Asymmetric Catalysis

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Z-Selective Hydrothiolation of Racemic 1,3-Disubstituted Allenes: An Atom-Economic Rhodium-Catalyzed Dynamic Kinetic Resolution

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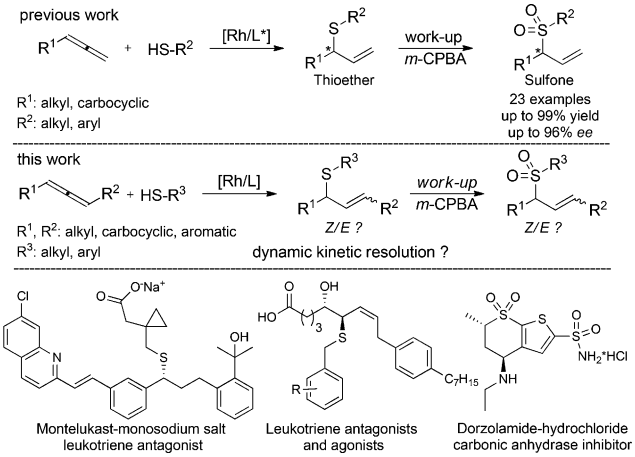
Abstract: *A Z-selective rhodium-catalyzed hydrothiolation of 1,3-disubstituted allenes and subsequent oxidation towards the corresponding allylic sulfones is described. Using the bidentate 1,4-bis(diphenylphosphino)butane (dppb) ligand, Z/E-selectivities up to >99:1 were obtained. The highly atom-economic desymmetrization reaction tolerates functionalized aromatic and aliphatic thiols. Additionally, a variety of symmetric internal allenes, as well as unsymmetrically disubstituted substrates were well tolerated, thus resulting in high regioselectivities. Starting from chiral but racemic 1,3-disubstituted allenes a dynamic kinetic resolution (DKR) could be achieved by applying (S,S)-Me-DuPhos as the chiral ligand. The desired Z-allylic sulfones were obtained in high yields and enantioselectivities up to 96% ee.*

Recently we described several highly selective methods for the addition of pronucleophiles to terminal allenes[1,2] and alkynes,[3] which can be regarded as atom-economic[4] alternatives to known allylic substitutions[5] and allylic oxidations.[6] In this respect we developed the first asymmetric hydrothiolation[7] of free aromatic and aliphatic thiols to terminal allenes to obtain branched allylic thioethers, and after oxidation, the corresponding allylic sulfones with excellent regio- and enantioselectivities (Scheme 1).[8]

Since many bioactive compounds such as Montelukast,[9a] Hepatitis C virus NS3/4A inhibitors,[9b] and others[9c–e] include α-stereogenic C–S bonds, the synthesis of higher-substituted allylic thioethers[10,11] and sulfones[12,13] could be seen as an important synthetic tool in organic chemistry[14,15] and drug synthesis. Furthermore, α-stereogenic allylic *Z*-configured thioethers showed activity against allergic asthma and other immediate hypersensitivity diseases.[16] Thus we were curious to see whether we could transfer our initial methodology to 1,3-disubstituted allenes. Herein we describe the first rhodium-catalyzed, highly *Z*-selective and, if desired, asymmetric, hydrothiolation of 1,3-disubstituted allenes. After optimization of the reaction conditions using naphthalene-2-thiol and nona-4,5-diene with addition of *p*-toluenesulfonic acid (PTSA), the sulfone **1** was obtained in 80% yield and 91:9 *Z* selectivity (Table 1).[17–19] Furthermore, we investigated the scope of different aromatic thiols for this hydrothiolation. Applying thiophenol as a suitable nucleophile the sulfone **2** was obtained in moderate *Z*/*E* selectivity of 78:22. The lower



Scheme 1. Rhodium-catalyzed hydrothiolation of allenes and bioactive compounds including α-stereogenic C–S bonds. *m*-CPBA = *m*-chloroperbenzoic acid.

selectivity compared with naphthalene-2-thiol (**1**) suggested that steric reasons are important for a high *Z* selectivity. Accordingly, *Z* selectivities increased when going from *p*-methylthiophenol (**3**; 74:26) to *o*-methylthiophenol (**5**; 91:9). When using the sterically demanding naphthalene-1-thiol, the allylic sulfone **6** was obtained in excellent *Z*/*E* selectivity of 93:7.

A number of functionalized thiophenol derivatives were tolerated (**7**–**12**; Table 1). Especially, sulfones with electron-withdrawing substituents gave excellent *Z* selectivities with up to >98:2 (77%), for example, when using *p*-fluorothiophenol (**8**). Also other electron-deficient thiols such as *p*-chloro- and *p*-bromothiophenol resulted in good selectivities and high yields of up to 86% (**9** and **10**). In addition to this, a free phenol function is well tolerated (**11**). We next focused on the use of aliphatic thiols. To our surprise, the use of (4-methoxyphenyl)methanethiol gave the product **13** with an *E* selectivity of 70:30. Conversely when 2,2,2-trifluoroethanethiol was used the sulfone **14** was obtained exclusively in the *Z* configuration. Also a homobenzyl- and furfurylmercaptane were compatible with this methodology where high *Z* selectivities of up to 91:9 could be achieved (**15** and **16**).

Next we focused on the scope of the allene coupling partners (Table 2). Symmetrically alkylated allenes were found to be suitable for this reaction and *Z*/*E* selectivities of up to 93:7 were obtained (**17** and **18**). Even cyclic internal allenes were tolerated. The coupling worked particularly well with cyclotrideca-1,2-diene, where the desired product **20** was obtained in a high yield with a good *Z* selectivity of 92:8. By applying cyclonona-1,2-diene, this methodology gave access

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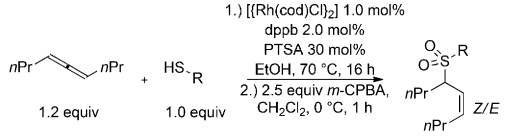
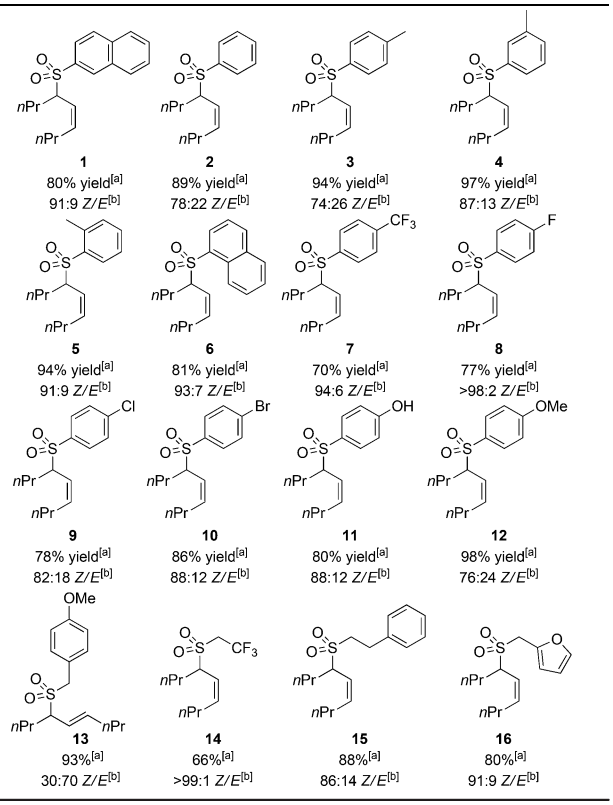
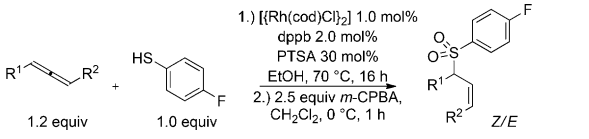
Table 1: Scope with respect to aromatic and aliphatic thiols with nona-4,5-diene.

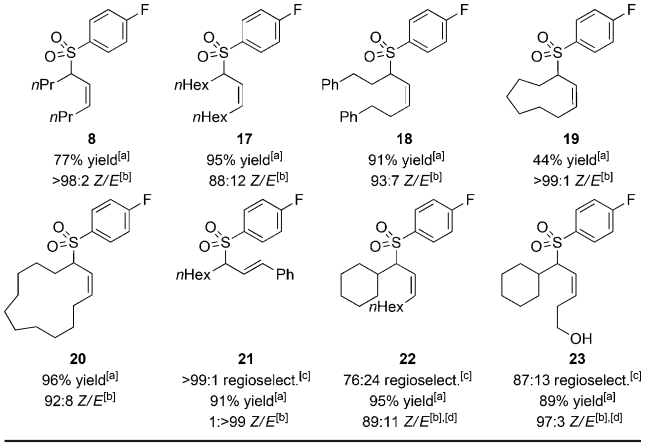




[a] Yield of the isolated isomeric mixtures. [b] *Z*/*E* selectivity of the sulfone determined by ^{1}H NMR analysis of the crude reaction mixture. cod = 1,5-cyclooctadiene, dppb = 1,4-bis(diphenylphosphino)butane.

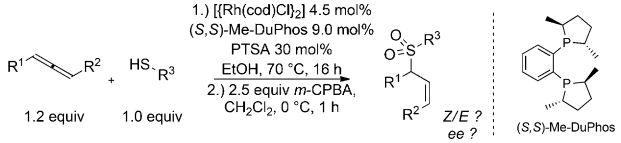
Table 2: Scope with respect to different 1,3-disubstituted allenes using *p*-fluorothiophenol.

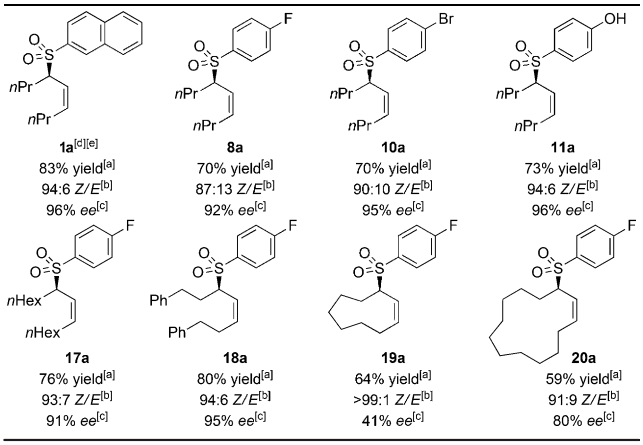




[a] Yield of the isolated isomeric mixtures. [b] *Z*/*E* selectivity of the sulfone determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Regioselectivity of the sulfone determined by ^{1}H NMR analysis of the crude reaction mixture; only allylic products detected. [d] *Z*/*E* selectivity of major regioisomer.

Table 3: Asymmetric hydrothiolation of 1,3-disubstituted allenes.





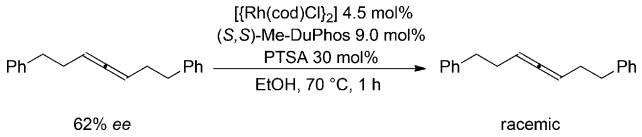
[a] Yield of the isolated isomeric mixtures. [b] *Z*/*E* selectivity of the sulfone determined by ^{1}H NMR analysis of the crude reaction mixture. [c] The *ee* value was determined by HPLC analysis using chiral stationary phase. [d] Using 1.0 mol% [{Rh(cod)Cl}$_2$] and 2.0 mol% (*S*,*S*)-Me-DuPhos, sulfone **1a** was obtained in 57% yield, 95:5 *Z*/*E* selectivity, and 91% *ee*. [e] Absolute configuration was determined by single-crystal X-ray analysis of **1a**.[17]

to the unique functionalized medium-ring-sized product **19**, exclusively with the *Z* configuration. Furthermore, unsymmetrical 1,3-disubstituted allenes were applied (**21**–**23**). As the reaction was performed with nona-1,2-dien-1-ylbenzene, **21** was obtained as a single regioisomer, showing exclusively *E* configuration.[20] In addition to this, we also performed the reaction using nona-1,2-dien-1-ylcyclohexane. The α-cyclohexylsulfone **22** was obtained with a high *Z* selectivity of 89:11 and a regioselectivity of 76:24. Even a free alcohol function is well tolerated (**23**).

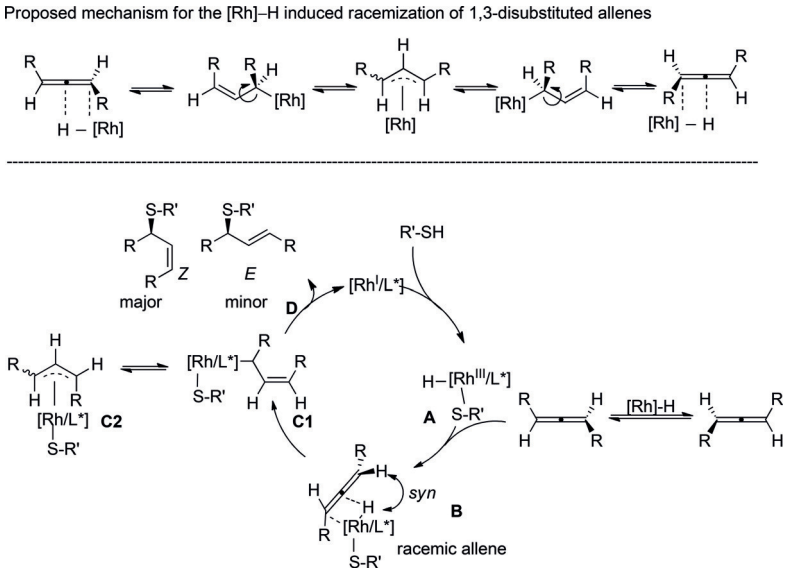
To explore whether this methodology allows the preparation of enantiomerically enriched thioethers and sulfones starting from racemic 1,3-disubstituted allenes, a screening of chiral ligands was undertaken. As a result, (*S*,*S*)-Me-DuPhos led to the desired product **1a** albeit a higher catalyst loading was needed (Table 3). Control experiments revealed that this process occurs as a dynamic kinetic resolution.[17] Thus, yields up to 83% and enantioselectivities up to 96% *ee* were achieved. When utilizing cyclonona-1,2-diene, the fully *Z*-configured product **19a** was obtained in good yield, albeit with only a moderate *ee* value. However when the 13-membered cyclic allene was applied the desired sulfone **20a** could be achieved with a *Z*/*E* selectivity of 91:9 in 80% *ee*.

To gain first insights into the mechanism for this dynamic kinetic resolution we synthesized an enantioenriched 1,7-

diphenylhepta-3,4-diene (62% *ee*). By applying the presented reaction conditions (in absence of thiol) we observed a complete racemization of the allene within less than 1 hour (Scheme 2).[21,22] Additionally, kinetic experiments for the catalysis were pursued, and gave a yield of only 27% within the first hour, thus showing that the hydrothiolation is by far slower than the racemization of the allene. Furthermore, the hydrothiolation with the enantioenriched 1,7-diphenylhepta-3,4-diene and *p*-fluorothiophenol led to the product **18a** with apparently the same results as when racemic allene was applied. Based on these experiments we propose the following mechanism (Scheme 3).[23] An oxida-



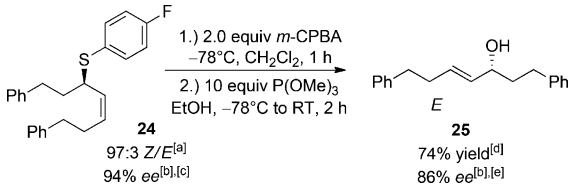
Scheme 2. Racemization experiment of enantioenriched 1,7-diphenylhepta-3,4-diene.[17,21,22]



Scheme 3. Mechanistic proposal for the highly *Z*-selective dynamic kinetic resolution.[17]

tive addition of the thiol forms the rhodium(III) species **A**.[7h] The following hydrometalation of the racemized allene, forming the *Z* double bond (**B**),[23a] will deliver the σ-allylcomplex **C1** which might be in equilibrium with the π-allyl isomer **C2**. The product is likely to be formed either by reductive elimination or by an intermolecular attack of a second thiolate (**D**).

To demonstrate the synthetic utility of this methodology, we subjected the thioether **24** to the reaction conditions of an Evans–Mislow rearrangement (Scheme 4).[24] To our delight, when using 2.0 equivalents of *m*-CPBA, the in situ generated sulfoxide directly underwent a [2,3] sigmatropic rearrangement to form the pure *E*-configurated allylic alcohol **25**.[25a] In



Scheme 4. 1,3-*syn*-Chirality transfer by a [2,3] Evans–Mislow rearrangement. [a] *Z*/*E* Selectivity determined by ^{1}H NMR spectroscopy of the crude reaction mixture of the corresponding sulfone. [b] The *ee* value was determined by HPLC analysis using chiral stationary phase. [c] The *ee* value of **24** was determined after oxidation to sulfone. [d] Yield of isolated product. [e] Absolute configuration was determined by comparison of the specific rotation of the literature known reduced alcohol.[26]

accordance with previous reports, this transformation proceeded by a 1,3-*syn*-chirality transfer to generate **25** with an enantioselectivity of 86% *ee* in 74% yield.[25b]

To conclude, we have found the first rhodium-catalyzed atom-economic addition of free thiols to 1,3-disubstituted allenes. By using dppb as bidentate ligand and 30 mol% PTSA as an additive, the reaction led to the desired higher substituted allylic sulfones with excellent *Z* selectivities and high yields. The reaction tolerates a broad variety of aromatic and aliphatic thiols. Furthermore, a wide scope of different symmetrical and unsymmetrical acyclic and cyclic 1,3-disubstituted allenes were efficient reaction partners. Starting from racemic internal allenes with a rhodium(I)/(*S,S*)-Me-DuPhos catalyst a dynamic kinetic resolution occurred, thus furnishing the corresponding *Z*-allylic thioethers and sulfones in high enantioselectivities. Extension of this powerful methodology to more complex systems is ongoing in our group.

Acknowledgements

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[17] See the Supporting Information for further details.
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[21] We propose the racemization of 1,3-disubstituted allenes as follows: After a hydrometalation by a given [Rh]−H species (generated either by PTSA or via oxidation of ethanol) a σ-π-σ allyl-rhodium-isomerization might take place. For recent publication of a similar mechanism, see: D. N. Tran, N. Cramer, *Angew. Chem. Int. Ed.* **2013**, *52*, 10630 – 10634; *Angew. Chem.* **2013**, *125*, 10824 – 10828. For the first example of a dynamic kinetic resolution of allenes, see: J. Deska, C. del Pozo Ochoa, J. E. Bäckvall, *Chem. Eur. J.* **2010**, *16*, 4447 – 4451.
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