Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201400306

Palladium-Catalyzed Intramolecular Oxidative C–H Sulfuration of Aryl Thiocarbamates

Yingwei Zhao,[a] Yinjun Xie,[a] Chungu Xia,[a,*] and Hanmin Huang[a,*]

[a] State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, People's Republic of China
Fax: (+86)-931-496-8129; e-mail: cgxia@licp.cas.cn or hmhuang@licp.cas.cn

Received: March 26, 2014; Revised: April 20, 2014; Published online: July 17, 2014

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201400306.

Abstract: A palladium-catalyzed intramolecular C–H bond sulfuration reaction of aryl thiocarbamates has been developed. This strategy provides a new route to benzo[*d*][1,3]oxathiol-2-ones with tolerance of a wide range of substituents. Mechanistic studies suggested that the C–H activation–sulfuration to afford 2-imino-1,3-benzoxathiole intermediate might involve an electrophilic palladation process.

Keywords: benzo[*d*][1,3]oxathiol-2-ones; C–H activation; palladium; sulfuration; thiocarbamates

The benzo[*d*][1,3]oxathiol-2-one structure is an important structural motif, which exists in a variety of biologically active compounds, pharmaceuticals such as antipsychotic[1] and antibacterial drugs,[2] neuroprotective agents,[3] and antioxidants[4] (Figure 1). In addition, it has also been used as an unique building block for organic synthesis.[5] Current strategies for the construction of such compounds have largely relied on functional group exchange, leading to inefficient synthetic procedures with poor atom and step economy and waste generation.[6] A streamlined synthetic approach to this structural motif would rely on a catalytic system capable of the direct intramolecular sulfuration of aromatic C–H bonds. Inspired by the recent progress on the transition metal-catalyzed C–S bond formation reactions,[7,8] herein, we disclose a palladium catalyst capable of catalyzing the intramolecular sulfuration with aryl thiocarbamates leading to benzo[*d*]-[1,3]oxathiol-2-ones *via* cleavage of C–H and C–N bonds.[9] To the best of our knowledge, the reaction described herein is the first example for the synthesis of such heterocycles *via* C–H bond activation, which provides a general and flexible approach to a wide range of substituted benzo[*d*][1,3]oxathiol-2-ones.

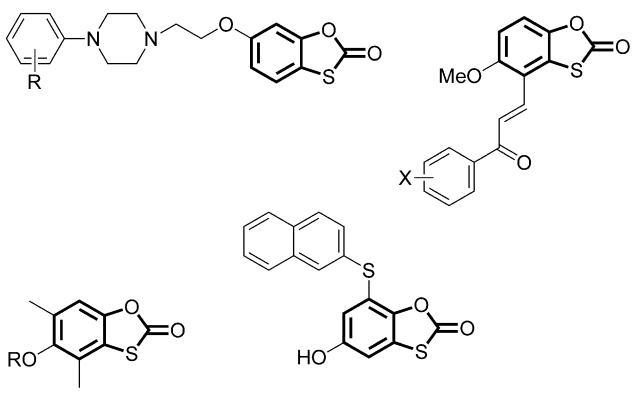
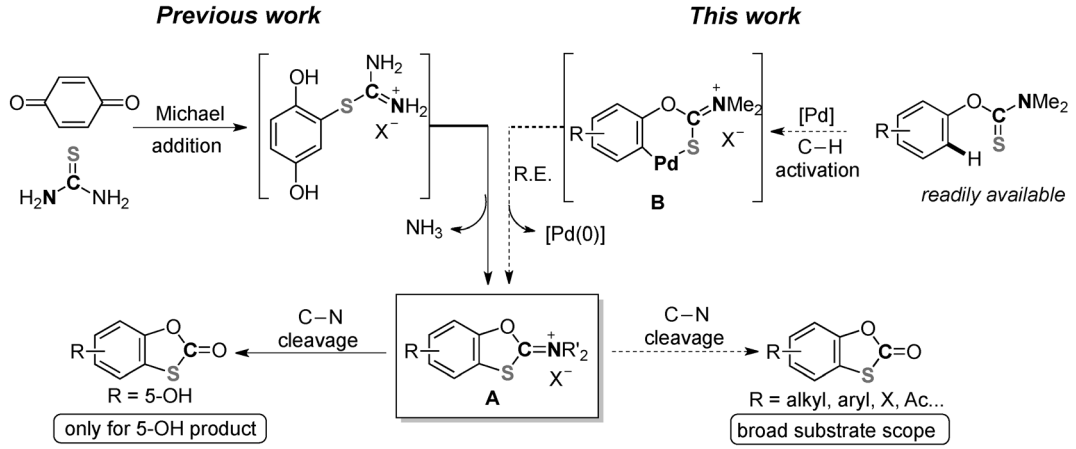


Figure 1. Important compounds containing the benzo[*d*]-[1,3]oxathiol-2-one motif.

Since the seminal report in 1943,[10] the 2-iminium-l,3-benzoxathiole salt intermediate (**A**) has been proposed as a useful precursor for the synthesis of benzo[*d*][1,3]oxathiol-2-ones *via* acid-mediated C–N bond cleavage (Scheme 1). However, for such intermediates, there is hardly any catalytic generation process that is accessible. The conventional strategy toward such a key intermediate generally relied on some non-catalytic procedures such as Michael addition of thioureas to benzoquinones[11] or Cu-mediated thiocyanation of resorcinols,[1,10] which are significantly limited not only by the generally harsh reaction conditions, but also by the inherent substitution pattern of the substrates imposed by the electronic and steric properties required by these reactions. Recent progress on transition metal-catalyzed intramolecular C–H sulfuration[8] together with our continuing studies on the area of C–H[12] bond and C–N bond activation[13] have prompted us to envisage that aryl thiocarbamates might be potentially ideal substrate candidates for C–H sulfuration, since they have been widely utilized as useful starting materials for the synthesis of benzenethiols *via* the Newman–Kwart rearrangement (NKR) reactions.[14]



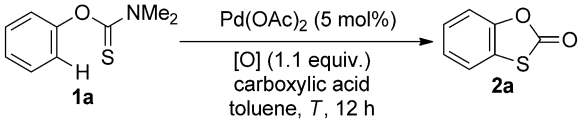
Scheme 1. Synthetic routes to benzo[*d*][1,3]oxathiol-2-one *via* 2-imino-1,3-benzoxathiole intermediate.

We anticipated that a thioenolate would be generated as a directing group to catch a metal species and selectivity to deliver the catalyst to the proximal C–H bond. After cleavage of the aryl C–H bond under suitable conditions, the cyclometalated intermediate **B** might be formed, which is converted into the key intermediate **A** by reductive elimination.

To test our above mentioned proposal, the model cyclization of *O*-phenyl *N*,*N*-dimethylthiocarbamate (**1a**) was used to identify the optimal reaction conditions. Initially, the catalytic system containing $Pd(OAc)_2$, benzoquinone (BQ), acetic acid and a catalytic amount of *para*-methylbenzenesulfonic acid ($TsOH{\cdot}H_2O$) was employed in this model reaction. To our delight, we found that under these conditions the substrate was converted to the desired benzo[*d*]-[1,3]oxathiol-2-one (**2a**) smoothly when the reaction was performed at 100 °C for 12 h (Table 1, entry 1). Ligand screening demonstrated that the best result was obtained in the absence of ligands, which is in sharp contrast to the previous reports that an excess of phosphine ligands is generally required for sustaining the catalytic cycle by suppressing the catalyst poisoning.[15] A control experiment showed that no reaction occurred in the absence of the Pd catalyst (see the Supporting Information). Other terminal oxidants such as $Cu(OAc)_2{\cdot}H_2O$, $Na_2S_2O_8$ and molecular oxygen were less efficient (Table 1, entries 2–4). The acetic acid was believed to the promote the C–N bond cleavage of 2-iminium-1,3-benzoxathiole salt intermediate (**A**) as well as act as an oxygen source to deliver the final product with the elimination of the dimethylamino moiety. A few control experiments were carried out to gain a better understand of this process. Control reactions in the absence of acetic acid or in the presence of 1.2 equivalents of acetic acid failed to give the desired product (Table 1, entries 5 and 6). Furthermore, over 90% of thiocarbamate (**1a**) was recovered when the reaction was conducted in the absence of acetic acid.

These results revealed that acetic acid is not only important for the C–N bond cleavage, but also plays an important role for promoting the C–H bond cleavage. Other commonly used carboxylic acids such as propionic acid and trifluoroacetic acid, were also used instead of acetic acid, but they proved to be inefficient (Table 1, entries 7 and 8). The catalytic amount of $TsOH{\cdot}H_2O$ has a beneficial effect (Table 1, entry 9), which can be explained in terms of increasing electrophilicity of the Pd(II) center by replace-

Table 1. Effect of reaction parameters.[a]

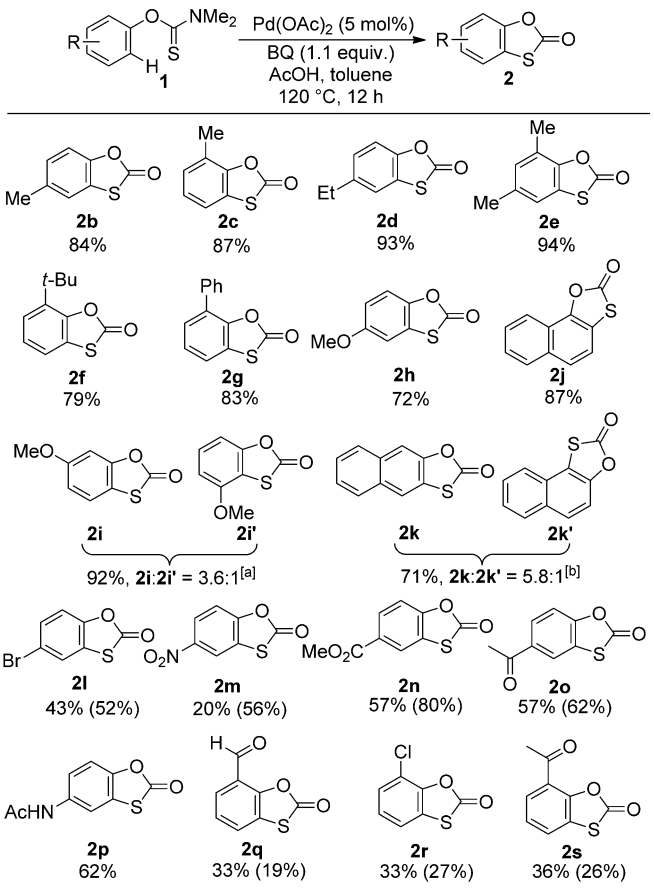


Entry	Oxidant	Acid	T [°C]	Yield [%][b]
1	BQ	CH_3CO_2H	100	70
2	$Cu(OAc)_2{\cdot}H_2O$	CH_3CO_2H	100	0
3[c]	O_2	CH_3CO_2H	100	0
4	$Na_2S_2O_8$	CH_3CO_2H	100	0
5	BQ	–	100	0
6	BQ	CH_3CO_2H[d]	100	trace
7	BQ	$CH_3CH_2CO_2H$	100	18
8	BQ	CF_3CO_2H	100	0
9[e]	BQ	CH_3CO_2H	100	49
10	BQ	CH_3CO_2H	60	18
11	BQ	CH_3CO_2H	120	75
12	BQ	CH_3CO_2H	150	77

[a] All the reactions were performed on a 1-mmol scale in sealed tubes. 10 mol% of $TsOH{\cdot}H_2O$ additive, 1.5 mL of carboxylic acid and 1 mL of toluene were used.
[b] Isolated yield.
[c] 1 atm of oxygen.
[d] 1.2 mmol of acetic acid were used.
[e] No $TsOH{\cdot}H_2O$ was added.

ment of its coordinating anion, resulting in faster metalation of the aromatic C–H bond.[16] Higher temperature results in a slightly higher yield (Table 1, entries 11 and 12) and lowering of the reaction temperature to 60 °C led to a sluggish reaction (Table 1, entry 10).

With the optimized reaction conditions in hand, we next explored the scope and generality of this process (Scheme 2). A variety of substituted aryl thiocarbamates **1**, which could be readily prepared from the condensation of corresponding phenols with dimethylthiocarbamoyl chloride, was subjected to the optimized reaction conditions. All of these aryl thiocarbamates with electron-donating substituents such as alkyl and methoxy groups on the phenyl ring gave high yields, irrespective of whether the substituent was on the *ortho* or *para* position (**2b**–**2f**). The reaction of 2-phenyl-substituted substrate **1g** led to the *ortho*-sulfuration product **2g** in 83% yield, which was confirmed by a single crystal X-ray diffraction analysis[17] (see the Supporting Information), while the C–H activation did not happen on the 2-phenyl group. The *meta*-methoxy-substituted precursor cyclized to give a mixture of 4-substituted product **2i** and 6-substituted product **2i′** in 92% total yield with 3.6:1 regioselectivity. Similarly, 2-naphthyl thiocarbamate also reacted to afford a mixture of **2k** and **2k′**. Both examples indicate that the cyclization tends to take place at the side of less steric hindrance. Compared to the electron-rich thiocarbamates, the electron-deficient thiocarbamates exhibited lower reactivity. For the thiocarbamates containing electron-withdrawing groups on the *para* position of the phenyl ring, the reactivity could be efficiently enhanced by increasing the reaction temperature (**2l**, **2m**, **2n**, and **2o**). However, in the case of *ortho*-substituted substrates **2q**, **2r** and **2s**, higher temperature led to lower yield. It was noteworthy that halide substituents (Br and Cl) were tolerated, as this is advantageous for further transformations with transition metal catalysis. In addition, a series of other functional groups, such as ester (**2n**), nitro (**2m**), aldehyde (**2q**), ketone (**2o** and **2s**), acetamide (**2p**), were also tolerated. The observed electron effect is consistent with a mechanism of electrophilic palladation which have been observed in many oxidative C–H functionalization reactions.[8]

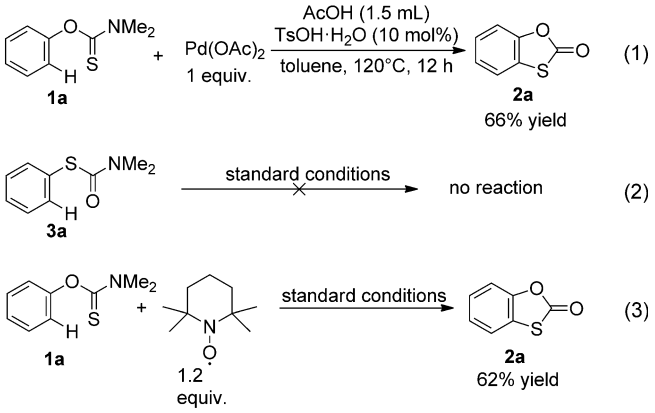


[a] The ratio was based on ^{1}H NMR.
[b] The ratio was based on GC.

Scheme 2. Substrate generality. All the reactions were performed on a 1-mmol scale in sealed tubes without the extrusion of air. 10 mol% of $TsOH{\cdot}H_2O$ additive, 1.5 mL of carboxylate acid and 1 mL of toluene were used. Values in parenthesis indicate the yield of the reaction carried out at 150 °C.

To get some insight into the mechanism of the present reaction, some control experiments were carried out under the standard reaction conditions (Scheme 3). A stoichiometric amount of $Pd(OAc)_2$ was allowed to react with **1a** under the standard conditions in the absence of BQ [Eq. (1)]. A yield of 66% of **2a** could be obtained, which indicated that a Pd(II)-Pd(0) cycle might be involved in this reaction.

In addition, *S*-phenyl dimethylcarbamothioate (**3a**) could not transfer to the same product **2a** under the standard conditions [Eq. (2)]. This result indicates



Scheme 3. Control experiments.

that the Pd(0) promoted Newman–Kwart rearrangement process, which was reported by Lloyd-Jones,[14b] is not involved in our catalytic system. Moreover, the free radical mechanism can be ruled out because this reaction is not affected by a radical scavenger [62% yield was still obtained in the presence of TEMPO, Eq. (3)].

On the basis of these results, a tentative reaction pathway involving a Pd(II)-Pd(0) redox catalytic cycle is proposed as shown in Scheme 4. The thioenolate was formed in the presence of acid, which reacted with $Pd(OAc)_2$ to furnish the palladium-*S*-enolate species **C**. Electrophilic palladation took place to give the cyclopalladium species **B** *via* cleavage of the aryl C–H bond. Subsequent reductive elimination of **B** released the key iminium salt **A** and Pd(0) which can be reoxidized by BQ in the presence of acetic acid to furnish the catalytic cycle. An intramolecular O–N exchange reaction occurred in the intermediate **A** to deliver the desired product **2a** and DMA *via* C–N bond cleavage.

To probe the feasibility of the pathway and detect the formation of 2-iminium-1,3-benzoxathiole salt **A**, we attempted to use *in situ* IR to monitor the standard reaction. A reaction profile was obtained in the cyclization of *O*-phenyl *N*,*N*-dimethylthiocarbamate (**1a**) under the standard conditions (Figure 2). Within 15 min, *O*-phenyl *N*,*N*-dimethylthiocarbamate (**1a**) was detected to be consumed to more than 80% and with the concomitant disappearance of **1a**, the benzo[*d*][1,3]oxathiol-2-one (**2a**) started to be produced slowly and an induction period was observed, thus implying that an intermediate existed in the course of this cyclization reaction, but outside of this Pd-mediated catalytic cycle. Indeed, the HR-MS (ESI) analysis of the crude reaction mixture of the standard reaction showed a peak at $m/z = 180.0474$, which corresponded to the mass of $[\mathbf{A}-\mathrm{OAc}]^+$. Another peak at $m/z = 262.0508$ was also detected, corresponding to the mass of $[\mathbf{D}+\mathrm{Na}]^+$. Moreover, a strong peak at $m/z = 285.9525$, assigned to the mass of cyclometalated Pd(II) complex $[\mathbf{B}-\mathrm{OAc}]^+$, was also detected in the reaction of **1a** promoted by stoichiometric $Pd(OAc)_2$ at room temperature, which revealed that the C–H cleavage can proceed even at room temperature (see the Supporting Information). These above results support that the intermediates **A**, **B** and **D** are most likely involved in the course of this cyclization reaction.

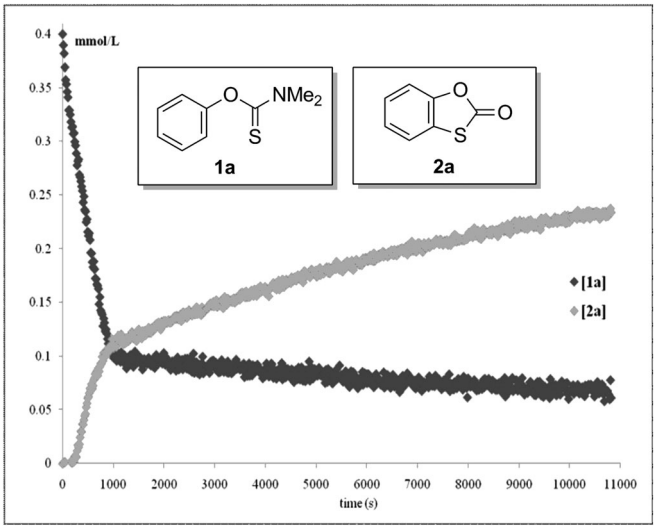
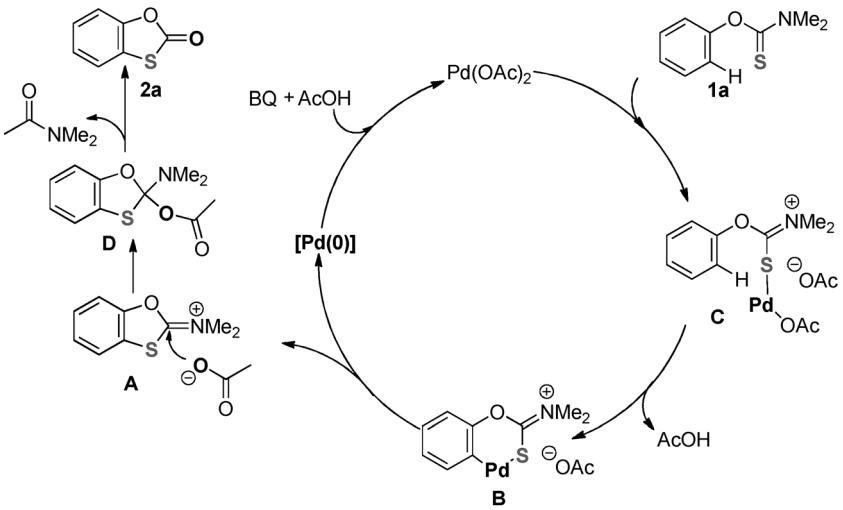


Figure 2. The reaction profile monitored by *in situ* IR.

The kinetic isotope effect ($k_H/k_D = 2.7$) was observed by comparison with the consumption rates of **1a** and **1a**-d_5, suggesting that C–H bond cleavage is the rate-determining step for the Pd-mediated catalyt-



Scheme 4. Plausible reaction mechanism.

ic cycle. But for the whole reaction, the C–N cleavage of intermediate **A** might be involved in the rate-limiting step, which was supported from the kinetic isotope effect ($k_H/k_D = 1.5$) by comparison with the produced rates of the products from **1a** and **1a**-d_5 (see the Supporting Information for details). Finally, the analysis of the crude solution of the standard reaction by GC-MS confirmed that *N,N*-dimethylacetamide was formed, suggesting that the desired product benzo[*d*][1,3]oxathiol-2-one (**2a**) was generated through the O–N exchange between the intermediate **A** and acetic acid.

In summary, we have developed a new and efficient oxidative cyclization/C–H sulfuration process. Aryl thiocarbamates could undergo oxidative cyclization smoothly in the presence of $Pd(OAc)_2$ in acetic acid/toluene using BQ as a terminal oxidant without ligands. Various benzo[*d*][1,3]oxathiol-2-ones could be efficiently synthesized from this novel method, which provides a facile route to such important biologically active molecules bearing a wide range of substituents and makes its applicable in future drug discovery. Evidence suggests that the reaction proceeds through a 2-iminium-1,3-benzoxathiole salt generated by Pd-catalyzed C–H sulfuration of aryl thiocarbamates. Control experiments and mechanism studies revealed that acetic acid plays a critical role in mediating the C–H and C–N bond cleavage, which enables the C–H bond activation to proceed at room temperature. Further investigations to gain a detailed mechanistic understanding of this reaction and the extension of this reaction are currently in progress.

Experimental Section

General Procedure

To a 25-mL dried Young-type tube were added aryl thiocarbamate **1** (1 mmol), $Pd(OAc)_2$ (0.05 mmol, 11.2 mg), benzoquinone (1.1 mmol, 119 mg), *para*-methylbenzenesulfonic acid (0.1 mmol, 19 mg), acetic acid (1.5 mL), and toluene (1 mL). Then the Young-type tube was sealed and the resulting mixture was stirred at 120 °C [***caution***!] for 12 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the residue was purified by chromatography on silica gel with ethyl acetate/petroleum ether (1:50) to give the corresponding product **2**.

Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China (21203222, 21133011 and 21173241).

References

[1] a) R. Dash, M. Suryawanshi, S. Shelke, S. Bhosale, K. Mahadik, *Med. Chem. Res.* **2011**, *20*, 29–35; b) R. C. Dash, S. H. Bhosale, K. R. Mahadik, *Dig. J. Nanomater. Bios.* **2010**, *5*, 739–747.

[2] a) M. T. Konieczny, W. Konieczny, M. Sabisz, A. Skladanowski, R. Wakieć, E. Augustynowicz-Kopeć, Z. Zwolska, *Eur. J. Med. Chem.* **2007**, *42*, 729–733; b) M. T. Konieczny, W. Konieczny, M. Sabisz, A. Skladanowski, R. Wakieć, E. Augustynowicz-Kopeć, Z. Zwolska, *Chem. Pharm. Bull.* **2007**, *55*, 817–820.

[3] J. B. Jaquith, G. Villeneuve, P. Bureau, A. Boudreault, Worldwide Patent 2005,012,281, **2005**.

[4] V. N. Povalishev, G. I. Polozov, O. I. Shadyro, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1236–1239.

[5] a) J. Martynow, M. Dimitroff, A. G. Fallis, *Tetrahedron Lett.* **1993**, *34*, 8201–8204; b) M. T. Konieczny, W. Konieczny, S. Wolniewicz, K. Wierzba, Y. Suda, P. Sowiński, *Tetrahedron* **2005**, *61*, 8648–8655.

[6] a) Y. Yoshida, M. Ogura, Y. Tanabe, *Heterocycles* **1999**, *50*, 681–692; b) J. T. Traxler, *J. Org. Chem.* **1979**, *44*, 4971–4973.

[7] For leading reviews on metal catalyzed C–S bond formation, see: a) I. P. Beletskaya, V. P. Ananikov, *Chem. Rev.* **2011**, *111*, 1596–1636; b) C.-F. Lee, Y.-C. Liu, S. S. Badsara, *Chem. Asian J.* **2014**, *9*, 706–722; c) T. Kondo, T. A. Mitsudo, *Chem. Rev.* **2000**, *100*, 3205–3220; d) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558–5607; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449.

[8] For selected recent examples on C–H sulfuration, see: a) L. L. Joyce, R. A. Batey, *Org. Lett.* **2009**, *11*, 2792–2795; b) K. Inamoto, Y. Arai, K. Hiroya, T. Doi, *Chem. Commun.* **2008**, 5529–5531; c) K. Inamoto, C. Hasegawa, K. Hiroya, T. Doi, *Org. Lett.* **2008**, *10*, 5147–5150; d) H. Wang, L. Wang, J. Shang, X. Li, H. Wang, J. Gui, A. Lei, *Chem. Commun.* **2012**, *48*, 76–78; e) A. Banerjee, S. K. Santra, S. K. Rout, B. K. Patel, *Tetrahedron* **2013**, *69*, 9096–9104; f) S. K. Rout, S. Guin, J. Nath, B. K. Patel, *Green Chem.* **2012**, *14*, 2491–2498; g) S. K. Sahoo, N. Khatun, A. Gogoi, A. Deb, B. K. Patel, *RSC Adv.* **2013**, *3*, 438–446; h) S. K. Sahoo, A. Banerjee, S. Chakraborty, B. K. Patel, *ACS Catal.* **2012**, *2*, 544–551; i) S. Murru, H. Ghosh, S. K. Sahoo, B. K. Patel, *Org. Lett.* **2009**, *11*, 4254–4257.

[9] For leading reviews on C–H bond activation, see: a) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731–1769; b) C. I. Herrerias, X. Yao, Z. Li, C. Li, *Chem. Rev.* **2007**, *107*, 2546–2562; c) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; d) J. C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013–1025; e) X. Chen, K. M. Engle, D. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196–5217; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115; f) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624–655; g) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169; h) M. C. Willis, *Chem. Rev.* **2010**, *110*, 725–748; i) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654–2672; j) A. Gunay, K. H. Theopold, *Chem. Rev.* **2010**, *110*, 1060–1081; k) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315–1345; l) C. Sun, B. Li, Z.

Shi, *Chem. Rev.* **2011**, *111*, 1293–1314; m) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879–5918; n) L. Yang, H. Huang, *Catal. Sci. Technol.* **2012**, *2*, 1099–1112; o) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780–1824.

[10] G. Werner, U.S. Patent 2,332,418, **1943**.

[11] a) H. Burton, S. B. David, *J. Chem. Soc.* **1952**, 2193–2196; b) P. T. S. Lau, M. Kestner, *J. Org. Chem.* **1968**, *33*, 4426–4431; c) D. Greenwood, H. A. Stevenson, *J. Chem. Soc.* **1953**, 1514–1519.

[12] a) B. Qian, S. Guo, J. Shao, Q. Zhu, L. Yang, C. Xia, H. Huang, *J. Am. Chem. Soc.* **2010**, *132*, 3650–3651; b) P. Xie, Y. Xie, B. Qian, H. Zhou, C. Xia, H. Huang, *J. Am. Chem. Soc.* **2012**, *134*, 9902–9905.

[13] a) S. Guo, B. Qian, Y. Xie, C. Xia, H. Huang, *Org. Lett.* **2011**, *13*, 522–525; b) Y. Xie, J. Hu, Y. Wang, C. Xia, H. Huang, *J. Am. Chem. Soc.* **2012**, *134*, 20613–20616.

[14] a) M. S. Newman, H. A. Karnes, *J. Org. Chem.* **1966**, *31*, 3980–3984; b) M. Burns, G. C. Lloyd-Jones, J. D. Moseley, J. S. Renny, *J. Org. Chem.* **2010**, *75*, 6347–6353; c) J. N. Harvey, J. Jover, G. C. Lloyd-Jones, J. D. Moseley, P. Murray, J. S. Renny, *Angew. Chem.* **2009**, *121*, 7748–7751; *Angew. Chem. Int. Ed.* **2009**, *48*, 7612–7615; d) Y. Zhao, M. Lei, L. Yang, F. Han, Z. Li, C. Xia, *Org. Biomol. Chem.* **2012**, *10*, 8956–8959.

[15] a) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534–1544; b) J. Louie, J. F. Hartwig, *J. Am. Chem. Soc.* **1995**, *117*, 11598–11599; c) E. Alvaro, J. F. Hartwig, *J. Am. Chem. Soc.* **2009**, *131*, 7858–7868; d) G. Mann, D. Baranano, J. F. Hartwig, A. L. Rheingold, I. A. Guzei, *J. Am. Chem. Soc.* **1998**, *120*, 9205–9219; e) D. Baranano, J. F. Hartwig, *J. Am. Chem. Soc.* **1995**, *117*, 2937–2938; f) J. F. Hartwig, *Inorg. Chem.* **2007**, *46*, 1936–1947.

[16] M. D. K. Boele, G. P. F. van Strijdonck, A. H. M. de Vries, P. C. J. Kamer, J. G. de Vries, P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* **2002**, *124*, 1586–1587.

[17] CCDC 951566 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

