Asymmetric Catalysis

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Asymmetric Rhodium-Catalyzed Addition of Thiols to Allenes: Synthesis of Branched Allylic Thioethers and Sulfones**

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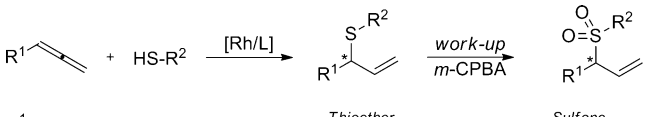
Abstract: *A highly regio- and enantioselective hydrothiolation of terminal allenes, a reaction which fulfills the criteria of atom economy, is reported. Applying two chiral rhodium catalyst systems, a wide variety of thiols and allenes could be coupled. Oxidation gave access to the corresponding allylic sulfones in essentially enantiomerically pure form. The reaction tolerates a variety of functional groups and labeling experiments gave first insights into the reaction mechanism of this new methodology.*

The development of new asymmetric carbon–heteroatom bond-forming reactions which fulfill the criteria of atom economy are of immanent importance to the evolution of chemical synthesis.[1] In this respect we recently developed atom-economic rhodium-catalyzed addition reactions of pronucleophiles to allenes[2] and alkynes,[3] which could be regarded as an atom-economic alternative to the metal-catalyzed allylic substitution[4] and allylic oxidation.[5] These reactions allow highly branched regio- and enantioselective formation of C–O, C–N, and C–C bonds and hence, give direct access to a number of synthetically and medicinally interesting building blocks.[6,7] With the goal to further extend the synthetic utility of this methodology, we became interested in developing a hitherto unknown asymmetric addition of thiols to allenes, which would enable a direct atom-economic entry to α-chiral thioethers[8] and after oxidation, to α-chiral sulfones,[9] both of which are well-known as valuable building blocks in organic synthesis (Scheme 1).[10,11]



R^1: alkyl, carbocyclic
R^2: alkyl, aryl

Scheme 1. Rhodium-catalyzed hydrothiolation of terminal allenes. *m*-CPBA = *m*-chloroperbenzoic acid.

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Furthermore, α-chiral thioethers and sulfones are important structural motifs in natural products and drugs such as Dorzolamide,[12a] Montelukast,[12b] Hepatitis C virus NS3 inhibitors,[12c] and others[13] (Figure 1). The thioether spongiacysteine showed antimicrobial activity against rice blast fungus *Pyricularia oryzae*.[14] Allylic thioethers, and especially the diallylsulfide, are known for their chemopreventive properties in several tumor models.[15]

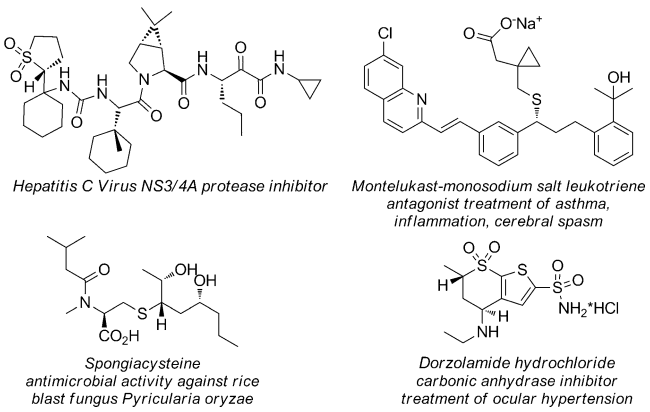
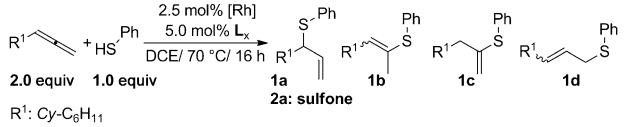


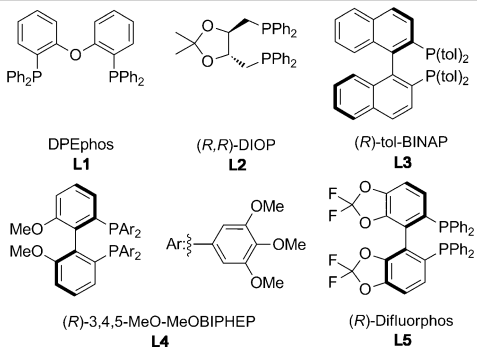
Figure 1. α-Chiral thioethers and sulfones in drugs and natural products.

Although there are several examples for the hydrothiolation of unsaturated C–C bonds towards vinylic thioethers,[16] the direct hydrothiolation of terminal allenes to the branched allylic products is rare.[17] Herein we report the first highly enantioselective rhodium-catalyzed atom-economic hydrothiolation of terminal allenes with free thiols towards branched allylic thioethers and their corresponding sulfones. In initial experiments with cyclohexylallene and thiophenol, we discovered that when employing the nonchiral DPEphos ligand (**L1**) the title reaction did indeed proceed, thus yielding the branched allylic thioether **1a** in good regioselectivity but with moderate yield (Table 1, entry 1). After further optimization (entry 2–5), we were delighted to identify (*R*)-Difluorphos (**L5**) as the best ligand, which performed with increased yield (92%), regioselectivity (>99%), and a satisfying *ee* value of 92% (entry 6). To avoid an isomerization towards the linear isomer, we decided to generate the allylic sulfone **2a** by performing an oxidative work-up with *m*-CPBA.[18,19]

With these optimal catalysts and reaction conditions in hand, we next focused on the scope of thiols (Table 2). We were pleased to find that a number of thiophenol derivatives were excellent reaction partners and gave the corresponding allylic sulfones in good to excellent yields, along with high

Table 1: Ligand screening and optimization.

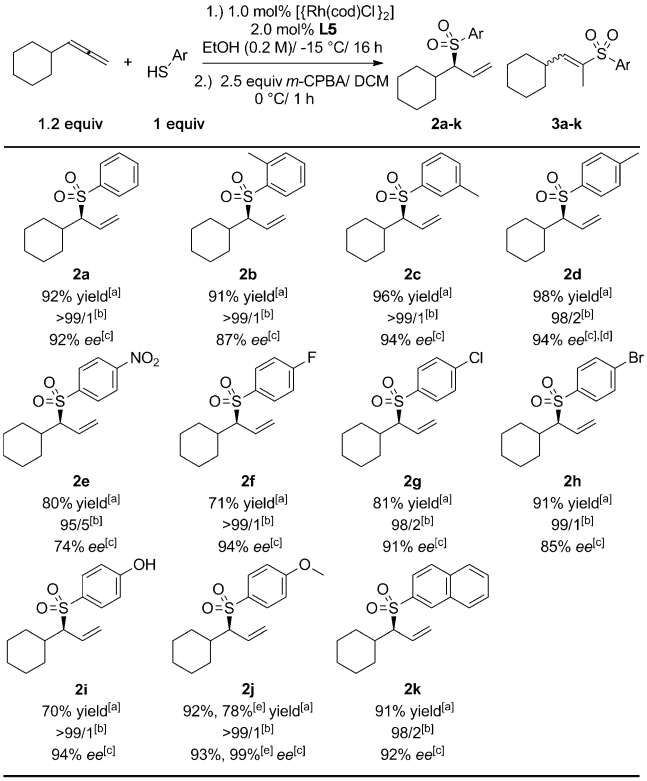




Entry	Ligand	**1a**/**1b**^{E,Z}/**1c**/**1d**[a]	Yield [%][b]	*ee* [%][c]
1	1	82:18:0:0	52	rac.
2	2	> 99:1:0:0	77	4
3	3	70:30:0:0	59	62
4	4	59:39:2:0	62	93
5[d]	4	80:20:0:0	74	90
6[e]	5	> 99:1:0:0	92	92

[a] Regioselectivity determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Combined yield of all product isomers. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Reaction performed in pure EtOH, 0.2 M, 1.2 equiv allene, 10 °C, 16 h, 1.0 mol% [{Rh(cod)Cl}$_2$], 2.0 mol% ligand **L4** and 10 mol% PTSA·H_2O followed by an oxidative work-up with *m*-CPBA. [e] Reaction performed in pure EtOH, 0.2 M, 1.2 equiv allene, −15 °C, 16 h, 1.0 mol% [{Rh(cod)Cl}$_2$], 2.0 mol% ligand **L5** followed by an oxidative work-up with *m*-CPBA. cod = 1,5-cyclooctadiene, DCE = 1,2-dichloroethane.

Table 2: Scope of aromatic thiols with cyclohexylallene.



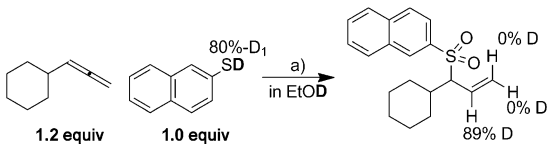
[a] Combined yield of all product isomers. [b] Regioselectivity determined by ^{1}H NMR analysis of crude reaction mixture. [c] The *ee* value was determined by HPLC analysis using a chiral stationary phase. [d] Absolute configuration was determined by comparison of the specific rotation with literature data.[9a] [e] After trituration with *n*-pentane.

regio- and enantioselectivities (**2a**–**k**). For the *o*-methylthiophenol, the *ee* value fell slightly to 87% (**2b**), while excellent enantioselectivities of 94% *ee* each were obtained for *m*- and *p*-methylthiophenol (**2c**–**d**). While the reaction with fluorine, chlorine, and bromine substituents proved compatible, a significant drop in enantioselectivity occurred when applying *p*-nitro-substituted thiophenol (**2e**). Conversely, an electron-donating substituent such as the *p*-methoxythiophenol gave excellent results in both yield and selectivities (**2j**). Upon trituration with *n*-pentane, the sulfone **2j** could be obtained in essentially enantiomerically pure form (99% *ee*) in good yield (78%), thus demonstrating the practicality of this new method for the preparation of enantiopure allylic sulfones. Additionally, naphthalene-2-thiol was an excellent substrate (**2k**). The naphthalene-2-thiol was chosen as the model thiol for the allene screening, since we hoped to increase the chances to obtain crystalline products.

As expected, α-alicyclic allenes were suitable coupling partners in the title reaction, and led to the corresponding allylic sulfones in high yields and enantioselectivities (**4**–**5**; Table 3). Linear-alkyl-substituted allenes also behaved well in terms of yield and enantioselectivties (**6**–**8**). In addition, a benzoate, a silylether and even a free hydroxy group were well-tolerated (**9**–**12**).

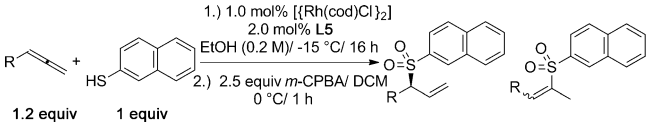
Moreover, aliphatic thiols were explored. Since the aliphatic thioethers are more stable, oxidative work-up was considered unnecessary in these cases. However, under the standard reaction conditions with **L5**, the reaction completely failed. Fortunately, by applying more forcing conditions and employing ligand **L4** good yields and enantioselectivities could be obtained (Table 4). The highest *ee* value of 96% was observed with 2-mercaptoethanol.

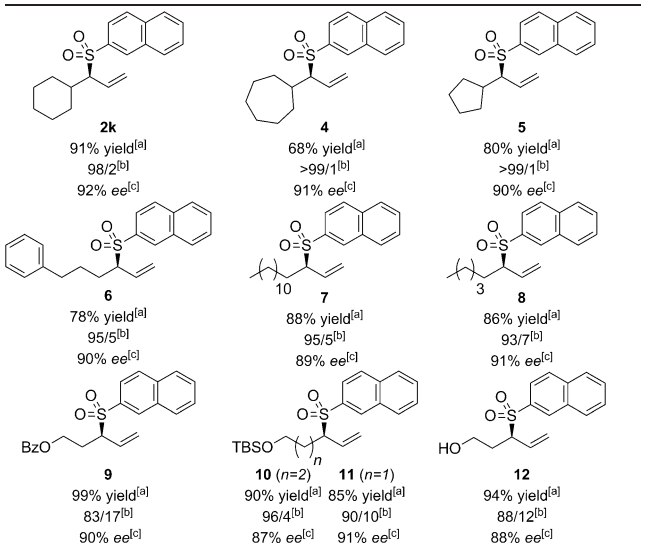
A preliminary investigation of the mechanism was done by deuterium-labeling experiments using [D_1]naphthalene-2-thiol. Based on earlier results with carboxylic acids and anilines we expected deuterium incorporation at all positions of the double bond (Scheme 2).[6a,b]



Scheme 2. Deuterium-labeling experiments with [D_1]naphthalene-2-thiol. a) [{Rh(cod)Cl}$_2$] (1.0 mol%), (*R*)-Difluorphos (2.0 mol%), solvent 0.2 M, −15 °C, 16 h, then work-up with *m*-CPBA. Incorporation of deuterium was determined by ^{1}H NMR spectroscopy and mass spectrometry (see the Supporting Information for further details).

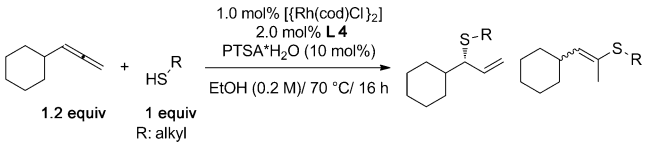
Table 3: Scope of terminal allenes using naphthalene-2-thiol.

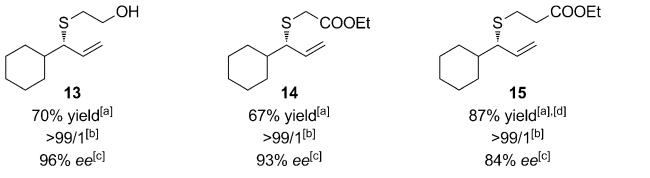




[a] Combined yield of all product isomers. [b] Regioselectivity determined by ^{1}H NMR analysis of crude reaction mixture. [c] The *ee* value was determined by HPLC analysis using a chiral stationary phase. Bz = benzoyl, TBS = *tert*-butyldimethylsilyl.

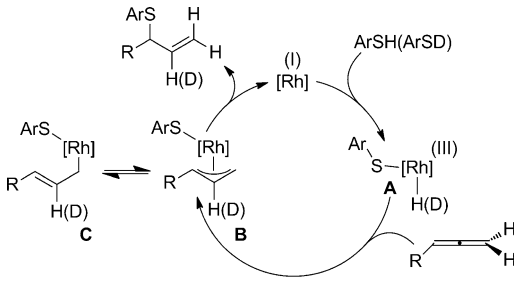
Table 4: Asymmetric hydrothiolation with aliphatic thiols.



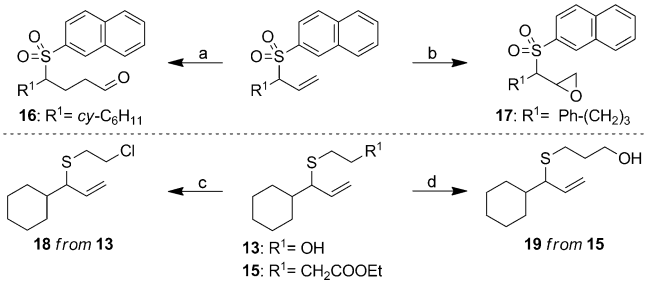


[a] Yield of isolated product. [b] Regioselectivity determined by ^{1}H NMR analysis of crude reaction mixture. [c] The *ee* value was determined by HPLC analysis using a chiral stationary phase. [d] Starting from the corresponding 3-mercaptopropionic acid an in situ esterification occurred, where *ee* values of 86% were obtained. PTSA = *p*-toluenesulfonic acid.

Interestingly, we found deuterium incorporation exclusively at the 2-position of the allylic sulfone, and it suggests the mechanism depicted in Scheme 3. An oxidative addition of the thiol forms the Rh^{III} species **A**.[16j] Here, in contrast to previous observations, an exclusive hydrometalation of the more substituted double bond of the allene will deliver the π-allyl complex **B** which might be in equilibrium with the σ-allyl isomer **C**.[20] The product is likely to be formed from **B** either by reductive elimination, or by an intermolecular attack of a second thiolate.



Scheme 3. Plausible mechanism for the rhodium-catalyzed hydrothiolation.



Scheme 4. Functionalization of branched allylic sulfones and thioethers. a) $[Rh(CO)_2acac]$ (0.5 mol%), 6-DPPon (10 mol%), H_2/CO (1:1), 20 bar, toluene, 80 °C, 20 h, linear/branched > 98%, yield: 94%. b) DCE, *m*-CPBA, 80 °C, 16 h, yield: 89%, d.r. = 2.3:1.0. c) Et_2O, $SOCl_2$, yield: 86% d) Et_2O, $LiAlH_4$, HCl 1 M, yield: 78%. acac = acetylacetonate.

To explore the possible functionalization of the allylic sulfones, we performed a variety of different transformations (Scheme 4). The hydroformylation of the terminal double bond using our self-assembling 6-diphenylphosphinopyridone (6-DPPon) hydroformylation catalyst led to the aldehyde **16** in an excellent linear/branched selectivity of greater than 98% with a 94% yield.[21] Reaction with *m*-CPBA furnished the corresponding epoxide **17** in good yield of 89% (d.r. = 2.3:1.0). Additionally, the functionalization of the thioether part was explored. Hence, the primary alcohol **13** was successfully transformed into the corresponding chloride **18** in 86% yield by using thionyl chloride. Reduction of the ethyl ester **15** with $LiAlH_4$ resulted in thioether **19** with 78% yield.

In conclusion, we have developed a highly regio- and enantioselective hydrothiolation of terminal allenes which fulfills the criteria of atom economy. Applying two chiral rhodium catalyst systems, a wide variety of thiols and allenes could be coupled. Oxidation gave access to the corresponding allylic sulfones in enantiomerically pure form. The reaction tolerates a variety of functional groups and labeling experiments gave first insights into the reaction mechanism of this new methodology. Further mechanistic investigations and extension of the methodology to more complex thiols and allenes are ongoing.

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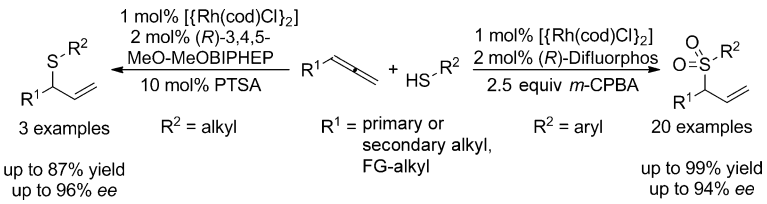
Communications

Asymmetric Catalysis

A. B. Pritzius, B. Breit* _____ ■■■–■■■

Asymmetric Rhodium-Catalyzed Addition of Thiols to Allenes: Synthesis of Branched Allylic Thioethers and Sulfones



All about S: The rhodium-catalyzed enantioselective hydrothiolation of terminal monosubstituted allenes with aromatic and functionalized aliphatic thiols permits the atom-economic synthesis of valuable branched allylic thioethers and sulfones in high regio- and enantioselectivity. By varying the ligand and reaction conditions both aromatic and aliphatic thiols were tolerated.