

Ligand-Free Ni-Catalyzed Reductive
Cleavage of Inert Carbon–Sulfur Bonds

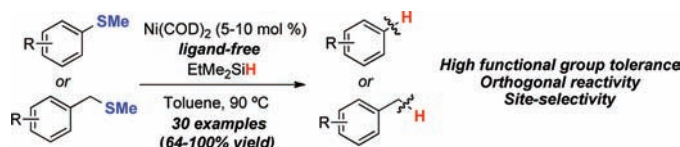
Nekane Barbero and Ruben Martin*

Institute of Chemical Research of Catalonia (ICIQ), Av Paisos Catalans 16, 43007,
Tarragona, Spain

rmartinromo@iciq.es

Received December 13, 2011

ABSTRACT



A catalytic reductive cleavage of C(sp²)– and C(sp³)–SMe bonds under ligandless conditions is presented. The method is characterized by its wide scope and high chemoselectivity profile including challenging substrate combinations, allowing the design of orthogonal and site-selectivity approaches.

The discovery of new catalytic methods for activating inert molecular bonds constitutes one of the most active areas of research in modern organic chemistry.¹ These methods provide unique strategies for converting rather ubiquitous and unreactive motifs into valuable molecules. Despite recent advances, particularly in the field of C–H bond functionalization, the development of procedures for C–heteroatom bond functionalization has received much less attention.^{2,3}

Although carbon–sulfur bonds are inherently disposed to cross-coupling reactions, the strong affinity of sulfur atoms to metal centers constitutes a significant barrier for further functionalization.^{3,4} Among all aryl sulfides, the use of aryl methyl thioethers (ArSMe) would be especially attractive as coupling counterparts due to the fact that (a)

ArSMe are the simplest derivatives from thiophenols (ArSH) and (b) the use of ArSMe electrophiles is much more atom economical than other ArSR motifs (R ≠ Me) described in the literature.⁵ Still, however, the development of coupling reactions with *unactivated* C–SMe bonds⁶ has been less explored, and few examples have been reported in this regard.⁷

Particularly interesting would be the development of a catalytic reductive cleavage of *unactivated* C–SMe bonds, thus opening up the possibility of using aryl sulfides as temporary removable directing groups⁸ in organic synthesis (Scheme 1). To the best of our knowledge, such a procedure can only be carried out with *stoichiometric amounts* of highly reactive Grignard reagents possessing β -hydrogens⁹ or with a large excess of Raney Nickel¹⁰ as reducing agents (Scheme 1, path a), thus drastically

(1) Murai, S. Activation of unreactive bonds and organic synthesis. *Topics in Organometallic Chemistry*; Springer-Verlag: Berlin, 1999.

(2) For recent reviews on C–O bond activation: (a) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346. (b) Li, B.-J.; Yu, D.-G.; Sun, C.-L.; Shi, Z.-J. *Chem.—Eur. J.* **2011**, *17*, 1728. (c) McGlacken, G. P.; Clarke, S. L. *ChemCatChem* **2011**, *3*, 1260. (d) Tobisu, M.; Chatani, N. *ChemCatChem* **2011**, *3*, 1410.

(3) For a recent review on C–S bond activation: Dubbaka, S. R.; Vogel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 7674.

(4) For a review dealing with thioether coordination to transition metals, see: Murray, S. G.; Hartley, F. R. *Chem. Rev.* **1981**, *81*, 365.

(5) For selected catalytic C–SR bond-activation reactions (R ≠ Me): (a) Ishizuka, K.; Seike, H.; Hatakeyama, T.; Nakamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 13117. (b) Itami, K.; Higashi, S.; Mineno, M.; Yoshida, J.-I. *Org. Lett.* **2005**, *7*, 1219. (c) Cho, C.-H.; Yun, H.-S.; Park, K. *J. Org. Chem.* **2003**, *68*, 3017. (d) Srogl, J.; Liu, W.; Marshall, D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1999**, *121*, 9449. (e) Tseng, H.-R.; Lee, C.-F.; Yang, L.-M.; Luh, T.-Y. *J. Org. Chem.* **1999**, *64*, 8582.

(6) For selected coupling reactions of *activated* C–SMe bonds: (a) Graham, T. H.; Liu, W.; Shen, D.-M. *Org. Lett.* **2011**, *13*, 6232. (b) Melzig, L.; Metzger, A.; Knochel, P. *Chem.—Eur. J.* **2011**, *17*, 2948. (c) Melzig, L.; Metzger, A.; Knochel, P. *J. Org. Chem.* **2010**, *75*, 2131. (d) Begouin, J.-M.; Rivard, M.; Gosmini, C. *Chem. Commun.* **2010**, 5972.

(7) Isolated examples when coupling *unactivated* C–SMe bonds with stoichiometric and highly reactive Grignard reagents have been described: (a) Kanemura, S.; Kondoh, A.; Yorimitsu, H.; Oshima, K. *Synthesis* **2008**, 2659. (b) Wenkert, E.; Ferreira, T. W.; Michelotti, E. L. *J. Chem. Soc., Chem. Commun.* **1979**, 637.

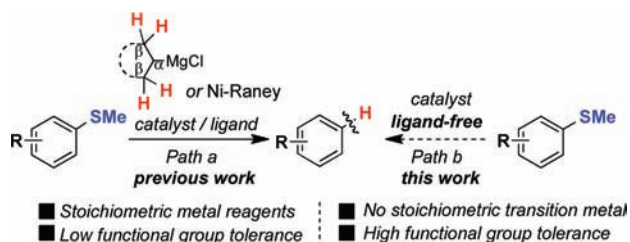
(8) Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450.

(9) For desulfurative procedures of C–SMe bonds using stoichiometric and highly reactive Grignard reagents as reducing agents: (a) Wenkert, E.; Hanna, J. M.; Leftin, M. H.; Michelotti, E. L.; Potes, K. T.; Usifer, D. *J. Org. Chem.* **1985**, *50*, 1125. (b) Wenkert, E.; Ferreira, T. W. *J. Chem. Soc., Chem. Commun.* **1982**, 840.

(10) Mazingo, R.; Wolf, D. E.; Harris, S. A.; Folkers, K. *J. Am. Chem. Soc.* **1943**, *65*, 1013.

reducing the preparative scope of these transformations as a powerful tool in organic synthesis. Furthermore, while the use of supporting ligands is typically needed for promoting C–S bond activation,³ ancillary ligands are elaborate, difficult to modify, and can be significantly more expensive than the metal they bind to; therefore, the development of a flexible, orthogonal and general catalytic protocol for promoting a catalytic reductive cleavage of functionalized aryl methyl thioethers under ligandless conditions in the presence of other reactive motifs would be highly desirable.¹¹

Scheme 1. Metal-Catalyzed Reduction of Unactivated C–S bonds



As part of our ongoing interest in the field of inert bond activation,¹² we present herein the first metal-catalyzed reductive cleavage of C–S bonds under “ligand-free” conditions¹³ (Scheme 1, path b). Unlike related desulfurative processes using Grignard reagents or Raney Nickel (Scheme 1, path a),^{9,10} our protocol does not require the use of stoichiometric amounts of metal complexes, tolerates a wide range of functional groups, shows a broad substrate scope, and exhibits excellent site selectivity and orthogonal reactivity toward other reactive motifs (Scheme 1, path b).

We initiated our study with 2-(methylthio)naphthalene **1a** as the model substrate, and the effects of Ni precatalyst, ligand, reducing agent, solvent and temperature were systematically examined. Although structurally related larger alkyl groups on sulfur such as ethyl, propyl, isopropyl, or pivaloyl groups could also be employed,¹⁴ we found that C–SMe motifs provided the best yields. Intriguingly, the inclusion of a supporting ligand had a deleterious effect, resulting in low yields of **2a**. After some experimentation, we found that the use of dimethylethylsilane as a reducing agent under ligand-free conditions¹³ provided the best results, affording **2a** in 87% isolated yield.¹⁵ This is particularly noteworthy as C–S bond cleavage has typically been achieved in the presence of

strong σ -donor ligands.³ At present, we believe that sulfur atoms in **1a** may serve as ancillary ligands¹⁶ facilitating the oxidative addition step within the catalytic cycle. *To the best of our knowledge, these results represent the first catalytic, “ligand-free”,¹³ reductive cleavage of C–S bonds reported to date.*

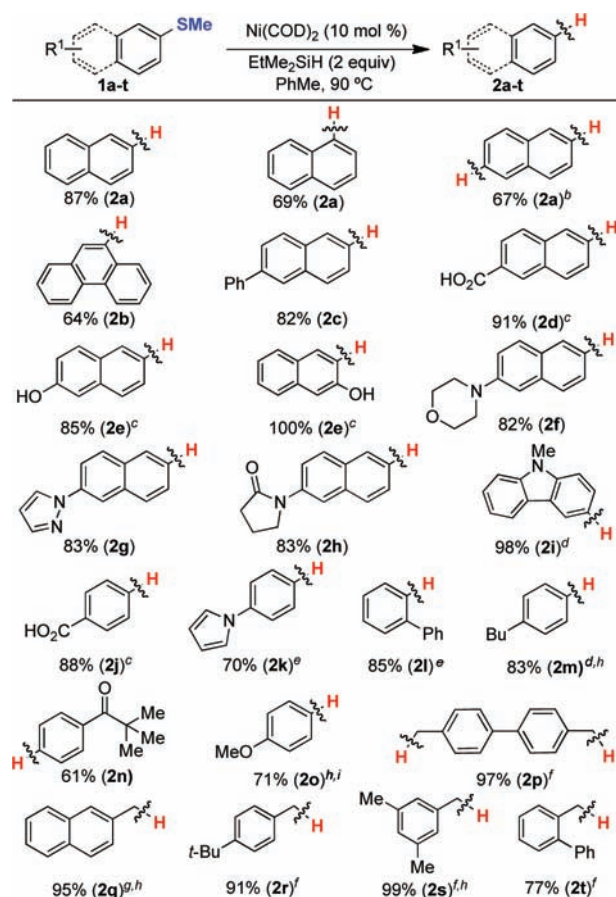


Figure 1. Ni-catalyzed reductive cleavage of C–SMe bonds. ^aArSMe (0.50 mmol), Ni(COD)₂ (10 mol %), EtMe₂SiH (1.0 mmol), PhMe (0.5 M) at 90 °C; isolated yields, average of at least two independent runs. ^bNi(COD)₂ (20 mol %). ^cEtMe₂SiH (2.50 mmol) at 130 °C. ^dEtMe₂SiH (1.50 mmol) at 130 °C. ^eEtMe₂SiH (2.00 mmol) at 130 °C. ^fEtMe₂SiH (2.50 mmol) at 110 °C. ^gNi(COD)₂ (5 mol %). ^hProduct was volatile; GC yield using decane as internal standard. ⁱ140 °C.

Encouraged by these findings, we turned our attention to the scope of the reaction (Figure 1). The Ni-catalyzed reductive cleavage of aryl methyl thioethers shows an excellent chemoselectivity profile, as heterocycles (**2g**, **2i**, and **2k**), amines (**2f**), amides (**2h**), and even ketones (**2n**) were all tolerated under our reaction conditions. The ability to furnish **2g** indicated that the active nickel species were not deactivated by the presence of strong nitrogen

(11) *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998.

(12) (a) Novák, P.; Correa, A.; Gallardo-Donaire, J.; Martin, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 12236. (b) Flores-Gaspar, A.; Martin, R. *Adv. Synth. Catal.* **2011**, *353*, 1223. (c) Alvarez-Bercedo, P.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 17352. (d) Alvarez-Bercedo, P.; Flores-Gaspar, A.; Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 466. (e) Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2009**, *131*, 15974.

(13) By “ligand-free”, we mean that typical σ -donor ligands such as phosphines, nitrogen-containing heterocycles, or *N*-heterocyclic carbenes are not present.

(14) For more details, see Supporting Information.

(15) No conversion was observed in the absence of Ni(COD)₂.

(16) Lam, F. L.; Kwong, F. Y.; Chang, A. S. C. *Chem. Commun.* **2010**, 4649.

(17) The reactions of **1d**, **1e**, and **1j** initially afforded O-silylated compounds, as judged by NMR spectroscopy of the crude reaction mixtures. A simple acidic workup gave **2d**, **2e**, and **2j** in pure form.

donors. Unprotected alcohols (**2e**) and even carboxylic acids (**2d** and **2j**) could be efficiently coupled in high yields.¹⁷ This is quite interesting taking into account that the classical use of Grignard reagents as reducing agents results in the undesired addition to the carboxylic acid moiety.⁹ Interestingly, *ortho*-substitution did not hinder the reaction (**2l** and **2t**). In sharp contrast to other catalysts used for hydrogenolysis of C–OMe bonds,^{12c,18} no *ortho*-directing groups are necessary to facilitate C–SMe bond cleavage in simple thiophenol derivatives with different electronic environments and substitution patterns (**2j–2o**). Gratifyingly, our procedure could also be applied to the reduction of benzylic C(sp³)–SMe backbones with equal efficiency (**2p–2t**).

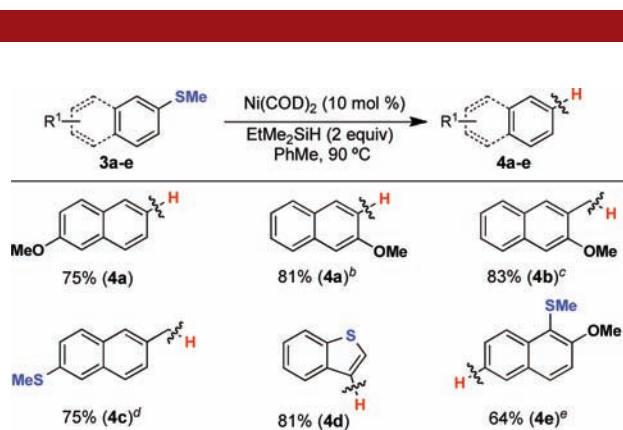


Figure 2. Site selectivity in C–S bond cleavage. ^aSame as for Figure 1. ^bEtMe₂SiH (2.0 mmol) at 130 °C. ^c110 °C. ^dEtMe₂SiH (0.90 mmol) at 130 °C. ^eEtMe₂SiH (1.50 mmol) at 130 °C.

The orthogonality of the Ni-catalyzed reductive protocol is evident from the results compiled in Figure 2. As can be seen, the selective reduction of C–SMe bonds has been achieved in the presence of additional C–OMe bonds (**4a**, **4b**, and **4e**), which remained untouched under our catalytic conditions. *The preparation of 4a is particularly noteworthy*; all attempts to conduct either C–SMe or C–OMe bond cleavage in **3a** under the exact conditions reported in the literature were completely unsuccessful,^{9,10,12c,19} thus illustrating the potential of our new catalytic reductive protocol. Site selectivity could also be achieved among multiple C–S bonds (**4c**, **4d**, and **4e**). While exhaustive reduction was observed for simple substrates (Figure 1, **2a** and **2p**), benzylic C(sp³)–SMe bonds could selectively be activated in the presence of C(sp²)–SMe bonds (Figure 2, **4c**). This is in

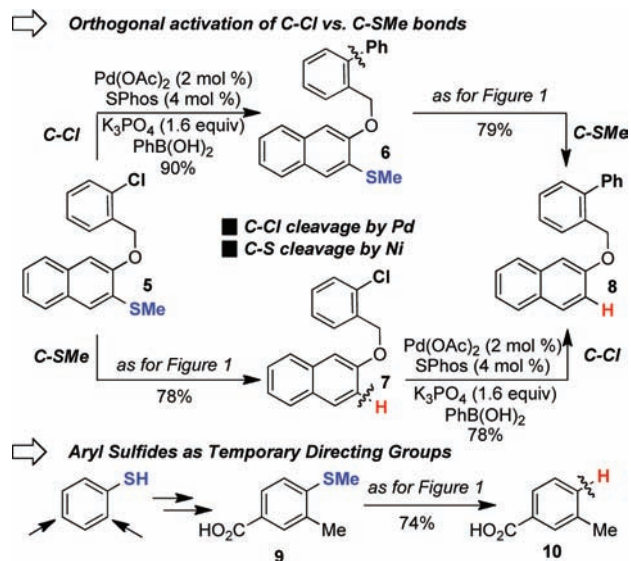
(18) (a) Tobisu, M.; Yamakawa, K.; Shimasakia, T.; Chatani, N. *Chem. Commun.* **2011**, 2946. (b) Sergeev, A. G.; Hartwig, J. F. *Science* **2011**, 332, 439.

(19) For C–N coupling: (a) Tobisu, M.; Shimasaki, T.; Chatani, N. *Chem. Lett.* **2009**, 38, 710. For Suzuki–Miyaura reaction: (b) Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2008**, 47, 4866. For Kumada-type reaction: (c) Guan, B.-T.; Xiang, S.-K.; Wu, T.; Sun, Z.-P.; Wang, B.-Q.; Zhao, K.-Q.; Shi, Z.-J. *Chem. Commun.* **2008**, 1437.

(20) For a Ni-catalyzed selective coupling of C(sp³)–OMe over C(sp²)–OMe bonds: Guan, B.-T.; Xiang, B.-Q.; Wang, S.-K.; Sun, Z. P.; Wang, Y.; Zhao, K.-Q.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, 130, 3268.

sharp contrast with the preferred cleavage of C(sp²)–OMe bonds over benzylic C(sp³)–OMe bonds.^{12c,20} Equally intriguing is the site selectivity achieved for the C(sp²)–SMe motif in **4d** as there are many Ni-catalyzed procedures reported in the literature for the activation of C–S bonds within the benzo[*b*]thiophene backbone.²¹ Additionally, the preparation of **4e** highlights that our method can be used as a predictable synthetic tool for performing selective functionalization among multiple C–O or C–S bonds.

Scheme 2. Synthetic Applicability of Aryl Methyl Thioethers



The results in Figures 1 and 2 suggest that we can turn our orthogonal protocol into a strategic advantage (Scheme 2). While the Suzuki–Miyaura reaction via C–Cl bond activation can selectively be achieved by Pd-catalysts (**6**),²² C–SMe bond cleavage is preferred (**7**) when employing our Ni-catalyzed, “ligand-free” reductive method (Scheme 2, top). These results are particularly interesting as C–Cl bonds are typically more reactive than C–heteroatom bonds in metal-catalyzed reactions.¹¹ *To our knowledge, there are no reports of selective Ni-catalyzed C–heteroatom bond-activation procedures in the presence of aryl halides.*²³ Final reaction of **6** or **7** via the above-mentioned Ni- or Pd-catalyzed procedures affords **8** in a similar overall yield.

As shown in Scheme 2 (bottom), **10** could be selectively prepared from benzenethiol in a few synthetic steps using the ability of aryl thiols to direct functionalization in the *ortho*- and *para*-positions of aromatic

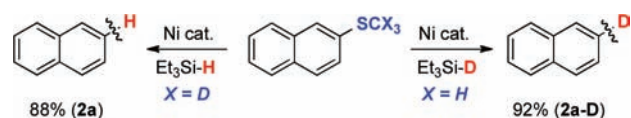
(21) For selected references: (a) Hintermann, L.; Schmitz, M.; Chen, Y. *Adv. Synth. Catal.* **2010**, 352, 2411. (b) Torres-Nieto, J.; Arévalo, A.; Garcia, J. J. *Organometallics* **2007**, 26, 2228. (c) Cho, Y.-H.; Kina, A.; Shimada, T.; Hayashi, T. *J. Org. Chem.* **2004**, 69, 3811.

(22) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, 41, 1461.

(23) It has specifically been described that Ni-catalyzed reaction of Grignard reagents with chlorophenyl alkyl sulfides occurs with selective cleavage of the C–Cl bond, leaving the C–SMe backbone intact: Tiecco, M.; Testaferri, L.; Tingoli, M.; Wenkert, E. *Tetrahedron* **1983**, 39, 2289.

rings¹⁴ and without the need for using *ortho*-directing groups in the Ni-catalyzed reductive cleavage step. An analogous sequence using 4-methoxy-3-methylbenzoic acid (**9-OMe**) under the conditions reported in the literature^{12c} did not give rise to **10**, thus showing the striking differences when using C–OMe or C–SMe electrophiles in Ni-catalyzed reductive cleavage reactions. We strongly believe these results demonstrate the high versatility of aryl methyl thioethers as synthetic intermediates, illustrating the use of aryl sulfides as temporary directing groups in organic synthesis.⁹

Scheme 3. Mechanistic Considerations



To shed light onto the mechanism, we decided to gather indirect evidence by performing deuterium-labeling experi-

(24) Et₃SiH (130 °C) gave comparable results to EtMe₂SiH (90 °C)

(25) For related stoichiometric studies: Baxter, R. D.; Montgomery, J. *J. Am. Chem. Soc.* **2011**, *133*, 5728.

(26) For a recent disclosure based on a σ -bond metathesis of C–S bonds with R₃SiH: Klare, H. F. T.; Oestreich, M.; Ito, J.-I.; Nishiyama, H.; Ohki, Y.; Tatsumi, K. *J. Am. Chem. Soc.* **2011**, *133*, 3312.

(27) It is worth mentioning that, while the coupling of 3-(methylthio)benzo[*b*]thiophene resulted in good yields of **4d** (Figure 2), the use of other heteroaromatics such as 3-(thiomethyl)quinoline gave no conversion to products.

ments (Scheme 3). In line with our expectations, **2a** and **2a-D** were exclusively obtained when employing Et₃SiH or Et₃SiD.²⁴ We believe these results rule out a mechanistic pathway consisting of a β -hydride elimination from preformed arylnickel(II)–SMe intermediates. Additionally, we did not observe Ni-hydride species by NMR spectroscopy when Ni(COD)₂ was reacted with Et₃SiH.²⁵ At present, we propose a mechanistic pathway consisting of C–SMe oxidative addition, σ -bond metathesis with the Si–H bond,²⁶ and reductive elimination from a Ni(II) hydride intermediate.

In summary, a “ligand-free” Ni-catalyzed reductive cleavage of C–S bonds has been achieved. The broad scope, high chemoselectivity profile, mild reaction conditions, and the excellent site selectivity achieved make this method a new strategy for the ever-growing synthetic arsenal.²⁷ In further studies, we aim to unravel the mechanism and fully explore the potential of this and related transformations.

Acknowledgment. We thank the ICIQ Foundation, Consolider Ingenio 2010 (CSD2006-0003), and MICINN (CTQ2009-13840) for financial support. Johnson Matthey, Umicore, and Nippon Chemical Industrial are acknowledged for a gift of metal and ligand sources. R.M. thanks MICINN for a RyC fellowship.

Supporting Information Available. Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.