

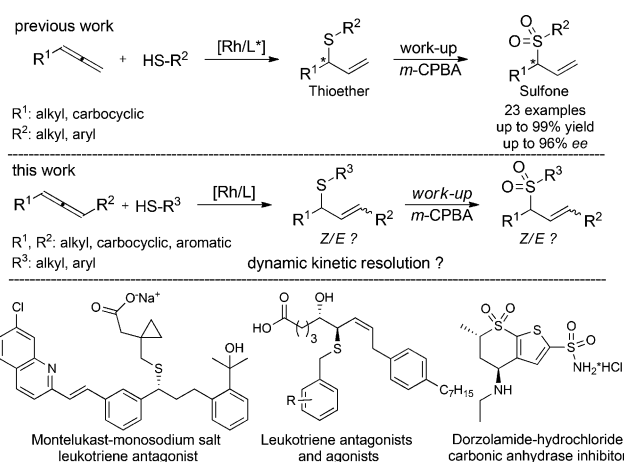
# Z-Selective Hydrothiolation of Racemic 1,3-Disubstituted Allenes: An Atom-Economic Rhodium-Catalyzed Dynamic Kinetic Resolution

Adrian B. Pritzius and Bernhard Breit\*

**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<sup>[1,2]</sup> and alkynes,<sup>[3]</sup> which can be regarded as atom-economic<sup>[4]</sup> alternatives to known allylic substitutions<sup>[5]</sup> and allylic oxidations.<sup>[6]</sup> In this respect we developed the first asymmetric hydrothiolation<sup>[7]</sup> 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).<sup>[8]</sup>

Since many bioactive compounds such as Montelukast,<sup>[9a]</sup> Hepatitis C virus NS3/4A inhibitors,<sup>[9b]</sup> and others<sup>[9c-e]</sup> include  $\alpha$ -stereogenic C–S bonds, the synthesis of higher-substituted allylic thioethers<sup>[10,11]</sup> and sulfones<sup>[12,13]</sup> could be seen as an important synthetic tool in organic chemistry<sup>[14,15]</sup> and drug synthesis. Furthermore,  $\alpha$ -stereogenic allylic Z-configured thioethers showed activity against allergic asthma and other immediate hypersensitivity diseases.<sup>[16]</sup> 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).<sup>[17–19]</sup> 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  $\alpha$ -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

[\*] A. B. Pritzius, Prof. Dr. B. Breit  
Institut für Organische Chemie, Albert-Ludwigs-Universität Freiburg  
Albertstrasse 21, 79104 Freiburg im Breisgau (Germany)  
E-mail: bernhard.breit@chemie.uni-freiburg.de

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201507623>.

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

| $\text{nPr}-\text{CH}=\text{CH}-\text{nPr} + \text{HS}-\text{R} \xrightarrow[\text{2.) 2.5 equiv } m\text{-CPBA, CH}_2\text{Cl}_2, 0^\circ\text{C}, 1\text{ h}]{\text{1.) } [\text{Rh}(\text{cod})\text{Cl}]_2, 1.0\text{ mol\%}, \text{dppb } 2.0\text{ mol\%}, \text{PTSA } 30\text{ mol\%}, \text{EtOH}, 70^\circ\text{C}, 16\text{ h}}$ |                                                      | $\text{O}_2\text{S}-\text{R}$                        | $\text{nPr}-\text{CH}=\text{CH}-\text{nPr}$          | $\text{Z/E}$ |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|------------------------------------------------------|--------------|
| 1.2 equiv                                                                                                                                                                                                                                                                                                                                   | 1.0 equiv                                            |                                                      |                                                      |              |
|                                                                                                                                                                                                                                                                                                                                             |                                                      |                                                      |                                                      |              |
| 1                                                                                                                                                                                                                                                                                                                                           | 2                                                    | 3                                                    | 4                                                    |              |
| 80% yield <sup>[a]</sup><br>91:9 Z/E <sup>[b]</sup>                                                                                                                                                                                                                                                                                         | 89% yield <sup>[a]</sup><br>78:22 Z/E <sup>[b]</sup> | 94% yield <sup>[a]</sup><br>74:26 Z/E <sup>[b]</sup> | 97% yield <sup>[a]</sup><br>87:13 Z/E <sup>[b]</sup> |              |
|                                                                                                                                                                                                                                                                                                                                             |                                                      |                                                      |                                                      |              |
| 5                                                                                                                                                                                                                                                                                                                                           | 6                                                    | 7                                                    | 8                                                    |              |
| 94% yield <sup>[a]</sup><br>91:9 Z/E <sup>[b]</sup>                                                                                                                                                                                                                                                                                         | 81% yield <sup>[a]</sup><br>93:7 Z/E <sup>[b]</sup>  | 70% yield <sup>[a]</sup><br>94:6 Z/E <sup>[b]</sup>  | 77% yield <sup>[a]</sup><br>>98:2 Z/E <sup>[b]</sup> |              |
|                                                                                                                                                                                                                                                                                                                                             |                                                      |                                                      |                                                      |              |
| 9                                                                                                                                                                                                                                                                                                                                           | 10                                                   | 11                                                   | 12                                                   |              |
| 78% yield <sup>[a]</sup><br>82:18 Z/E <sup>[b]</sup>                                                                                                                                                                                                                                                                                        | 86% yield <sup>[a]</sup><br>88:12 Z/E <sup>[b]</sup> | 80% yield <sup>[a]</sup><br>88:12 Z/E <sup>[b]</sup> | 98% yield <sup>[a]</sup><br>76:24 Z/E <sup>[b]</sup> |              |
|                                                                                                                                                                                                                                                                                                                                             |                                                      |                                                      |                                                      |              |
| 13                                                                                                                                                                                                                                                                                                                                          | 14                                                   | 15                                                   | 16                                                   |              |
| 93% <sup>[a]</sup><br>30:70 Z/E <sup>[b]</sup>                                                                                                                                                                                                                                                                                              | 66% <sup>[a]</sup><br>>99:1 Z/E <sup>[b]</sup>       | 88% <sup>[a]</sup><br>86:14 Z/E <sup>[b]</sup>       | 80% <sup>[a]</sup><br>91:9 Z/E <sup>[b]</sup>        |              |

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

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.<sup>[20]</sup> In addition to this, we also performed the reaction using nona-1,2-dien-1-ylcyclohexane. The  $\alpha$ -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.<sup>[17]</sup> 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-

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

| $\text{R}^1-\text{CH}=\text{CH}-\text{R}^2 + \text{HS}-\text{C}_6\text{H}_4\text{F} \xrightarrow[\text{2.) 2.5 equiv } m\text{-CPBA, CH}_2\text{Cl}_2, 0^\circ\text{C}, 1\text{ h}]{\text{1.) } [\text{Rh}(\text{cod})\text{Cl}]_2, 1.0\text{ mol\%}, \text{dppb } 2.0\text{ mol\%}, \text{PTSA } 30\text{ mol\%}, \text{EtOH}, 70^\circ\text{C}, 16\text{ h}}$ |                                                                                           | $\text{O}_2\text{S}-\text{C}_6\text{H}_4\text{F}$                                         | $\text{R}^1-\text{CH}=\text{CH}-\text{R}^2$                                              | $\text{Z/E}$ |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|--------------|
| 1.2 equiv                                                                                                                                                                                                                                                                                                                                                       | 1.0 equiv                                                                                 |                                                                                           |                                                                                          |              |
|                                                                                                                                                                                                                                                                                                                                                                 |                                                                                           |                                                                                           |                                                                                          |              |
| 8                                                                                                                                                                                                                                                                                                                                                               | 17                                                                                        | 18                                                                                        | 19                                                                                       |              |
| 77% yield <sup>[a]</sup><br>>98:2 Z/E <sup>[b]</sup>                                                                                                                                                                                                                                                                                                            | 95% yield <sup>[a]</sup><br>88:12 Z/E <sup>[b]</sup>                                      | 91% yield <sup>[a]</sup><br>93:7 Z/E <sup>[b]</sup>                                       | 44% yield <sup>[a]</sup><br>>99:1 Z/E <sup>[b]</sup>                                     |              |
|                                                                                                                                                                                                                                                                                                                                                                 |                                                                                           |                                                                                           |                                                                                          |              |
| 20                                                                                                                                                                                                                                                                                                                                                              | 21                                                                                        | 22                                                                                        | 23                                                                                       |              |
| 96% yield <sup>[a]</sup><br>92:8 Z/E <sup>[b]</sup>                                                                                                                                                                                                                                                                                                             | >99:1 regioselect. <sup>[c]</sup><br>91% yield <sup>[a]</sup><br>1:>99 Z/E <sup>[b]</sup> | 76:24 regioselect. <sup>[c]</sup><br>95% yield <sup>[a]</sup><br>89:11 Z/E <sup>[b]</sup> | 87:13 regioselect. <sup>[c]</sup><br>89% yield <sup>[a]</sup><br>97:3 Z/E <sup>[b]</sup> |              |

[a] Yield of the isolated isomeric mixtures. [b] Z/E selectivity of the sulfone determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. [c] Regioselectivity of the sulfone determined by <sup>1</sup>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.

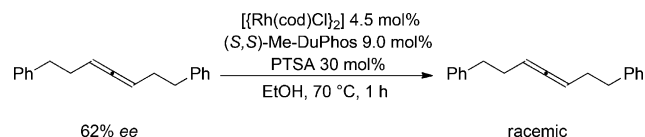
| $\text{R}^1-\text{CH}=\text{CH}-\text{R}^2 + \text{HS}-\text{R}^3 \xrightarrow[\text{2.) 2.5 equiv } m\text{-CPBA, CH}_2\text{Cl}_2, 0^\circ\text{C}, 1\text{ h}]{\text{1.) } [\text{Rh}(\text{cod})\text{Cl}]_2, 4.5\text{ mol\%}, (\text{S,S})\text{-Me-DuPhos } 9.0\text{ mol\%}, \text{PTSA } 30\text{ mol\%}, \text{EtOH}, 70^\circ\text{C}, 16\text{ h}}$ |                                                                               | $\text{O}_2\text{S}-\text{R}^3$                                               | $\text{R}^1-\text{CH}=\text{CH}-\text{R}^2$                                  | $\text{Z/E ?}$ | $\text{ee ?}$ |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------|----------------|---------------|
| 1.2 equiv                                                                                                                                                                                                                                                                                                                                                       | 1.0 equiv                                                                     |                                                                               |                                                                              |                |               |
|                                                                                                                                                                                                                                                                                                                                                                 |                                                                               |                                                                               |                                                                              |                |               |
| 1a <sup>[c]</sup>                                                                                                                                                                                                                                                                                                                                               | 8a                                                                            | 10a                                                                           | 11a                                                                          |                |               |
| 83% yield <sup>[a]</sup><br>94:6 Z/E <sup>[b]</sup><br>96% ee <sup>[c]</sup>                                                                                                                                                                                                                                                                                    | 70% yield <sup>[a]</sup><br>87:13 Z/E <sup>[b]</sup><br>92% ee <sup>[c]</sup> | 70% yield <sup>[a]</sup><br>90:10 Z/E <sup>[b]</sup><br>95% ee <sup>[c]</sup> | 73% yield <sup>[a]</sup><br>94:6 Z/E <sup>[b]</sup><br>96% ee <sup>[c]</sup> |                |               |
|                                                                                                                                                                                                                                                                                                                                                                 |                                                                               |                                                                               |                                                                              |                |               |
| 17a                                                                                                                                                                                                                                                                                                                                                             | 18a                                                                           | 19a                                                                           | 20a                                                                          |                |               |
| 76% yield <sup>[a]</sup><br>93:7 Z/E <sup>[b]</sup><br>91% ee <sup>[c]</sup>                                                                                                                                                                                                                                                                                    | 80% yield <sup>[a]</sup><br>94:6 Z/E <sup>[b]</sup><br>95% ee <sup>[c]</sup>  | 64% yield <sup>[a]</sup><br>>99:1 Z/E <sup>[b]</sup><br>41% ee <sup>[c]</sup> | 59% yield <sup>[a]</sup><br>91:9 Z/E <sup>[b]</sup><br>80% ee <sup>[c]</sup> |                |               |

[a] Yield of the isolated isomeric mixtures. [b] Z/E selectivity of the sulfone determined by <sup>1</sup>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% [ $\text{Rh}(\text{cod})\text{Cl}$ ]<sub>2</sub> 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**.<sup>[17]</sup>

membered cyclic allene was applied the desired sulfone **20a** could be achieved with a Z/E selectivity of 91:9 in 80% *ee*.

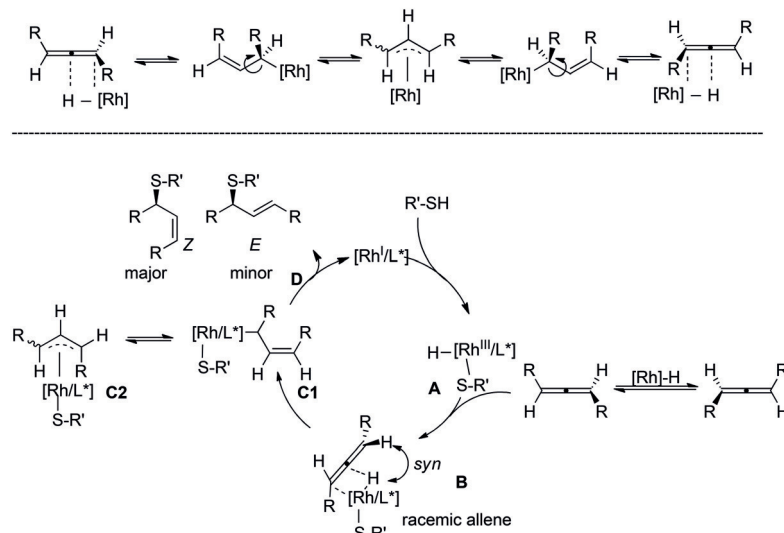
To gain first insights into the mechanism for this dynamic kinetic resolution we synthesized an enantioenriched 1,7-

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).<sup>[21,22]</sup> 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).<sup>[23]</sup> An oxida-



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

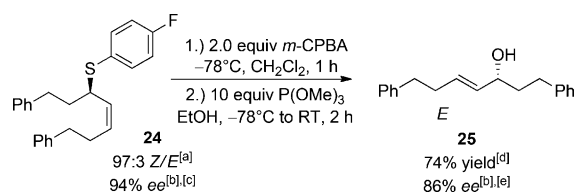
Proposed mechanism for the [Rh]–H induced racemization of 1,3-disubstituted allenes



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

tive addition of the thiol forms the rhodium(III) species **A**.<sup>[7h]</sup> The following hydrometalation of the racemized allene, forming the *Z* double bond (**B**),<sup>[23a]</sup> will deliver the  $\sigma$ -allyl complex **C1** which might be in equilibrium with the  $\pi$ -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).<sup>[24]</sup> 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*-configured allylic alcohol **25**.<sup>[25a]</sup> In



**Scheme 4.** 1,3-*syn*-Chirality transfer by a [2,3] Evans–Mislow rearrangement. [a] *Z/E* Selectivity determined by <sup>1</sup>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.<sup>[26]</sup>

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.<sup>[25b]</sup>

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

This work was supported by the DFG, the International Research Training Group “Catalysts and Catalytic Reactions for Organic Synthesis” (IRTG 1038), the Fonds der Chemischen Industrie, and the Krupp Foundation. We thank Umicore, BASF, and Wacker for generous gifts of chemicals. Ina Rohleff and Dr. Daniel Kratzert are acknowledged for skillful technical assistance and X-ray analysis.

**Keywords:** allenes · asymmetric catalysis · dynamic kinetic resolution · rhodium · sulfones

**How to cite:** *Angew. Chem. Int. Ed.* **2015**, *54*, 15818–15822  
*Angew. Chem.* **2015**, *127*, 16044–16048

- [1] a) P. Koschker, A. Lumbroso, B. Breit, *J. Am. Chem. Soc.* **2011**, *133*, 20746–20749; b) M. L. Cooke, K. Xu, B. Breit, *Angew. Chem. Int. Ed.* **2012**, *51*, 10876–10879; *Angew. Chem.* **2012**, *124*,

- 11034–11037; c) K. Xu, N. Thieme, B. Breit, *Angew. Chem. Int. Ed.* **2014**, *53*, 7268–7271; *Angew. Chem.* **2014**, *126*, 7396–7399; d) K. Xu, N. Thieme, B. Breit, *Angew. Chem. Int. Ed.* **2014**, *53*, 2162–2165; *Angew. Chem.* **2014**, *126*, 2194–2197; e) C. Li, B. Breit, *J. Am. Chem. Soc.* **2014**, *136*, 862–865; f) A. M. Haydl, K. Xu, B. Breit, *Angew. Chem. Int. Ed.* **2015**, *54*, 7149–7153; *Angew. Chem.* **2015**, *127*, 7255–7259.
- [2] For recent publications for the addition of pronucleophiles to allenes, see: a) R. Zimmer, C. Dinesh, E. Nandan, A. F. Khan, *Chem. Rev.* **2000**, *100*, 3067–3125; b) I. S. Kim, M. J. Krische, *Org. Lett.* **2008**, *10*, 513–515; c) T. Kawamoto, S. Hirabayashi, X. Guo, T. Nishimura, T. Hayashi, *Chem. Commun.* **2009**, 3528–3530; d) J. Moran, A. Preetz, R. A. Mesch, M. J. Krische, *Nat. Chem.* **2011**, *3*, 287–290; e) N. Morita, N. Krause, *Angew. Chem. Int. Ed.* **2006**, *45*, 1897–1899; *Angew. Chem.* **2006**, *118*, 1930–1933; f) G. Takahashi, E. Shirakawa, T. Tsuchimoto, Y. Kawakami, *Adv. Synth. Catal.* **2006**, *348*, 837–840; g) N. Nishina, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2006**, *45*, 3314–3317; *Angew. Chem.* **2006**, *118*, 3392–3395; h) C. Zhang, S.-Q. Zhang, H.-J. Cai, D.-M. Cui, *Beilstein J. Org. Chem.* **2013**, *9*, 1045–1050; i) C. Hurtado-Rodrigo, S. Hoehne, M. Paz Muñoz, *Chem. Commun.* **2014**, *50*, 1494–1496; j) J. D. Osborne, H. E. Randell-Sly, G. S. Currie, A. R. Cowley, M. C. Willis, *J. Am. Chem. Soc.* **2008**, *130*, 17232–17233; k) Z. Zhang, R. A. Widenhoefer, *Org. Lett.* **2008**, *10*, 2079–2081; l) R. E. Kinder, Z. Zhang, R. A. Widenhoefer, *Org. Lett.* **2008**, *10*, 3157–3159; m) H. E. Randell-Sly, J. D. Osborne, R. L. Woodward, G. S. Currie, M. C. Willis, *Tetrahedron* **2009**, *65*, 5110–5117; n) N. Nishina, Y. Yamamoto, *Tetrahedron Lett.* **2008**, *49*, 4908–4911; o) Z. D. Miller, R. Dorel, J. Montgomery, *Angew. Chem. Int. Ed.* **2015**, *54*, 9088–9091; *Angew. Chem.* **2015**, *127*, 9216–9219; p) W.-J. Xiao, H. Alper, *J. Org. Chem.* **1999**, *64*, 9646–9652; q) K. L. Butler, M. Tragni, R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2012**, *51*, 5175–5178; *Angew. Chem.* **2012**, *124*, 5265–5268.
- [3] a) A. Lumbroso, P. Koschker, N. R. Vautravers, B. Breit, *J. Am. Chem. Soc.* **2011**, *133*, 2386–2389; b) A. Lumbroso, N. Abermil, B. Breit, *Chem. Sci.* **2012**, *3*, 789–793; c) K. Xu, V. Khakyzadeh, T. Bury, B. Breit, *J. Am. Chem. Soc.* **2014**, *136*, 16124–16127; d) P. Koschker, M. Kähny, B. Breit, *J. Am. Chem. Soc.* **2015**, *137*, 3131–3137.
- [4] B. M. Trost, *Science* **1991**, *254*, 1471–1477.
- [5] a) B. M. Trost, *Chem. Rev.* **1996**, *96*, 395–422; b) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921–2943; c) Z. Lu, S. Ma, *Angew. Chem. Int. Ed.* **2008**, *47*, 258–297; *Angew. Chem.* **2008**, *120*, 264–303; d) T. Hayashi, A. Okada, T. Suzuka, M. Kawatsura, *Org. Lett.* **2003**, *5*, 1713–1715; e) P. A. Evans, D. K. Leahy, *J. Am. Chem. Soc.* **2002**, *124*, 7882–7883.
- [6] a) G. Liu, Y. Wu, *Top. Curr. Chem.* **2010**, *292*, 195–209; b) M. S. Chen, M. C. White, *J. Am. Chem. Soc.* **2004**, *126*, 1346–1347; c) G. Liu, S. S. Stahl, *J. Am. Chem. Soc.* **2007**, *129*, 6328–6335; d) G. Yin, Y. Wu, G. Liu, *J. Am. Chem. Soc.* **2010**, *132*, 11978–11987.
- [7] a) R. Castarlenas, A. Di Giuseppe, J. J. Pérez-Torrente, L. A. Oro, *Angew. Chem. Int. Ed.* **2013**, *52*, 211–222; *Angew. Chem.* **2013**, *125*, 223–234; b) T. Kondo, T. Mitsudo, *Chem. Rev.* **2000**, *100*, 3205–3220; c) I. P. Beletskaya, V. P. Ananikov, *Chem. Rev.* **2011**, *111*, 1596–1636; d) Menggenbateer, M. Narsireddy, G. Ferrara, N. Nishina, T. Jin, Y. Yamamoto, *Tetrahedron Lett.* **2010**, *51*, 4627–4629; e) S. Kodama, A. Nomoto, M. Kajitani, E. Nishinaka, M. Sonoda, A. Ogawa, *J. Sulfur Chem.* **2009**, *30*, 309–318; f) A. Di Giuseppe, R. Castarlenas, J. J. Pérez-Torrente, M. Crucianelli, V. Polo, R. Sancho, F. J. Lahoz, L. A. Oro, *J. Am. Chem. Soc.* **2012**, *134*, 8171–8183; g) C. Cao, L. R. Fraser, J. A. Love, *J. Am. Chem. Soc.* **2005**, *127*, 17614–17615; h) S. Shuai, P. Bichler, B. Kang, H. Buckley, J. A. Love, *Organometallics* **2007**, *26*, 5778–5781; i) J. Yang, A. Sabarre, L. R. Fraser, B. O. Patrick, J. A. Love, *J. Org. Chem.* **2009**, *74*, 182–187.
- [8] A. B. Pritzius, B. Breit, *Angew. Chem. Int. Ed.* **2015**, *54*, 3121–3125; *Angew. Chem.* **2015**, *127*, 3164–3168.
- [9] a) “Process for the preparation of leukotrien antagonists and intermediates thereof”: L. Coppi, M. Bartrata Sanmarti, Y. Gasanz Guillén, M. Monsalvatje Llagostera, P. Talavera Escasany, EP 1783117A1, **2005**; b) F. Velázquez, M. Sannigrahi, F. Bennett, R. G. Lovey, A. Arasappan, S. Bogen, L. Nair, S. Venkatraman, M. Blackman, S. Hendrata, Y. Huang, R. Huelgas, P. Pinto, K.-C. Cheng, X. Tong, A. T. McPhail, F. G. Njoroge, *J. Med. Chem.* **2010**, *53*, 3075–3085; c) A. S. Morgan, P. E. Sanderson, R. F. Borch, K. D. Tew, Y. Niitsu, T. Takayama, D. D. Von Hoff, E. Izbicka, G. Mangold, C. Paul, U. Broberg, B. Mannervik, W. D. Henner, L. M. Kauvar, *Cancer Res.* **1998**, *58*, 2568–2575; d) F. Reck, F. Zhou, M. Girardot, G. Kern, C. J. Eyermann, N. J. Hales, R. R. Ramsay, M. B. Gravestock, *J. Med. Chem.* **2005**, *48*, 499–506; e) “(CIPLA LIMITED) Process for preparing Dorzolamide”: R. N. Kankan, D. R. Rao, S. S. Mudgal, US 2010/0113804A1, **2008**.
- [10] For synthesis of the branched internal allylic thioethers, see: a) X. Zahng, W. Roa, P. W. H. Chan, *Synlett* **2008**, 2204–2208; b) Y. Yatsumonji, Y. Ishida, A. Tsubouchi, T. Takeda, *Org. Lett.* **2007**, *9*, 4603–4606; c) H.-J. Gais, N. Spalthoff, T. Jagusch, M. Frank, G. Raabe, *Tetrahedron Lett.* **2000**, *41*, 3809–3812; d) H.-J. Gais, T. Jagusch, N. Spalthoff, F. Gerhards, M. Frank, G. Raabe, *Chem. Eur. J.* **2003**, *9*, 4202–4221; e) Y. Fujiwara, J. Sun, G. C. Fu, *Chem. Sci.* **2011**, *2*, 2196–2198; f) J. Sun, G. C. Fu, *J. Am. Chem. Soc.* **2010**, *132*, 4568–4569; g) B. M. Trost, T. S. Scanlan, *Tetrahedron Lett.* **1986**, *27*, 4141–4144; h) W. Liu, X. Zhao, *Synthesis* **2013**, 2051–2069.
- [11] a) M. Roggen, E. M. Carreira, *Angew. Chem. Int. Ed.* **2012**, *51*, 8652–8655; *Angew. Chem.* **2012**, *124*, 8780–8783; b) N. Gao, S. Zheng, W. Yang, X. Zhao, *Org. Lett.* **2011**, *13*, 1514–1516; c) S. Zheng, N. Gao, W. Liu, D. Liu, X. Zhao, T. Cohen, *Org. Lett.* **2010**, *12*, 4454–4457; d) W. Huang, S. Zheng, J. Tang, X. Zhao, *Org. Biomol. Chem.* **2011**, *9*, 7897–7903.
- [12] a) H. Eichelmann, H.-J. Gais, *Tetrahedron: Asymmetry* **1995**, *6*, 643–646; b) F. X. Felpin, Y. Landais, *J. Org. Chem.* **2005**, *70*, 6441–6446; c) Y. Uozumi, T. Suzuka, *Synthesis* **2008**, 1960–1964; d) S. Kamijo, M. AI-Masum, Y. Yamamoto, *Tetrahedron Lett.* **1998**, *39*, 691–694.
- [13] a) M. Ueda, J. F. Hartwig, *Org. Lett.* **2010**, *12*, 92–94; b) K. Hiroi, K. Makino, *Chem. Lett.* **1986**, *4*, 617–620; c) B. M. Trost, M. J. Krische, R. Radinov, G. J. Zanoni, *J. Am. Chem. Soc.* **1996**, *118*, 6297–6298; d) B. M. Trost, M. L. Crawley, C. B. Lee, *J. Am. Chem. Soc.* **2000**, *122*, 6120–6121; e) M. Jegelka, B. Plietker, *Org. Lett.* **2009**, *11*, 3462–3465; f) M. C. Liao, X. H. Duan, Y. M. Liang, *Tetrahedron Lett.* **2005**, *46*, 3469–3472.
- [14] a) A. M. Masdeu-Bultó, M. Diéguez, E. Martín, M. Gómez, *Coord. Chem. Rev.* **2003**, *242*, 159–201; b) Y. A. Lin, J. M. Chalker, N. Floyd, G. J. L. Bernardes, B. G. Davis, *J. Am. Chem. Soc.* **2008**, *130*, 9642–9643; c) S. Barluenga, P. Lopez, E. Moulin, N. Winssinger, *Angew. Chem. Int. Ed.* **2004**, *43*, 3467–3470; *Angew. Chem.* **2004**, *116*, 3549–3552; d) T. Liu, X. Zhao, L. Lu, T. Cohen, *Org. Lett.* **2009**, *11*, 4576–4579; e) K. M. Engstrom, M. R. Mendoza, M. Navarro-Villalobos, D. Y. Gin, *Angew. Chem. Int. Ed.* **2001**, *40*, 1128–1130; *Angew. Chem.* **2001**, *113*, 1162–1164.
- [15] a) P. L. Fuchs, T. F. Braish, *Chem. Rev.* **1986**, *86*, 903–917; b) B. M. Trost, M. G. Organ, G. A. O'Doherty, *J. Am. Chem. Soc.* **1995**, *117*, 9662–9670; c) R. Scholz, G. Hellmann, S. Rohs, D. Özdemir, G. Raabe, C. Vermeeren, H.-J. Gais, *Eur. J. Org. Chem.* **2010**, 4588–4616; d) G. Hellmann, A. Hack, E. Thiemermann, O. Luche, G. Raabe, H.-J. Gais, *Chem. Eur. J.* **2013**, *19*, 3869–3897; e) A. El-Awa, M. N. Noshi, X. Mollat du Jourdin, P. L. Fuchs, *Chem. Rev.* **2009**, *109*, 2315–2349; f) A.-N. R. Alba, X. Companyó, R. Rios, *Chem. Soc. Rev.* **2010**, *39*, 2018–2033.

- [16] a) T. W. Ku, M. E. McCarthy, B. M. Weichman, J. G. Gleason, *J. Med. Chem.* **1985**, 28, 1847–1853; b) P. R. Bernstein, E. P. Vacek, E. J. Adams, D. W. Snyder, R. D. Krellt, *J. Med. Chem.* **1988**, 31, 692–696.
- [17] See the Supporting Information for further details.
- [18] Trisubstituted allenes, subjected to the given conditions, did not furnish any product.
- [19] Sulfonic acids are known for their ability to generate [Rh]–H species. Thus, we assume the formal oxidative addition of the thiol is facilitated by the PTSA. For recent literature in this field see: Y. Yang, E. G. Moschetta, R. M. Rioux, *ChemCatChem* **2013**, 5, 3005–3013.
- [20] We assumed that under the given reaction conditions an acid-catalyzed isomerization via the benzylic cation led to the thermodynamically favored *E* isomer. See the Supporting Information for a plausible mechanism.
- [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  $\sigma$ - $\pi$  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.
- [22] Since a racemization of the allene took place even in the absence of PTSA we assume that a formation of a [Rh]–H species, generated by the oxidation of ethanol, might be plausible. For ethanol-based formation of a [Rh]–H species, see: J. C. Trebellas, J. R. Olechowski, H. B. Jonassen, D. W. Moore, *J. Organomet. Chem.* **1967**, 9, 153–158.
- [23] a) M. Arisawa, M. Yamaguchi, *Adv. Synth. Catal.* **2001**, 343, 27–28; b) B. Cazes, *Pure Appl. Chem.* **1990**, 62, 1867–1878; c) M. Ahmar, J.-J. Barieuxh, B. Cazes, J. Gore, *Tetrahedron* **1987**, 43, 513–526; d) G. Onodera, R. Hachisuka, T. Noguchi, H. Miura, T. Hashimoto, R. Takeuchi, *Tetrahedron Lett.* **2014**, 55, 310–313; e) G. Liu, M. Garland, *J. Organomet. Chem.* **2000**, 608, 76–85; f) A. Padwa, Q. Wang, *J. Org. Chem.* **2006**, 71, 3210–3220.
- [24] a) R. Tang, K. Mislow, *J. Am. Chem. Soc.* **1970**, 92, 2100–2104; b) D. A. Evans, G. C. Andrews, *Acc. Chem. Res.* **1974**, 7, 147–155; c) S. Raghavan, V. V. Kumar, L. R. Chowhan, *Synlett* **2010**, 1807–1810; d) Y. Baba, G. Saha, S. Nakao, C. Iwata, T. Tanaka, T. Ibuka, H. Ohishi, Y. Takemoto, *J. Org. Chem.* **2001**, 66, 81–88; e) D. F. Taber, M. Xu, J. C. Hartnett, *J. Am. Chem. Soc.* **2002**, 124, 13121–13126; f) D. F. Taber, D. Teng, *J. Org. Chem.* **2002**, 67, 1607–1612.
- [25] a) To prevent an oxidation towards the sulfone the reaction must be performed at very low temperature. b) A plausible explanation for the slightly erosion of the *ee* value might be the fact that the minor *E* isomer of **24** forms the (*S*)-allyl alcohol **25**.
- [26] S. Ohta, *Bull. Chem. Soc. Jpn.* **1986**, 59, 1181–1188.

Received: August 17, 2015

Published online: September 29, 2015