ACS Catalysis
Letter
pubs.acs.org/acscatalysis

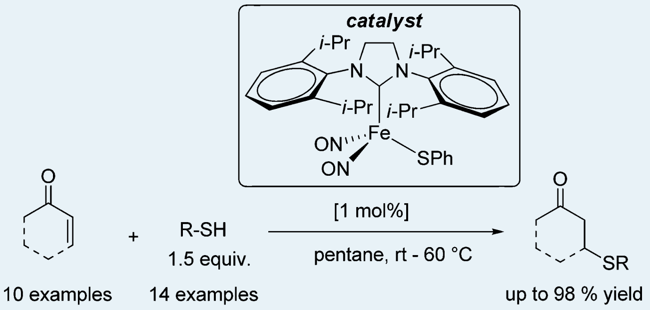
Mild Hydrosulfenylation of Olefins under Neutral Conditions Using a Defined NHC-Ligated Iron–Sulfur Catalyst

Isabel Alt, Philipp Rohse, and Bernd Plietker*

Institut für Organische Chemie, Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany

Supporting Information

ABSTRACT: A defined NHC-Fe–S complex proved to be an efficient catalyst for the selective hydrosulfenylation of *α*,*β*-unsaturated ketones or vinylnitriles. A wide range of different aliphatic thiols were transferred in this atom-economic reaction into the corresponding thioethers. Mild reaction conditions, equimolar amounts of substrates, low catalyst loadings, and mild reaction conditions are characteristic for this transformation.



KEYWORDS: *iron, sulfur, catalysis, addition, carbene ligand*

The development of catalytic methods for a selective formation of C–S bonds represents a major challenge in organometallic catalysis. For a long time, organic compounds possessing sulfur in a low oxidation state were considered to coordinate irreversibly to the metal center and, hence, inhibit its catalytic activity.[1] Within the past years, the field of catalytic sulfenylations has faced an almost explosive development. Catalytic aromatic[2] or allylic[3] sulfenylations and hydrosulfenylations have been reported that complement the organic chemist's C–S-bond-forming toolbox.[4]

Within the portfolio of C–S-bond-forming processes, the 1,4-addition of thiols to *α*,*β*-unsaturated ketones or aldehydes occupies an important place. Various metal-catalyzed conjugate additions of thiols have been reported in the literature.[5] In most of these transformations, the catalyst acts as a Lewis acid and activates the olefin. In the vast majority of methods, activated (acidic) aromatic or benzylic thiols were employed. Gunnoe and co-workers reported a new catalytic scenario in which a monomeric mercapto copper–NHC complex was used for a metal-to-olefin transfer of the mercapto ligand with "anti-Markovnikov" selectivity.[6]

Recently, the group of Darensbourg[7] and our group[8] reported the structure of a NHC–Fe–S complex in which the metal occupies a formal oxidation state of −1. This unusual electronic configuration and the potential of these complexes to be active in a direct metal-to-olefin mercapto transfer inspired us to initiate a project on Fe-catalyzed[9] hydrosulfenylations. Herein, we report these complexes are highly active in the direct catalytic 1,4-addition of aromatic and aliphatic thiols to olefins.

We initiated our studies with a screening of different NHC–Fe–S complexes in the conjugate addition of benzylmercaptan to cyclohexenone (Table 1).

Already, initial experiments using Gunnoe's conditions[6] indicated the catalysts **4** and **5** to be active in the direct conjugate addition reaction (entries 2 and 3, Table 1). Thiophenol-derived catalyst **5** was chosen for the subsequent optimization study due to its higher stability. Even at a catalyst loading of 1.25 mol %, good conversion rates were observed (entry 5, Table 1). The solvent had a profound effect on the reactivity. Polar solvents turned out to be not suitable for this type of catalysis. Pentane proved to be the solvent of choice that allowed an efficient hydrosulfenylation at temperatures of about 60 °C (entry 14, Table 1).

With this result in hand, we set out to explore the scope of potential Michael acceptors (Table 2).

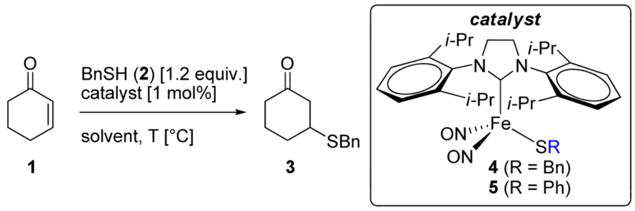
Various *α*,*β*-unsaturated cyclic and acyclic ketones proved to be reactive. Using benzylmercaptan in slight excess, good to excellent yields were obtained. Even the 2-fold addition to ketones **8** and **10** gave the desired bis-sulfenylated products **9** and **11** in high yields, albeit as a mixture of stereoisomers (entries 2 and 3, Table 2). Substituents at both the *α*- and the *β*-positions within the Michael acceptor are tolerated. Even acrylnitrile **20** proved to be reactive (entry 8, Table 2). Nonactivated olefins such as styrene or 1-octene, however, did not show significant conversion under the given reaction conditions.

Furthermore, the transformation is also applicable to a broad spectrum of different thiols (Table 3).

Both aromatic and aliphatic thiols are reactive. The reaction displays good functional group tolerance. Free hydroxyl groups, siloxanes, heterocycles, and even cysteine derivatives are S-

Received: August 23, 2013
Revised: November 11, 2013
Published: November 13, 2013

Table 1. Temperature and Solvent Effects in Fe-Catalyzed Hydrosulfenylation[a]

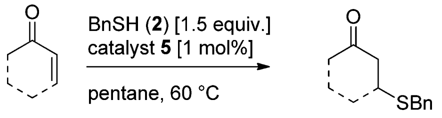


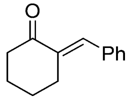
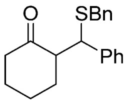
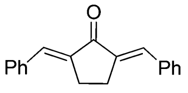
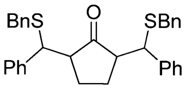
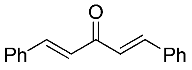
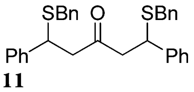
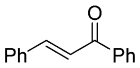
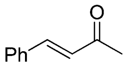
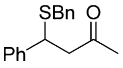
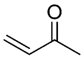
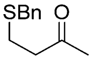
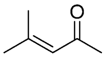
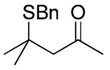
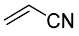
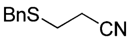
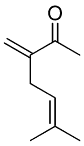
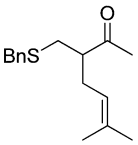
1 3

entry	catalyst	solvent	T (°C)	conversion (%)
1		benzene	80	– (86)[b]
2	**4** (5)	benzene	80	88
3	**5** (5)	benzene	80	91
4	**5** (2.5)	benzene	80	90
5	**5** (1.25)	benzene	80	64
6	**5** (0.5)	benzene	80	29
7	**5** (1)	THF	80	4
8	**5** (1)	1,4-dioxane	80	31
9	**5** (1)	CH_3CN	80	0
10	**5** (1)	CH_2Cl_2	80	0
11	**5** (1)	DMF	80	18
12	**5** (1)	MTBE	80	81
13	**5** (1)	heptane	80	85
13	**5** (1)	pentane	80	93
14	**5** (1)	pentane	60	92
15	**5** (1)	pentane	40	41
16	**5** (1)	pentane	rt	5

[a] The reactions were performed on a 0.3 mmol scale, using Fe catalyst, cyclohexenone (1 equiv) and BnSH (1.2 equiv) in 0.5 mL of solvent for 1 h under the conditions given in Table 1. [b] The number in brackets refers to the conversion of the uncatalyzed transformation after 24 h.

Table 2. The Fe-Catalyzed Hydrosulfenylation: Enone Scope[a]



entry	substrat	product	yield [%][b]
1	 **6**	 **7**	87
2	 **8**	 **9**	69
3	 **10**	 **11**	96
4	 **12**	 **13**	64
5	 **14**	 **15**	61
6	 **16**	 **17**	94
7	 **18**	 **19**	76
8	 **20**	 **21**	88
9	 **22**	 **23**	59

[a] The reactions were performed on a 0.5 mmol scale, using Fe catalyst (1 mol %), enone (1 equiv), and BnSH (1.5 equiv) in 1 mL of pentane for 18 h. [b] Isolated yield.

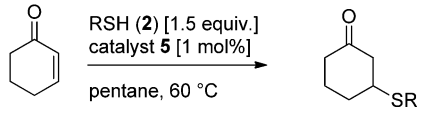
alkylated in good to excellent yields. No side products were observed.

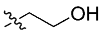
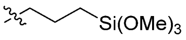
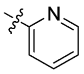
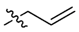
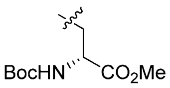
Although a variety of thiols are commercially available, their use in large scale is hampered for olfactory reasons and their oxidation sensitivity. To address some of these problems, we finally set out to develop an odorless alternative by employing thiosaccharose **38** as a nucleophile.[10] Treatment of this compound with allylbromide **39** results in clean formation of the corresponding thioether **40** (eq 1 in Scheme 1). This compound has been reported to be a suitable thiol synthon. Gratifyingly, the in situ liberation of the thiol using piperidine as a base in the presence of the Fe catalyst and cyclohexenone as the acceptor substrate led to the clean formation of hydrosulfenylation product **41** (eq 2 in Scheme 1).

From a mechanistic point of view, different pathways appear reasonable. To shed some light into this open question, various test experiments were performed. Darensbourg was able to show that complexes such as **5** are able to undergo a ligand exchange using CO gas with generation of disulfide.[7b] This report is significant because it shows that the Fe–S bond should be considered as a covalent σ-bond that is cleaved homolytically. With regard to our transformation, this finding excludes a simple anionic Michael-type addition of a thiolate to be operative. Two different mechanistic pathways remain to be considered. A homolytic cleavage of the Fe–S bond with concomitant addition of a thiyl radical could be excluded because the addition of various radical scavengers such as BHT (2,6-di-*t*-butyl-4-methyl phenol) or TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxide) did slow down the reaction as a result of catalyst decomposition, but no trapping of either a thiyl radical or a C radical was observed. Furthermore, we employed 50 mol % of catalyst **5** in the addition of benzylmercaptan to cyclohexenone and followed the formation of the two resulting products **24** and **28** over time (Figure 1).

From this experiment, it is obvious that a metal-to-carbon transfer of the sulfur ligand takes place. A competing exchange of the thiophenyl for the thiobenzyl ligand in a stoichimetric experiment was not observed. Furthermore, after full conversion of complex **5**, the corresponding thiobenzyl complex **4** was isolated out of the reaction mixture in 38% yield. These results led us to propose the following mechanistic picture (Figure 2). Due to Because of the low anionic character of the mercapto ligand in complex **5** and the fact that the thio

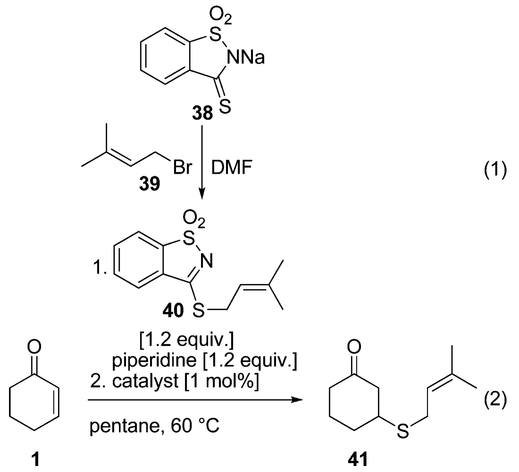
Table 3. The Fe-Catalyzed Hydrosulfenylation: Thiol Scope[a]



Entry	Product	T [°C]	yield [%][b]
1	**24** (R = C_6H_5)	40	94
2	**25** (R = pF-C_6H_4)	40	74
3	**26** (R = pMeO-C_6H_4)	40	98
4	**27** (R = 3,5-$(CH_3)_2C_6H_3$)	40	86
5	**28** (R = $CH_2C_6H_5$)	60	97
6	**29** (R = $CH_2CH_2C_6H_5$)	40	88
7	**30** (R = $(CH_2)_{11}CH_3$)	60	96
8	**31** (R = $(CH_2)_2CH_3$)	40	81
9	**32** (R = cyclohexyl)	60	89
10	 OH **33**	60	79
11	 Si(OMe)3 **34**	40	81
12	 N **35**	60	96
13	 **36**	60	79
14	 BocHN CO2Me **37**	60	83

[a]The reactions were performed on a 0.5 mmol scale, using Fe catalyst (1 mol %), cyclohexenone (1 equiv), and thiol (1.5 equiv) in 1 mL of pentane for 18 h under the conditions given in Table 2. [b]Isolated yield.

Scheme 1. Odorless Fe-Catalyzed Hydrosulfenylation of Olefins



transfer occurs from the metal to the olefin, a concerted neutral metallosulfenylation mechanism appears to us as the most probable explanation of the experimental results.

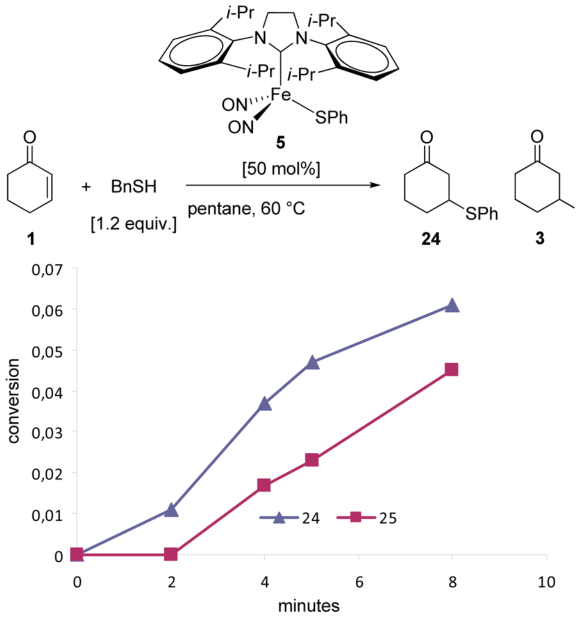


Figure 1. Competition experiment.

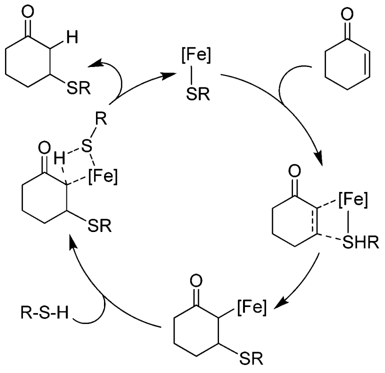


Figure 2. Mechanistic proposal.

In summary, we were able to show that defined Fe–NHC–mercapto complexes are highly active catalysts for the direct hydrosulfenylation of polar C=C double bonds. At slightly elevated temperatures, a variety of different olefins react with aliphatic (and aromatic)-functionalized thiols in good to excellent yields under otherwise neutral reaction conditions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, spectroscopic data, copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: bernd.plietker@oc.uni-stuttgart.de.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) (a) Hegedus, L. L.; McCabe, R. W. *Catalyst Poisoning*; Marcel Dekker: New York, 1984. (b) Hutton, A. T. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon Press: Oxford, UK, 1984, Vol 5, p 1151.

(2) Aromatic sulfenylations and hydrosulfenylations (a) Iron: (i) Correa, A.; Carril, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 2880−2883. (ii) Wu, J.-R.; Lin, C.-H.; Lee, C.-F. *Chem. Commun.* **2009**, 4450−4452. (b) Silica: Chen, C.-K.; Chen, Y.-W.; Lin, C.-H.; Lin, H.-P.; Lee, C.-F. *Chem. Commun.* **2010**, *46*, 282−284. (c) Palladium: Fernández-Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180−2181.

(3) Allylic sulfenylations and hydrosulfenylations: (a) Iridium: Zheng, S.; Gao, N.; Liu, W.; Liu, D.; Zhao, X.; Cohen, T. *Org. Lett.* **2010**, *12*, 4454. (b) Palladium: (i) Goux, C.; Lohste, P.; Sinou, D. *Tetrahedron Lett.* **1992**, *33*, 8099. (ii) Goux, C.; Lohste, P.; Sinou, D. *Tetrahedron Lett.* **1994**, *34*, 10321. (iii) Frank, M.; Gais, H.-J. *Tetrahedron: Asymmetry* **1998**, *9*, 3353. (iv) (i) Gais, H.-J.; Jagusch, T.; Spalthoff, N.; Gerhards, F.; Frank, M.; Raabe, G. *Chem.—Eur. J.* **2003**, *9*, 4202. (c) Ruthenium: Zaitsev, A. B.; Caldwell, H. F.; Pregosin, P. S.; Veiros, L. F. *Chem.—Eur. J.* **2009**, *15*, 6468. (d) Iron: Lin, Y.-Y.; Wang, Y.-J.; Lin, C.-H.; Cheng, J.-H.; Lee, C.-F. *J. Org. Chem.* **2012**, *77*, 6100−6106. (e) Gao, N.; Zheng, S.; Yang, W.; Zhao, X. *Org. Lett.* **2011**, *13*, 1514. (f) A review is found in Liu, W.; Zhao, Y. *Synthesis* **2013**, 2051.

(4) Reviews: (a) C,S bond formation in biological systems: Fontecave, M.; Ollagnier-De-Choudens, S.; Mulliez, E. *Chem. Rev.* **2003**, *103*, 2149. (b) "Click"-type chemistry using thiols: Hoyle, C. E.; Lowe, A. B.; Bowman, C. N. *Chem. Soc. Rev.* **2010**, *39*, 1355. (c) *Science of Synthesis: Category 5, Compounds with One Saturated Carbon Heteroatom Bond. Sulfur, Selenium, and Tellurium*; Kambe, N., Aleman, J., Eds.; Thieme-Verlag: Stuttgart, Germany, 2008. (d) Metal-catalyzed C,S bond formations: Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205.

(5) (a) Copper: Garg, S. K.; Kumar, R.; Chakraborti, A. K. *Tetrahedron Lett.* **2005**, *46*, 1721−1724. (b) Nickel: Kanemasa, S.; Oderaotoshi, Y.; Wada, E. *J. Am. Chem. Soc.* **1999**, *121*, 8675−8676. (c) For a review on sulfa-Michael additions, see: Enders, D.; Lüttgen, K.; Narine, A. A. *Synthesis* **2007**, 959 see also refs 2 and 3.

(6) Delp, S. A.; Munro-Leighton, C.; Goj, L. A.; Ramírez, M. A.; Gunnoe, T. B.; Petersen, J. L.; Boyle, P. D. *Inorg. Chem.* **2007**, *46*, 2365−2367.

(7) (a) Hsieh, C.-H.; Darensbourg, M. Y. *J. Am. Chem. Soc.* **2010**, *132*, 14118−14125. (b) Pulukkody, R.; Kyran, S. J.; Bethel, R. D.; Hsieh, C.-H.; Hall, M. B.; Darensbourg, D. J.; Darensbourg, M. Y. *J. Am. Chem. Soc.* **2013**, *135*, 8423−8430.

(8) Holzwarth, M. S.; Frey, W.; Plietker, B. *Chem. Commun.* **2011**, *47*, 11113−11115.

(9) For monographs on iron catalysis, see: (a) *Iron Catalysis: Fundamentals and Applications: 33 (Topics in Organometallic Chemistry)*; Plietker, B., Ed.; Springer: Berlin, 2010, Vol. *1*. (b) *Iron Catalysis in Organic Chemistry: Reactions and Applications*; Plietker, B., Ed.; Wiley-VCH: Weinheim, 2008, Vol. *1*. For selected reviews on iron catalysis,see: (c) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217−6254. (d) Correa, A.; Mancheno, O. G.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108−1117. (e) Czaplik, W. M.; Mayer, M.; Cvengros, J.; Jacobi von Wangelin, A. *ChemSusChem* **2009**, *38*, 396−417. (f) Morris, R. H. *Chem. Soc. Rev.* **2009**, *38*, 2282−2291. (g) Darwish, M.; Wills, M. *Catal. Sci. Technol.* **2012**, *2*, 243−255. For an account,see: (h) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500−1511.

(10) Yamada, H.; Kinoshita, H.; Inomata, K.; Kotake, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 949−950.