valuable precursors of anticancer agents.[27] In this particular reaction, minor amounts of the over reduced sulfide derived from product **5** were detected in the reaction crude (6%). However, this by-product could be easily separated by standard SiO_2 column chromatography. (*R*)-sulforaphene and (*S*)-sulforaphane can be easily prepared from the advanced synthetic intermediates (*R*)-**4** and (*S*)-**5** following well-established synthetic protocols.[28]

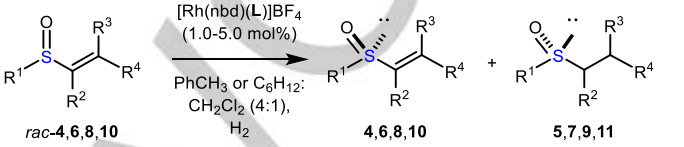
Gratifyingly, the kinetic resolution of *rac*-**6** (Scheme 5) took place in a highly chemo- and stereo-selective way and excellent values of enantioselectivity were obtained for both recovered and reduced products (99% and 94% *ee* for (*S*)-**6** and (*R*)-**7**, respectively; Scheme 5). Notably, the optimized reaction for the target intermediate (*R*)-**7** (Conditions B; Scheme 5) proceeded with a high selectivity factor (*s* = 65; Scheme 5) and the desired sulfoxide (*R*)-**7** could be efficiently isolated in high optical purity (41% isolated yield and 94% *ee*; Scheme 5). It should be noted herein that the formal synthesis of the HDAC inhibitor precursor indicated in Scheme 5 employing a hydrogenative kinetic resolution competes in terms of stereoselectivity with those previously reported in the literature using oxidative catalytic methods.[29]The resulting hydrogenated product (*R*)-**7** is a



Scheme 5. Preparation of the histone deacetylase (HDAC) inhibitor intermediate (*R*)-**7**.

valuable precursor to chiral drugs that are currently in clinical development for cancer therapy.[24] The advanced synthetic intermediate (*R*)-**7** could be transformed into the bioactive molecule following a well-established experimental procedure.[30] The results summarized in Table 1 indicate that kinetic resolutions of alkyl substituted α,β-unsaturated sulfoxides (*i.e.* R^1 = Me or benzyl) take place with lower selectivity factors than the kinetic resolutions of their aryl substituted counterparts **6** and **10** (*i.e.* R^1 = Ar). Though computational studies for rationalizing these results have not been performed, the higher difference in relative size between R^1 and R^4 in substrates **6** and **10** than in sulfoxides **4** and **8** could account for the higher selectivity factors that have been observed in the hydrogenative kinetic resolution of aryl substituted α,β-unsaturated sulfoxides.

Table 1. Kinetic resolutions of vinyl sulfoxides: Dependence of the selectivity factor on the substrate structure



Entry	R^1	R^2	R^3	R^4	Product	*s*-factor	%ee (conf.)
1[a]	Me	H	H	$(CH_2)_2OBz$	**4**	7	84 (*R*)
2[a]					**5**	7	50 (*S*)
3[a]	*p*-Cl-C_6H_4	H	H	$(CH_2)_3CO_2Me$	**6**	81	99 (*S*)
4[a]					**7**	65	94 (*R*)
5[b]	Bn	H	H	H	**8**	11	99 (*R*)
6[b]					**9**	13	80 (*S*)
7[b]	*o*-F-C_6H_4	H	H	H	**10**	56	99 (*S*)
8[b]					**11**	148	97 (*R*)

[a] Results from this manuscript. [b] Results published in reference [13]

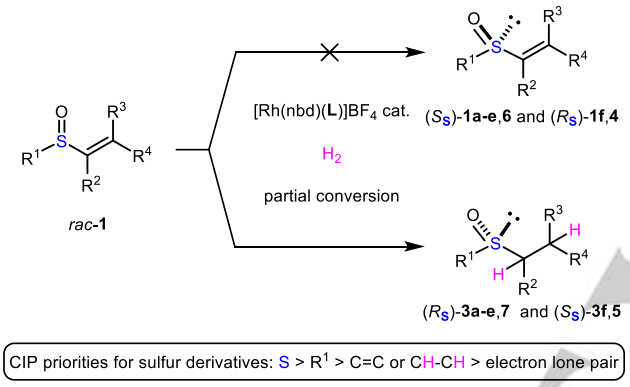
Finally, taking into consideration the experimental results above-mentioned, the stereochemical outcome of our hydrogenative kinetic resolution for structurally diverse substituted α,β-unsaturated vinyl sulfoxides can be summarized in Scheme 6. In the presence of the rhodium catalyst derived from ligand **L**, the (*S*)-configured enantiomers at the sulfur atom in the starting vinyl sulfoxide are less prone to hydrogenation of the alkenyl fragment and remain unreacted with high enantioselectivities in favor of the (*S*)-configured substrates (changes in the *S* configuration at the sulfur atom in **1f** and **4** are due to an inversion in the CIP priority rules as indicated in Scheme 6). On the other hand, the C=C double bond of the enantiomers of the starting material with a *R* configuration at the sulfur atom are hydrogenated faster and lead to the corresponding enantioenriched compounds (changes in the *R* configuration at the sulfur atom in **3f** and **5** are due to an inversion in the CIP priority rules as indicated in Scheme 6).

Conclusion

In summary, we have exploited the potentially high structural diversity of the substrates to be hydrogenatively resolved (*i.e.*

α,β-unsaturated sulfoxides with alkyl and aryl substituents at the α-, *E*- and *Z*-positions of the double bond) to give access to an array of new and valuable highly enantioenriched (or even enantiopure) sulfoxide-containing synthetic intermediates.

We have discovered a new catalytic tool that mediates the chemo- and stereo-selective hydrogenation of an allenyl sulfoxide with the exclusive formation of the corresponding (*Z*)-configured sulfinyl alkene, opening further avenues for the (stereo)selective preparation of valuable (*Z*)-configured alkenyl sulfoxides. Moreover, we have further expanded the applicability of the enantioselective Rh-mediated hydrogenative kinetic resolution by preparing enantioenriched advanced synthetic intermediates of biologically active sulfoxide-containing molecules. Catalytic hydrogenative kinetic resolutions have generally proceeded with high selectivity factors and enabled the preparation of the final sulfoxides in a highly enantioenriched (or even enantiopure) form. Ongoing investigations include the extension of the application of this chemistry to other substrates, to other transition metals and study of alternative ligand designs.



Scheme 6. Stereochemical outcome of the hydrogenative kinetic resolution of substituted α,β-unsaturated vinyl sulfoxides

Experimental Section

General considerations. Air- and moisture-sensitive manipulations or reactions were performed under inert atmosphere using anhydrous solvents, either in a glove box or with standard Schlenk techniques. Glassware was dried under vacuum and heated with a hot air gun before use. All solvents were dried in a Solvent Purification System (SPS). Silica gel 60 (230−400 mesh) was used for column chromatography. NMR spectra were recorded on a 400-MHz or 500-MHz UltraShield spectrometer in $CDCl_3$, unless otherwise cited. ^1H NMR and $^{13}C\{^1H\}$ NMR chemical shifts are quoted in ppm relative to the residual solvent peaks. $^{31}P\{^1H\}$ NMR chemical shifts are quoted in ppm relative to 85% phosphoric acid in water. High-resolution mass spectra (HRMS) were recorded using the ESI ionization method in positive mode, unless otherwise stated. Enantiomeric excesses were determined by HPLC analyses, using chiral stationary phases.

The preparation and characterisation of ligand **L** and its corresponding Rh-precatalyst [Rh(nbd)(**L**)]BF_4 have been previously described in the literature.[13,31]

General procedure for the KR by Rh-mediated asymmetric hydrogenations. A solution of the required amount of [Rh(nbd)(**L**)]BF_4 (5.0 mol%) and the corresponding vinyl sulfoxide substrate (0.1 mmol) in anhydrous and degassed CH_2Cl_2 (0.50 mL), unless otherwise indicated, was prepared in a glass vessel under a nitrogen atmosphere. In all cases, the concentration of the substrate in the reaction medium was adjusted to 0.20 M. Once the reaction mixture had been prepared, the glass vessel was placed into one of the positions of a steel autoclave reactor (HEL Cat-24 parallel pressure multireactor). The autoclave was taken out of the glove box. Then, the autoclave was purged three times with nitrogen gas and pressurized at 5 bar of nitrogen gas. The autoclave was cooled at the desired temperature and remained at this temperature for 45 minutes in order to stabilize the temperature. After that, the autoclave was slowly depressurized and purged five times with H_2 gas without stirring (at a pressure not higher than the selected one), and finally, the autoclave was pressurized under the required pressure of H_2 gas. The reaction mixture was stirred at this temperature during the adequate period of time. The autoclave was then slowly depressurized. The reaction mixture was filtered through a short pad of SiO_2, eluting with EtOAc (1.5 mL). The resulting solution was concentrated *in vacuo*, and the conversion was determined by ^1H NMR spectroscopy. Finally, purification by silica gel column chromatography afforded both the desired starting substrate and the hydrogenated product. Enantiomeric ratios for both isolated products were determined by HPLC analysis on chiral stationary phases.

Characterization of the reaction products and determination of the absolute configurations.

(*S*)-(*E*)-(prop-1-en-1-ylsulfinyl)benzene (*S*)-1a: (optimized result for product 1a; Scheme 3 in the article): This product was prepared following the general procedure starting from substrate *rac*-1a (27.8 mg, 0.2 mmol), and [Rh(nbd)(L)]BF_4 (9.2 mg, 8.3 μmol). The reaction mixture after hydrogenation was filtered through a short pad of SiO_2, eluting with EtOAc. This product could not be purified by standard chromatographic techniques from its hydrogenated analogue and was obtained as a mixture (molar ratio 1a:3a = 39:61). Enantiomeric excess: 99% ee in favor of the (*S*)-configured enantiomer (assumed configuration). The spectroscopic data were in agreement with those reported.[18b]

(*R*)-(propylsulfinyl)benzene (*R*)-3a (optimized result for product 3a; Scheme 3 in the article): This product was prepared following the general procedure starting from substrate *rac*-1a (27.9 mg, 0.2 mmol), and [Rh(nbd)(L)]BF_4 (9.2 mg, 8.3 μmol). The reaction mixture after hydrogenation was filtered through a short pad of SiO_2, eluting with EtOAc. This product could not be purified by standard chromatographic techniques from its vinyl analogue and was obtained as a mixture (molar ratio 1a:3a = 75:25). Enantiomeric ratio: 91% ee in favor of the (*R*)-configured enantiomer (assumed configuration). The spectroscopic data were in agreement with those reported.[18b]

(*S*)-(*E*)-(2-(phenylsulfinyl)vinyl)benzene (*S*)-1b (optimized result for product 1b; Scheme 3 in the article): This product was prepared following the general procedure starting from substrate *rac*-1b (26.2 mg, 0.1 mmol), and [Rh(nbd)(L)]BF_4 (6.4 mg, 5.7 μmol). The reaction mixture after hydrogenation was filtered through a short pad of SiO_2, eluting with EtOAc. This product could not be purified by standard chromatographic techniques from its hydrogenated analogue and was obtained as a mixture (molar ratio 1b:3b = 47:53). Enantiomeric ratio was a *racemic* mixture. The spectroscopic data were in agreement with those reported.[18b].

(*S*)-(*Z*)-(prop-1-en-1-ylsulfinyl)benzene (*S*)-1c (optimized result for product **1c**; Scheme 3 in the article): This product was prepared following the general procedure starting from substrate *rac*-**1c** (23.7 mg, 0.2 mmol), and [Rh(nbd)(**L**)]BF_4 (7.8 mg, 7.1 μmol). The reaction mixture after hydrogenation was filtered through a short pad of SiO_2, eluting with EtOAc. This product could not be purified by standard chromatographic techniques from its hydrogenated analogue and was obtained as a mixture (molar ratio **1c**:**3c** = 8:92). Enantiomeric ratio: 99% ee in favor of the (*S*)-configured enantiomer (assumed configuration). The spectroscopic data were in agreement with those reported. [18b, 32]

(*S*)-(*Z*)-(prop-1-en-1-ylsulfinyl)benzene (*S*)-1d (optimized result for product **1d**; Scheme 3 in the article): This product was prepared following

the general procedure starting from substrate *rac*-**1d** (28.1 mg, 0.1 mmol), and [Rh(nbd)(**L**)]BF_4 (6.8 mg, 6.2 µmol). The reaction mixture after hydrogenation was filtered through a short pad of SiO_2, eluting with EtOAc. This product could not be purified by standard chromatographic techniques from its hydrogenated analogue and was obtained as a mixture (molar ratio **1d**:**3d** = 25:75). Enantiomeric ratio: 62% ee in favor of the (*S*)-configured enantiomer (assumed configuration). The spectroscopic data were in agreement with those reported.[16]

(*R*)-(propylsulfinyl)benzene (*R*)-3d (optimized result for product **3d**; Scheme 3 in the article): This product was prepared following the general procedure starting from substrate *rac*-**1d** (24.8 mg, 0.1 mmol), and [Rh(nbd)(**L**)]BF_4 (6.0 mg, 5.4 µmol). The reaction mixture after hydrogenation was filtered through a short pad of SiO_2, eluting with EtOAc. This product could not be purified by standard chromatographic techniques from its vinyl analogue and was obtained as a mixture (molar ratio **1d**:**3d** = 76:24). Enantiomeric ratio: 56% ee in favor of the (*R*)-configured enantiomer (assumed configuration). The spectroscopic data were in agreement with those reported.[33]

(*S*)-(prop-1-en-2-ylsulfinyl)benzene (*S*)-1e (optimized result for product **1e**; Scheme 3 in the article): This product was prepared following the general procedure starting from substrate *rac*-**1e** (21.0 mg, 0.1 mmol), and [Rh(nbd)(**L**)]BF_4 (6.9 mg, 6.2 µmol). The reaction mixture after hydrogenation was filtered through a short pad of SiO_2, eluting with EtOAc. This product was purified by standard chromatographic techniques from its hydrogenated analogue and was obtained as a colorless liquid (2.0 mg, 20% isolated yield[25]). Enantiomeric ratio: 99% ee in favor of the (*S*)-configured enantiomer. $[\alpha]^{27}_D = -40$ (*c* 1.17, $CHCl_3$) [Lit:[11c] $[\alpha]^{20}_D = -72.2$ (*c* 0.6, $CHCl_3$) for 89% ee. (*S*)]. The spectroscopic data were in agreement with those reported.[34]

(*R*)-(isopropylsulfinyl)benzene (*R*)-3e (optimized result for product **3e**; Scheme 3 in the article): This product was prepared following the general procedure starting from substrate *rac*-**1e** (22.9 mg, 0.1 mmol), and [Rh(nbd)(**L**)]BF_4 (7.6 mg, 6.8 µmol). The reaction mixture after hydrogenation was filtered through a short pad of SiO_2, eluting with EtOAc. This product was purified by standard chromatographic techniques from its vinyl analogue as a colorless liquid (3.7 mg, 32% isolated yield[25]). Enantiomeric ratio: 89% ee in favor of the (*R*)-configured enantiomer. $[\alpha]^{27}_D = +126$ (*c* 0.31, $CHCl_3$) [Lit:[35] $[\alpha]^{20}_D = -146.9$ (*c* 0.42, $CHCl_3$) for 72% ee (*S*)]. The spectroscopic data were in agreement with those reported. [35]

(*R*)-(1-(phenylsulfinyl)vinyl)benzene (*R*)-1f (optimized result for product **1f**; Scheme 3 in the article): This product was prepared following the general procedure starting from substrate *rac*-**1f** (26.9 mg, 0.1 mmol), and [Rh(nbd)(**L**)]BF_4 (6.4 mg, 5.8 µmol). The reaction mixture after hydrogenation was filtered through a short pad of SiO_2, eluting with EtOAc. This product was purified by standard chromatographic techniques from its hydrogenated analogue and was obtained as a colorless liquid (10.2 mg, 76% isolated yield[25]). Enantiomeric ratio: 99% ee in favor of the (*R*)-configured enantiomer (assumed configuration). $[\alpha]^{24}_D = -53.1$ (*c* 0.28, acetone) for 99% ee (*R*). The spectroscopic data were in agreement with those reported.[36]

((R_S,R_C)-1-phenylethyl)sulfinyl)benzene (R_S,R_C)-3f (optimized result for product **3f**; Scheme 3 in the article): This product was prepared following the general procedure starting from substrate *rac*-**1f** (15.6 mg, 0.1 mmol), and [Rh(nbd)(**L**)]BF_4 (3.7 mg, 3.4 µmol). The reaction mixture after hydrogenation was filtered through a short pad of SiO_2, eluting with EtOAc. This product was purified by standard chromatographic techniques from its vinyl analogue and was obtained as a colorless liquid (3.8 mg, 49% isolated yield[25]). Enantiomeric ratio: 93% ee in favor of the (R_S,R_C)-configured enantiomer. $[\alpha]^{24}_D = +122.3$ (*c* 0.42, acetone) [Lit:[37] $[\alpha]^{25}_D = +204.2$ (*c* 1.5, acetone) for 99% ee. (R_S,R_C)]. The spectroscopic data were in agreement with those reported for *anti*-**3f**.[38]

(*R*)-(*E*)-4-(methylsulfinyl)but-3-en-1-yl benzoate (*R*)-4 (optimized result for product **4**; Scheme 4 in the article): New compound. 84% ee (*R*). $[\alpha]^{26}_D = -43.0$ (*c* 0.28, CH_2Cl_2) for 84% ee (*R*). This product was prepared following the general procedure starting from substrate *rac*-**4** (29.6 mg, 0.1 mmol), and [Rh(nbd)(**L**)]BF_4 (6.9 mg, 6.2 µmol). The reaction mixture after hydrogenation was filtered through a short pad of SiO_2, eluting with EtOAc. This product was purified by standard chromatographic techniques from its hydrogenated analogue and was obtained as a colorless liquid (5.5 mg, 37% isolated yield[25]). New compound. Enantiomeric ratio: 84% ee in favor of the (*R*)-configured enantiomer (assumed configuration). M.p. = 92.3-93.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06-8.04 (m, 2H, CH_{Ar}), 7.61-7.57 (m, 1H, CH_{Ar}), 7.48-7.45 (m, 2H, CH_{Ar}), 6.61-6.55 (m, 1H, CH), 6.45 (dt, *J* = 15.1 Hz, *J* = 1.2 Hz, 1H, CH), 4.48 (t, *J* = 6.3 Hz, 2H, CH_2), 2.76 (m, 2H, CH_2), 2.60 (s, 3H, CH_3);^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 166.3 (C=O), 136.5 (CH), 135.0 (CH), 133.1 (CH_{Ar}), 129.8 (C), 129.5 (CH_{Ar}), 128.4 (CH_{Ar}), 62.7 (CH_2), 40.6 (CH_3), 31.3 (CH_2). HRMS (ESI$^+$) *m*/*z* calcd for $C_{12}H_{14}NaO_3S$ $[M+Na]^+$ 261.0556, found 261.0552.

(*S*)-4-(methylsulfinyl)butyl benzoate (*S*)-5 (optimized result for product **5**; Scheme 4 in the article): This product was prepared following the general procedure starting from substrate *rac*-**4** (29.6 mg, 0.10 mmol), and [Rh(nbd)(**L**)]BF_4 (6.9 mg, 6.21 µmol). The reaction mixture after hydrogenation was filtered through a short pad of SiO_2, eluting with EtOAc. This product was purified by standard chromatographic techniques from its vinyl analogue and was obtained as a colorless liquid (3.0 mg, 20% isolated yield[25]). Enantiomeric ratio: 50% ee in favor of the (*S*)-configured enantiomer. New compound. Enantiomeric ratio: 50% ee in favor of the (*S*)-configured enantiomer (assumed configuration). $[\alpha]^{26}_D = +10$ (*c* 0.15, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-8.04 (m, 2H), 7.60-7.44 (m, 3H), 4.40 (bs, 2H), 2.84-2.73 (m, 2H), 2.61 (s, 3H), 2.01-1.96 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.5 (C=O), 133.0 (CH), 130.0 (C), 129.5 (CH), 128.4 (CH), 64.0 (CH_2), 54.1 (CH_2), 38.6 (CH_3), 27.9 (CH_2), 19.5 (CH_2); HRMS (ESI$^+$) *m*/*z* calcd for $C_{12}H_{16}NaO_3S$ $[M+Na]^+$ 263.0712, found 263.0721.

(*S*)-methyl-(*E*)-6-((4-chlorophenyl)sulfinyl)hex-5-enoate (*S*)-6 (optimized result for product **6**; Scheme 5 in the article): New compound. 99% ee (*S*). $[\alpha]^{25}_D = -78.8$ (*c* 0.64, $CHCl_3$) for 99% ee (*S*). This product was prepared following the general procedure starting from substrate *rac*-**6** (31.3 mg, 0.1 mmol), and [Rh(nbd)(**L**)]BF_4 (6.0 mg, 5.4 µmol). The reaction mixture after hydrogenation was filtered through a short pad of SiO_2, eluting with EtOAc. This product was purified by standard chromatographic techniques from its hydrogenated analogue and was obtained as a colorless liquid (11.0 mg, 71% isolated yield[25]). New compound. Enantiomeric ratio: 99% ee in favor of the (*S*)-configured enantiomer (assumed configuration). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57-7.49 (m, 4H), 6.64-6.58 (m, 1H), 6.25 (dt, *J* = 15.2 Hz, *J* = 1.4 Hz, 1H), 3.68 (s, 3H), 2.36-2.28 (m, 4H), 1.85-1.79 (m, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 173.3 (C), 142.6 (C), 139.9 (CH), 137.1 (C), 135.6 (CH), 129.6 (CH), 125.8 (CH), 51.6 (CH_3), 33.0 (CH_2), 31.2 (CH_2), 23.2 (CH_2); HRMS (ESI$^+$) *m*/*z* calcd for $C_{13}H_{15}ClNaO_3S$ $[M+Na]^+$ 309.0323, found 309.0319.

(*R*)-methyl-6-((4-chlorophenyl)sulfinyl)hexanoate (*R*)-7 (optimized result for product **7**; Scheme 5 in the article): This product was prepared following the general procedure starting from substrate *rac*-**6** (30.6 mg, 0.10 mmol), and [Rh(nbd)(**L**)]BF_4 (5.8 mg, 5.28 µmol). The reaction mixture after hydrogenation was filtered through a short pad of SiO_2, eluting with EtOAc. This product was purified by standard chromatographic techniques from its vinyl analogue and was obtained as a colorless liquid (6.2 mg, 41% isolated yield[25]). Enantiomeric ratio: 94% ee in favor of the (*R*)-configured enantiomer. Absolute configuration of the hydrogenated sulfoxide (*R*)-**7** was assigned by comparison of chromatographic elution orders with reported data (see *vide infra* in section 5).[39] $[\alpha]^{25}_D = +64$ (*c* 0.60, $CHCl_3$). The spectroscopic data were in agreement with those reported.

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Keywords: kinetic resolution • hydrogenation • asymmetric catalysis • rhodium • alkenes

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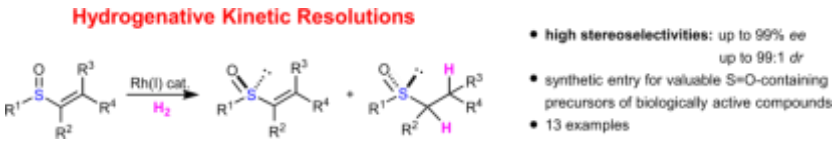

Key topic: **Hydrogenative Kinetic Resolutions**

The ability of a rhodium catalyst derived from phosphine-phosphite ligands to hydrogenatively resolve a set of structurally diverse α,β-unsaturated vinyl sulfoxides is reported. The practicality of the methodology was applied to the preparation of precursors of biologically active compounds.

References

[1] For the application of optically active sulfoxides as chiral auxiliaries or catalysts, see the following references and those cited therein: a) B. M. Trost, M. Rao, *Angew. Chem., Int. Ed.* **2015**, *54*, 5026-5043; b) G. Sipos, E. E. Drinkel, R. Dorta, *Chem. Soc. Rev.* **2015**, *44*, 3834-3860; c) S. Otocka, M. Kwiatkowska, L. Madalińska, P. Kiełbasiński, *Chem. Rev.* **2017**, *117*, 4147-4181.

[2] For the role of the sulfur atom in biological processes, see the following revision work: R. Bentley, *Chem. Soc. Rev.* **2005**, *34*, 609-624.

[3] T. Matsui, Y. Dekishima, M. Ueda, *Appl. Microbiol. Biotechnol.* **2014**, *98*, 7699-7706.

[4] C. M. Marson, *Anti-Cancer Agents Med. Chem.* **2009**, *9*, 661-692.

[5] B. J. Foster, D. C. Hunden, E. R. Lavagnino, US4902710A 1990.

[6] For comprehensive and general references, see: a) H. B. Kagan, Asymmetric Synthesis of Chiral Sulfoxides. *Organosulfur Chemistry in Asymmetric Synthesis* Eds. T. Toru, C. Bolm, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim (2008), pp 1-29; b) E. Wojaczyńska, J. Wojaczyński, *Chem. Rev.* **2010**, *110*, 4303-4356; c) J. Han, V. A. Soloshonok, K. D. Klika, J. Drabowicz, A. Wzorek, *Chem. Soc. Rev.* **2018**, *47*, 1307-1350.

[7] a) H. B. Kagan, J. C. Fiaud, Kinetic Resolution. *Topics in Stereochemistry* Eds. E. L. Eliel, S. H. Wilen, John Wiley & Sons, Inc. (1988), Vol. 18, pp 249-330; b) J. Wang, M. Frings, C. Bolm, *Chem. - Eur. J.* **2014**, *20*, 966-969.

[8] M. Kwiatkowska, I. Janicki, P. Kielbasinski, *J. Mol. Catal. B: Enzym.* **2015**, *118*, 23-28.

[9] P. K. Dornan, K. G. M. Kou, K. N. Houk, V. M. Dong, *J. Am. Chem. Soc.* **2014**, *136*, 291-298.

[10] Y. -C. Zhu, Y. Li, B. -C. Zhang, F. -X. Zhang, Y. -N. Yang, X. -S. Wang, *Angew. Chem., Int. Ed.* **2018**, *57*, 5129-5133.

[11] a) L. Zong, X. Ban, C. W. Kee, C. -H. Tan, *Angew. Chem., Int. Ed.* **2014**, *53*, 11849-11853; b) T. Jia, M. Zhang, S. P. McCollom, A. Bellomo, S. Montel, J. Mao, S. D. Dreher, C. J. Welch, E. L. Regalado, R. T. Williamson, B. C. Manor, N. C. Tomson, P. J. Walsh, *J. Am. Chem. Soc.* **2017**, *139*, 8337-8345; c) L. Wang, M. Chen, P. Zhang, W. Li, J. Zhang, *J. Am. Chem. Soc.* **2018**, *140*, 3467-3473; d) C. Wu, S. Berritt, X. Liang, P. J. Walsh, *Org. Lett.* **2019**, *21*, 960-964.

[12] For a revision work in the preparation and application of phosphine-phosphite ligands, see: H. Fernández-Pérez, P. Etayo, A. Panossian, A. Vidal-Ferran, *Chem. Rev.* **2011**, *111*, 2119-2176.

[13] J. R. Lao, H. Fernández-Pérez, A. Vidal-Ferran, *Org. Lett.* **2015**, *17*, 4114-4117.

[14] For stereoselective catalytic applications of phosphine-phosphite ligands developed in the group, see: a) S. M. A. Donald, A. Vidal-Ferran, F. Maseras, *Can. J. Chem.* **2009**, *87*, 1273-1279; b) H. Fernández-Pérez, S. M. A. Donald, I. J. Munslow, J. Benet-Buchholz, F. Maseras, A. Vidal-Ferran, *Chem. Eur. J.* **2010**, ***16***, 6495-6508; c) J. L. Núñez-Rico, H. Fernández-Pérez, J., Benet-Buchholz, A. Vidal-Ferran, *Organometallics* **2010**, *29*, 6627-6631; d) P. Etayo, J. L. Núñez-Rico, H. Fernández-Pérez, A. Vidal-Ferran, *Chem. Eur. J.* **2011**, *17*, 13978-13982; e) J. L. Núñez-Rico, P. Etayo, H. Fernández-Pérez, A. Vidal-Ferran, *Adv. Synth. Catal.* **2012**, *354*, 3025-3035; f) J. L. Núñez-Rico, A. Vidal-Ferran, *Org. Lett.* **2013**, *15*, 2066-2069; g) H. Fernández-Pérez, J. Benet-Buchholz, A. Vidal-Ferran, *Org. Lett.* **2013**, *15*, 3634-3637; h) J. L. Núñez-Rico, H. Fernández-Pérez, A. Vidal-Ferran, *Green Chem.* **2014**, *16*, 1153-1157; i) J. R. Lao, J. Benet-Buchholz, A. Vidal-Ferran, *Organometallics* **2014**, *33*, 2960-2963; j) H. Fernández-Pérez, J. Benet-Buchholz, A. Vidal-Ferran, *Chem. Eur. J.* **2014**, *20*, 15375-15384; k) H. Fernández-Pérez, J. R. Lao, A. Vidal-Ferran, *Org. Lett.* **2016**, *18*, 2836-2839; l) B. Balakrishna, A. Bauzá, A. Frontera, A. Vidal-Ferran, *Chem. Eur. J.* **2016**, *22*, 10607-10613; m) H. Fernández-Pérez, B. Balakrishna, A. Vidal-Ferran, *Eur. J. Org. Chem.* **2018**, *2018*, 1525-1532.

[15] For details, see the Supporting Information and the following reference: J. I. Grayson, S. Warren, *J. Chem. Soc., Perkin Trans. 1* **1977**, 2263-2272.

[16] I. G. Trostyanskaya, I. P. Beletskaya, *Synlett* **2012**, *23*, 535-540.

[17] To the best of our knowledge, there is only one report on the Rh mediated (*Z*)-selective hydrogenation of linear and cyclic unfunctionalized allenes towards the mono-alkene intermediates: M. M. Bhagwat, D. Devaprabhakara, *Tetrahedron Lett.* **1972**, 1391-1392.

[18] a) Z. Freixa, P. W. N. M. Van Leeuwen, *Dalton Trans.* **2003**, 1890-1901; b) J. H. Van Steenis, J. J. G. S. Van Es, A. Van der Gen, *Eur. J. Org. Chem.* **2000**, 2787-2793.

[19] See the Supporting Information for further details.

[20] a) N. D. Buezo, J. C. De la Rosa, J. Priego, I. Alonso, J. C. Carretero, *Chem. Eur. J.* **2001**, *7*, 3890-3900; b) B. Breit, D. Breuninger, *J. Am. Chem. Soc.* **2004**, *126*, 10244-10245.

[21] A complete list of the experiments performed can be found in Table SI-1 in the Supporting Information.

[22] A. K. Singla Shishu, I. P. Kaur, *Planta Med.* **2003**, *69*, 184-186.

[23] Y. Zhang, P. Talalay, C. G. Cho, G. H. Posner, *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 2399-2403.

[24] This compound is currently in clinical trials. For further information, see: *a*) S. Joel, C. Marson, P. Savy, WO2004046094A1 2004; *b*) C. M. Marson, P. Savy, A. S. Rioja, T. Mahadevan, C. Mikol, A. Veerupillai, E. Nsubuga, A. Chahwan, S. P. Joel, *J. Med. Chem.* **2006**, *49*, 800-805; *c*) M. Paris, M. Porcelloni, M. Binaschi, D. Fattori, *J. Med. Chem.* **2008**, *51*, 1505-1529.

[25] Yields are calculated with respect to the 50 mol% amount of starting material and product.

[26] The *anti*-arrangement of substituents in the hydrogenated product was established by comparison with the spectroscopic data reported in: D. Ando, C. Bevan, J. M. Brown, D. W. Price, *J. Chem. Soc., Chem. Commun.* **1992**, 592-594.

[27] For sulforaphane, see the following references: a) M. Yang, H. Wang, M. Zhou, W. Liu, P. Kuang, H. Liang, Q. Yuan, *Oncotarget* **2016**, *7*, 76656-76666; b) C. Zhang, J. Zhang, Q. Wu, B. Xu, G. Jin, Y, Qiao, S. Zhao, Y. Yang, J. Shang, X. Li, K. Liu, *Cancer Cell. Int.* **2019**, *19*, 342-351. For sulforaphane, see the following reference and those cited therein: c) E. Elhalem, R. Recio, S. Werner, F. Lieder, J. M. Calderón-Montaño, M. López-Lázaro, I. Fernández, N. Khiar, E. *Eur. J. Med. Chem.* **2014**, *87*, 552-563.

[28] For the ester cleavage reaction, see: a) A. Bury, H. A. Earl, C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2* **1987**, 1281-1287; For the conversion of the –OH to the –SCN group, see: b) S. Ruppenthal, R. Brueckner, *J. Org. Chem.* **2015**, *80*, 897-910.

[29] S. Liao, B. List, *Adv. Synth. Catal.* **2012**, *354*, 2363-2367.

[30] For the conversion of a –COOMe to a –CON(H)OH group in sulfoxide **7**, see ref. [26b].

[31] B. Balakrishna, A. Vidal-Ferran, *Synthesis* **2016**, *48*, 997-1001.

[32] Craig, D.; Daniels, K.; MacKenzie, A. R. *Tetrahedron* **1993**, *49*, 11263-11304.

[33] A. Fabretti, F. Ghelfi, R. Grandi, U. M. Pagnoni *Synth. Commun.*, **1994**, *24*, 2393-2398.

[34] J. M. Villar, A. Delgado, A. Llebaria, J. M. Moretó, E. Molins, C. Miravitlles *Tetrahedron* **1996**, *52*, 10525-10546.

[35] T. Hampel, S. Ruppenthal, D. Saelinger, R. Brueckner *Chem. Eur. J.* **2012**, *18*, 3136-3140.

[36] G. Mancha, A. B. Cuenca, N. Rodríguez, M. Medio-Simón, G. Asensio *Tetrahedron* **2010**, *66*, 6901-6905.

[37] G. Modena, U. Quintily, G. Scorrano *J. Am. Chem. Soc.* **1972**, *94*, 202-208.

[38] T. Sato, J. Otera *Synlett* **1995**, 365-366.

[39] Although product **7** is known [see ref. 29]; the value of its specific rotation is not described.