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Rhodium-Catalyzed Asymmetric Ring Opening of Oxabicyclic Alkenes with Sulfur Nucleophiles

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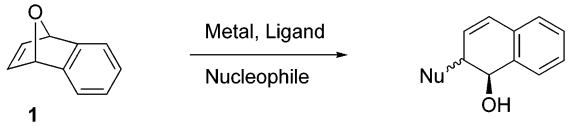
Abstract: The synthesis of 2-sulfanyl-1,2-dihydro-naphthalen-1-ols is described. This methodology is based on rhodium catalysis and enables various thiols to undergo an asymmetric S_N2' ring opening of oxabenzonorbornadiene. Under the reaction conditions ($[Rh(COD)Cl]_2$ (2.5 mol %), (*S*)-(*R*)-PPF-P^{t}Bu$_2$ (6 mol %), AgOTf (7 mol %), NH_4I (1.7 equiv), galvinoxyl (5 mol %), THF, 85 °C), aryl- and alkylsulfide adducts are obtained in good to excellent yield and in high enantiomeric excess (>90% ee).

Transition metal sulfur chemistry is prevalent in both biological systems and industrial applications. Here, the metal-sulfide component is an essential part for bioactivity in enzymes such as ferredoxin and nitrogenase, as well as in industrial technologies such as corrosion and lubrication.[1] However, the affinity of sulfur to form strong bonds with transition metals invariably complicates catalytic reactions. Consequently, there are very few reports of transition-metal-catalyzed reactions involving thiols,[2] in particular, those used to form C−S bonds.[3]

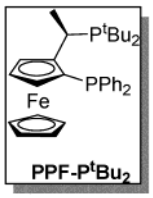
Our group has a long-standing interest in metal-catalyzed desymmetrization reactions of meso compounds as a strategy to generate stereocenters in a single enantio-determining step.[4] Depending on the metal, these reactions include addition of nucleophiles such as hydride, stabilized and nonstabilized carbanions, alcohols, amines, and carboxylates.[5] Particular attention has been placed on the desymmetrization of oxobenzonorbornadiene **1**, as the products are precursors to the medicinally important tetrahydronaphthalene moiety (Scheme 1).[6]

SCHEME 1



1

TABLE 1. Effect of Halide/Protic Additives on Enantioselectivity[a]



entry	nucleophile	additive	% ee[b]
1	thiophenol		38
2	thiophenol	TBAF	36
3	thiophenol	NH_4F	51
4	thiophenol	TBABr	64
5	thiophenol	NH_4Br	50
6	thiophenol	TBAI	80
7	thiophenol	NH_4I	88
8	thiophenol	NH_4I[c]	94

[a] Conditions: 2.5 mol % $[Rh(COD)Cl]_2$, 6 mol % ligand, 1.5 equiv of nucleophile, 2 equiv of halide additive, in 0.1 M THF. For typical conditions see Supporting Information. [b] ee was determined by CSP HPLC with a Chiracel OD column. [c] Prior to the addition of reagents, a halide exchange was performed; see Supporting Information for experimental details.

In contrast to our previous studies, the high polarizability and redox capability of sulfur-containing nucleophiles make them more prone to catalyst poisoning and background reactions. Herein, we report methodology that overcomes these obstacles and enables a highly enantioselective nucleophilic addition of thiols to oxabenzonorbornadiene **1** in good to excellent yield.

Our previous efforts in the asymmetric ring opening of **1** with oxygen- and nitrogen-based nucleophiles utilized $[Rh(COD)Cl]_2$ in combination with an electron-rich Josiphos-type ligand, PPF-P^{t}Bu$_2$.[5] From this starting point, screening of catalyst systems revealed that both the halide counterion and the protic additive dramatically affected the enantioselectivity of the desymmetrization reaction.[7] An increase in enantioselectivity was observed in changing the halide from F → Cl → Br → I (Table 1);[8] with triflate as a counterion, an intractable mixture of products was obtained. Furthermore, the protic nature of the ammonium halide additive proved beneficial,

(1) Stiefel, E. I.; Matsumoto, K. *Transition Metal Sulfur Chemistry: Biological and Industrial Significance*; ACS Symposium Series 653; American Chemical Society: Washington, DC, 1996.

(2) (a) Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* **2003**, *125*, 6624−6625. (b) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803−2806.

(3) (a) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517−3520. (b) Adam, W.; Bargon, R. M.; Bosio, S. G.; Schenk, W. A.; Stalke, D. *J. Org. Chem.* **2002**, *67*, 7037−7041. (c) Jacob, J.; Reynolds, K. A.; Jones, W. D. *Organometallics* **2001**, *20*, 1028−1031. (d) Kanemasa, S.; Oderaotoshi, Y.; Wada, E. *J. Am. Chem. Soc.* **1999**, *121*, 8675−8676. (e) Zhang, X.; Ma, M.; Wang, J. Catalytic Asymmetric S−H Insertion Reaction of Carbenoids. *ARKIVOC Gainsville, FL, U.S.* **2003**, *2*, 84−91.

(4) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48−58.

(5) (a) Lautens, M.; Rovis, T. *J. Org. Chem.* **1997**, *62*, 5246−5247. (b) Lautens, M.; Hiebert, S.; Renaud, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 6834−6839. (c) Lautens, M.; Fagnou, K.; Rovis, T. *J. Am. Chem. Soc.* **2000**, *122*, 5650−5651. (d) Lautens, M.; Fagnou, K.; Taylor, M. *Org. Lett.* **2000**, *2*, 1677−1679. (e) Lautens, M.; Fagnou, K. *Tetrahedron* **2001**, *57*, 5067−5072. (f) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311−1314.

(6) (a) Snyder, S. E.; Aviles-Garay, F. A.; Chakraborti, R.; Nichols, D. E.; Watts, V. J.; Mailman, R. B. *J. Med. Chem.* **1995**, *38*, 2395−2409. (b) Kamal, A.; Gayatri, N. L. *Tetrahedron Lett.* **1996**, *37*, 3359−3362. (c) Kim, K.; Guo, Y.; Sulikowski, G. A. *J. Org. Chem.* **1995**, *60*, 6866. (d) Perrone, R.; Berardi, F.; Colabufo, N. A.; Leopoldo, M.; Tortorella, V.; Fiorentini, F.; Olgiati, V.; Ghiglieri, A.; Govoni, S. *J. Med. Chem.* **1995**, *3*, 8, 942−949.

(7) For halide effects in transition metal catalyzed reactions, see: (a) Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26−47. (b) Lautens, M.; Fagnou, K. *J. Am. Chem. Soc.* **2001**, *123*, 7170−7171.

(8) This trend in enantioselectivity is different than that observed for oxygen- and nitrogen-based nucleophiles; see ref 7b.

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SCHEME 2

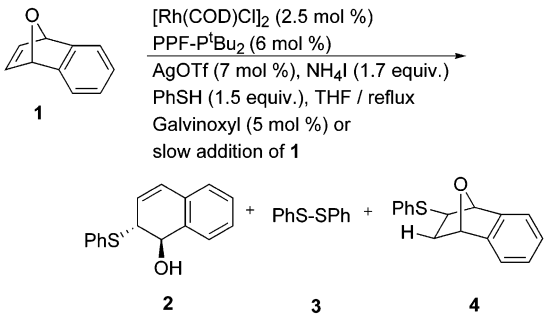
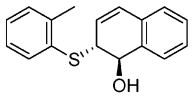
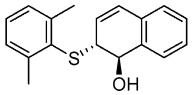
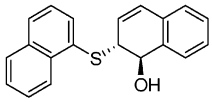
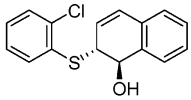
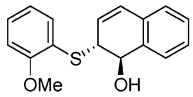
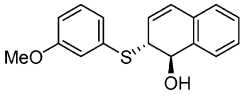
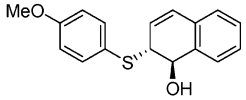
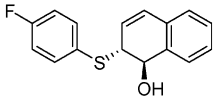
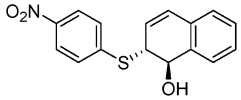


TABLE 2. Scope of Aryl Thiol Ring Opening Reactions[a]

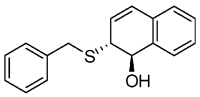
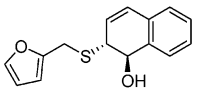
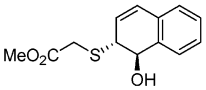
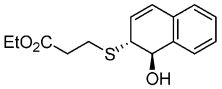
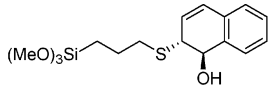
Entry	Product		Yield (%)[b]	% ee[c]
1		**5**	92	93
2		**6**[d]	79	98
3		**7**	66	92
4		**8**	91	91
5		**9**	65	95
6		**10**	75	94
7		**11**	81	92
8		**12**	90	90
9		**13**	88	96

[a] Conditions: 2.5 mol % $[Rh(COD)Cl]_2$, 6 mol % PPF-P^{t}Bu$_2$, 7 mol % AgOTf, 1.7 equiv of NH_4I, 1.5 of equiv nucleophile, 5 mol % galvinoxyl or slow addition of **1**, in 0.1 M THF. For typical conditions see Supporting Information. [b] Isolated yield. [c] ee was determined by CSP HPLC with a Chiracel OD column. [d] *trans* stereochemistry was determined by X-ray crystallography of compound **6**. The absolute configuration in product **6** is (*S*,*S*) using the (*S*)-(*R*)-PPF-P^{t}Bu$_2$ Josiphos-type ligand.

giving 88% ee using thiophenol as the nucleophile in the presence of NH_4I. Additional improvement to 94% ee could be achieved via a halide exchange protocol, where the initial chloride counterion is first sequestered by AgOTf and subsequently replaced by an iodide counterion (NH_4I).

Despite a catalyst system that induces high enantioselectivity, the reaction conditions were not synthetically

TABLE 3. Scope of Aliphatic Thiol Ring Opening Reactions[a]

Entry	Product		Yield (%)[b]	% ee[c]
1		**14**	75	96
2		**15**	52	96
3		**16**	63	97
4		**17**	64	96
5		**18**	64	95

[a] Conditions: 2.5 mol % $[Rh(COD)Cl]_2$, 6 mol % PPF-P^{t}Bu$_2$, 7 mol % AgOTf, 1.7 equiv of NH_4I, 1.5 equiv of nucleophile, 5 mol % galvinoxyl or slow addition of **1**, in 0.1 M THF. For typical conditions see Supporting Information. [b] Isolated yield. [c] ee was determined by CSP HPLC with a Chiracel OD column.

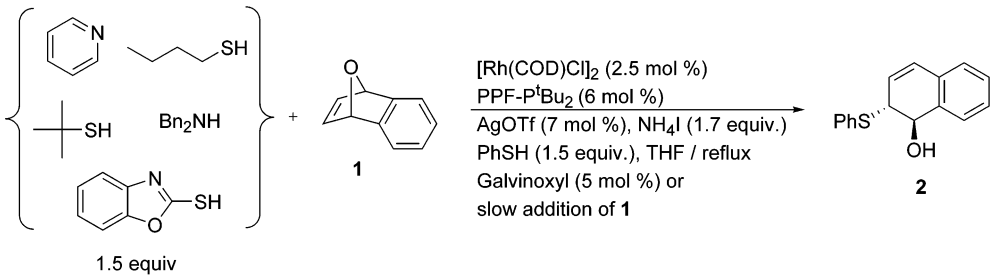
efficient, giving a 50% yield at complete conversion. Careful analysis showed the remaining material to be a mixture composed of 1-naphthol, disulfide **3**, and addition product **4**. Sulfide **4**, which forms in the absence of catalyst, was shown to be racemic. Suppression of this background reaction could be achieved by controlling the rate of substrate addition and/or addition of a radical inhibitor; galvinoxyl proved to be the most effective radical inhibitor in comparison to BHT and BHA. Moreover, addition of the thiol to the reaction flask prior to the catalyst minimized the production of 1-naphthol. Together, these modifications gave the desired product **2** in 92% yield and 94% ee (Scheme 2). Upon scale-up, the catalyst loading could be reduced to 2 mol % Rh with no adverse effect on enantioselectivity.

Substituted aromatic thiols were then examined to determine their effect on reactivity and enantioselectivity. Despite varying steric and electronic properties, the enantioselectivity remained consistently above 90% ee, reaching up to 98% ee in some cases (entry 2, Table 2). In contrast, reactivity was influenced by the nature of the nucleophile. Electron-rich aromatic thiols generally gave lower yields than their electron-poor counterparts, in addition to requiring longer reaction times. In the case of a sterically encumbered aryl thiol such as 2,6-dimethylthiophenol, a lower yield relative to the unsubstituted case was obtained, albeit in 98% ee.

Subsequent extension to aliphatic thiols also provided the products in high ee, albeit in lower yield (Table 3). Functionalized aliphatic thiols gave the desired sulfide adducts in good yield. Using a radical inhibitor in conjunction with slow addition of the substrate gave significantly higher yields (e.g., entry 5, Table 3; 42% → 64% yield). All further attempts to increase the reaction yield by modifying catalyst loading, temperature, solvent, radical inhibitor, and thiol equivalents were unsuccessful.

The apparent lack of reactivity for other thiols was initially attributed to catalyst poisoning.[9] However,

SCHEME 3. Competition Studies between Unreactive Nucleophiles and Thiophenol



competition studies refuted this possibility, as a competent nucleophile such as thiophenol, when mixed in a 1:1 equivalent ratio with an unreactive nucleophile, gave the desired sulfide product **2** (Scheme 3). Thiobenzoic and thioacetic acid are exceptions to these results, as they decomposed the acid sensitive substrate.

Empirically, a competent thiol nucleophile in this desymmetrization reaction requires a pK_a less than 16 but greater than 5.[10] This correlation between reactivity and S−H bond strength may be indicative of the ease of oxidative addition and/or the stability of a thiolate-hydrido metal complex.[11]

In summary, we have extended the desymmetrization of oxobenzonorbornadiene **1** to include sulfur nucleophiles. Using halide and protic additives, radical inhibitors, and slow addition of substrate, we were able to produce sulfide derivatives of the dihydronaphthalene scaffold in good to excellent yield, with high enantiomeric excess. Application of these scaffolds to generate ligands and further elaboration to natural products are currently under investigation.

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Supporting Information Available: Experimental procedures for the rhodium-catalyzed ring-opening reactions, crystallographic data and ORTEP diagram for the X-ray structure of compound **6**, and characterization data for all new compounds, including ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) In cases where the sulfide adduct did not form, the predominant product was 1-naphthol.

(10) Referenced to DMSO. For pK_a's of various thiols, see http://www.chem.wisc.edu/areas/reich/pkatable/index.htm

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