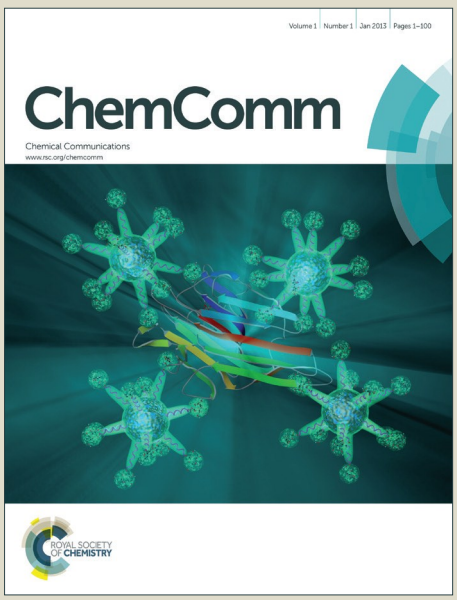
ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: S. Yan, Y. Liu, B. Liu, Y. Liu and B. Shi, *Chem. Commun.*, 2015, DOI: 10.1039/C4CC10446C.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

View Article Online
DOI: 10.1039/C4CC10446C

ARTICLE TYPE

Nickel-Catalyzed Thiolation of Unactivated Aryl C–H Bonds: An Efficient Access to Diverse Aryl Sulfides

Sheng-Yi Yan,‡ Yue-Jin Liu,‡ Bin Liu, Yan-Hua Liu, Bing-Feng Shi*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

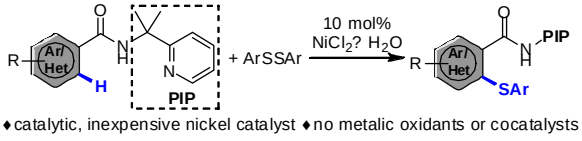
A nickel-catalyzed thiolation of unactivated C(sp^2)-H bonds with disulfides employing the PIP directing group was described. This process uses catalytic nickel catalyst and no metallic oxidants or cocatalysts are required. The reaction tolerates various important functional groups and heteroarenes, providing an efficient synthetic pathway to access diverse diaryl sulfides.

Organosulfur chemistry has attracted increasing attention due to their extensive application in organic synthesis, pharmaceuticals, agrochemicals, and functional materials.[1] For example, aryl sulfides are widely found in numerous drugs for the treatment of diabetes, immune, Alzheimer's and Parkinson's diseases.[2] Therefore, the formation of C-S bonds is of utmost importance in organic synthesis and has received tremendous interests. From the viewpoint of atom-economy, the direct thiolation of arenes to aryl sulfides via C-H activation offer a straightforward alternative to the traditional methods.[3] However, compared with the substantial advances in C-C, C-hetero bond-forming reactions via C-H activation,[4] the direct C-H thiolation is largely underexplored, mainly because of the deactivation of the metal catalysts by strong coordination.

Elegant works from the groups of Yu,[5a] Qing,[5b] Cheng[5c] and Daugulis[5d] have demonstrated the high potential of copper catalyst in the direct C-H thiolation.[6,7] Our group has also reported the synthesis of benzoisothiazolones via copper-mediated C-S/N-S formation using elemental sulfur.[8] However, these methods are largely restricted to the use of stoichiometric or substoichiometric copper catalysts. More recently, Li and Zhou reported a Rh(III)-catalyzed thiolation of arenes with disulfides using N-heteroarenes and N-oximes as directing groups.[9] Nishihara demonstrated the direct thiolation of aryl C-H bonds with disulfides or thiols catalyzed by palladium.[10] However, these methods relied on the use of expensive second-row transition metal catalysts and substoichiometric copper(II) or silver(I) slats as cocatalytic oxidants. Therefore, the development of a unified strategy for the expeditious synthesis of diverse aryl sulfides under more sustainable and efficient catalytic systems would be highly desirable.

Recently, Ni-catalyzed C-H functionalization has received tremendous interests owing to its abundance, inexpensiveness and relatively low toxicity. Early studies mainly focused on the direct functionalization of C-H bonds in electronically activated arenes.[11] The seminal work by Chatani showed that nickel-catalyzed direct alkylation of unactivated aryl C-H bonds could be achieved with the assistance of 8-aminoquinoline bidentate directing group.[12,13] Shortly after, several nickel-catalyzed C-H functionalization reactions were further reported by Chatani, Ge, You and Ackerman.[14] However, these transformations are mainly limited to C-C, C-N and C-O bond formation. The more challenging C-S bond formation has not been discovered. Herein, we report the first example of Ni-catalyzed thiolation of unactivated (hetero)aryl C-H bonds with disulfides employing our newly developed 2-(pyridine-2-yl)isopropylamine (PIP-amine) directing group (Scheme 1).[15] No metallic oxidants or cocatalysts are required and a variety of functional groups are tolerated, providing an efficient access to diverse aryl sulfides.

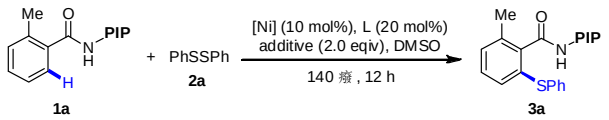
Scheme 1 Ni(II)-Catalyzed Thiolation of (Hetero)aryl C–H Bonds.



♦catalytic, inexpensive nickel catalyst ♦no metalic oxidants or cocatalysts

We commenced our studies by investigating the reaction of benzamide **1a** with PhSSPh **2a**. Gratifyingly, the desired thiolated product **3a** was obtained in 45% yield in DMSO in the presence of 10 mol% $Ni(OTf)_2$, PPh_3 and Na_2CO_3 (Table 1, entry 1). After extensive screening of nickel catalysts, $NiCl_2{\cdot}6H_2O$ was proved to be the best and gave the desired product **3a** in 59% yield (entry 5). Further optimization of various ligands revealed that BINOL was the most effective ligand (entries 6–11). We then examined the effect of weak bases as additives (entries 12-17). Finally, we were pleased to find the thiolated product **3a** was isolated in 84% yield when KTFA was used (entry 17). No desired product was observed in the absence of nickel catalyst, suggesting that nickel catalyst was crucial for this reaction (entry 18).

Table 1 Optimization of the Reaction Conditions[a]



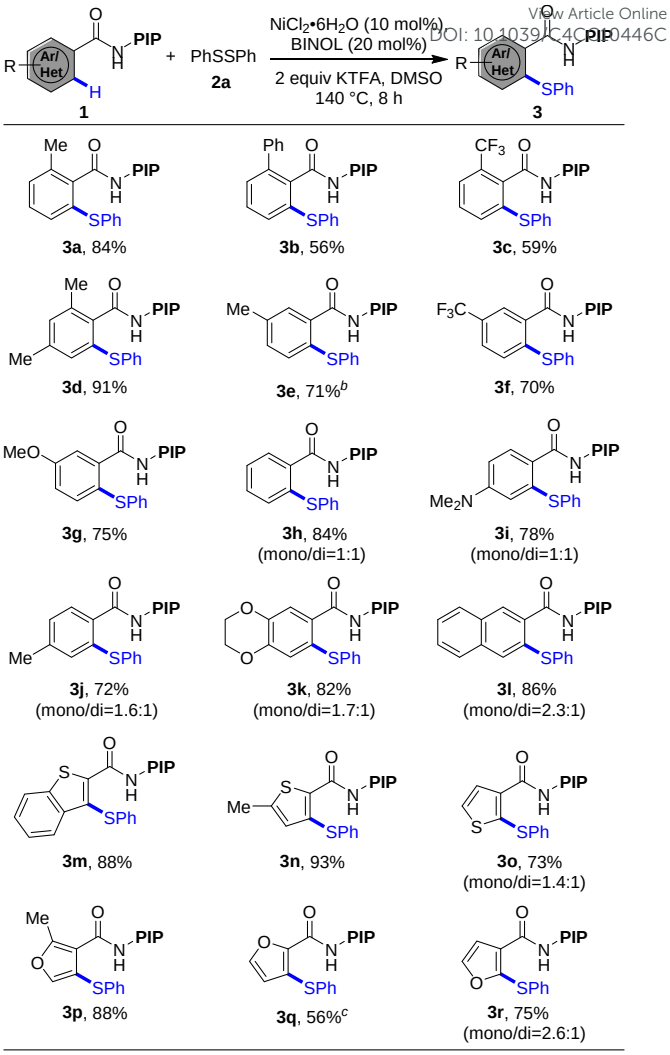
entry	[Ni]	ligand	additive	yield (%)[b]
1	$Ni(OTf)_2$	PPh_3	Na_2CO_3 (2.0)	45%
2	$NiBr_2$	PPh_3	Na_2CO_3 (2.0)	27%
3	$Ni(acac)_2$	PPh_3	Na_2CO_3 (2.0)	46%
4	$NiCl_2$	PPh_3	Na_2CO_3 (2.0)	50%
5	$NiCl_2·6H_2O$	PPh_3	Na_2CO_3 (2.0)	59%
6	$NiCl_2·6H_2O$	TMEDA	Na_2CO_3 (2.0)	50%
7	$NiCl_2·6H_2O$	dppp	Na_2CO_3 (2.0)	46%
8	$NiCl_2·6H_2O$	dppb	Na_2CO_3 (2.0)	72%
9	$NiCl_2·6H_2O$	dppe	Na_2CO_3 (2.0)	60%
10	$NiCl_2·6H_2O$	PCy_3	Na_2CO_3 (2.0)	49%
11	$NiCl_2·6H_2O$	BINOL	Na_2CO_3 (2.0)	78%
12	$NiCl_2·6H_2O$	BINOL	K_2CO_3 (2.0)	76%
13	$NiCl_2·6H_2O$	BINOL	$NaHCO_3$ (2.0)	66%
14	$NiCl_2·6H_2O$	BINOL	$KHCO_3$ (2.0)	55%
15	$NiCl_2·6H_2O$	BINOL	K_3PO_4 (2.0)	75%
16	$NiCl_2·6H_2O$	BINOL	NaTFA (2.0)	67%
17[c]	**$NiCl_2·6H_2O$**	**BINOL**	**KTFA (2.0)**	**88% (84%)**[d]
18	-	-	KTFA (2.0)	-

[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.3 mmol), [Ni] (10 mol%), L (20 mol%), 2equiv additive in DMSO (1 mL) at 140 °C. [b]^{1}H NMR yield using CH_2Br_2 as the internal standard. [c]8 h. [d]Isolated yield in parenthesis.

After identifying the optimal reaction conditions, we next tested the generality of the amide coupling partners. Generally, this thiolation reaction tolerated various functionalities and gave the desired thiolated products in moderate to high yield (Scheme 2). *ortho*-Phenyl substituted benzamide **1b** gave lower yield, probably due to the steric hindrance. When *meta*-substituted benzamides were employed, the thiolation tended to occur at the less sterically hindered position (**3e-3g**) and gave monothiolated products exclusively. In contrast, simple benzamide **1h** and benzamides bearing *para* substituents (**1i** and **1j**) gave a mixture of mono- and di-thiolated products. Furthermore, naphthalyl substrate **2l** also worked efficiently to provide the desired product in high yield, albeit with poor selectivity. Importantly, heterocycles such as benzothiophene (**1m**), thiophene (**1n** and **1o**) and furan **(1p-1r**) were also effective substrates and compatible with the optimal condtions. As was expected, a mixture of mono- and di-thiolated products was obtained when thiophene-3-carboxamide **1o** and furan-3-carboxamide **1r** were used.

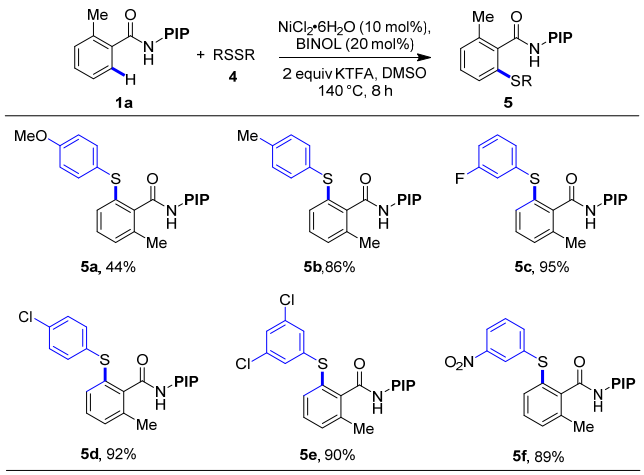
Encouraged by these results, we then further investigated the scope of disulfides.[16] As shown in Scheme 3, diaryl disulfides bearing both electron-donating and electron-withdrawing groups were compatible with the optimized conditions, although *para*-methoxy substituted disulfide gave a lower yield (**5a**, 44% yield). Halogenated diaryl disulfides **4c-4f** were also survived and delivered the desired products in excellent yields.

Scheme 2 Scope of benzamides[a]



[a]Reaction conditions: **1** (0.15 mmol), **2** (0.3 mmol), $NiCl_2•6H_2O$ (10 mol%), BINOL (20 mol%) and KTFA (0.3 mmol) in DMSO (1ml) at 140 °C for 8 h. Isolated yield. [b] 0.5 ml DMSO. [c]$NiCl_2•6H_2O$ (20 mol%), BINOL (40 mol%) in 0.5 mL DMSO.

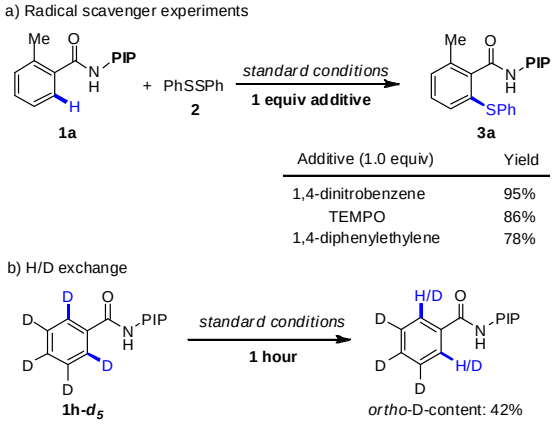
Scheme 3 Scope of disulfides[a]



[a]Reaction conditions: **1a** (0.15 mmol), **4** (0.3 mmol), $NiCl_2•6H_2O$ (10 mol%), BINOL (20 mol%) and KTFA (0.3 mmol) in DMSO (1 mL) at 140 oC for 8 h. Isolated yield.

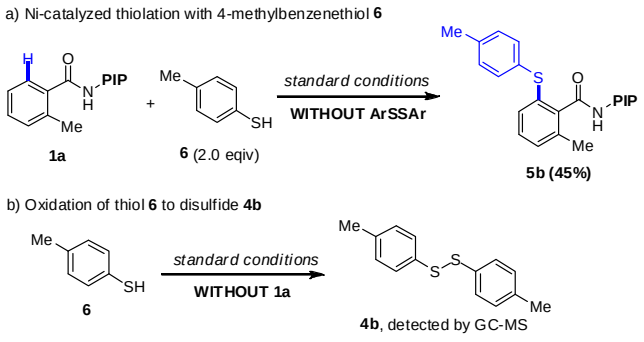
Subsequently, radical scavenger experiments were conducted to unravel the mode of the reaction. As shown in Scheme 4a, three separate reactions were carried out by the addition of 1 equivalent of electron-transfer scavenger (1,4-dinitrobenzene) or radical inhibitors, such as TEMPO and 1,4-diphenylethylene. These reactions proceeded smoothly to give the thiolated product **3a** without significantly affect the efficiency, suggesting the single-electron transfer (SET) process is not involved in this transformation. Furthermore, a significant H/D exchange was observed after 1 hour (Scheme 4b). This observation indicated that the C-H activation step is reversible.

Scheme 4 Radical scavenger and H/D exchange.



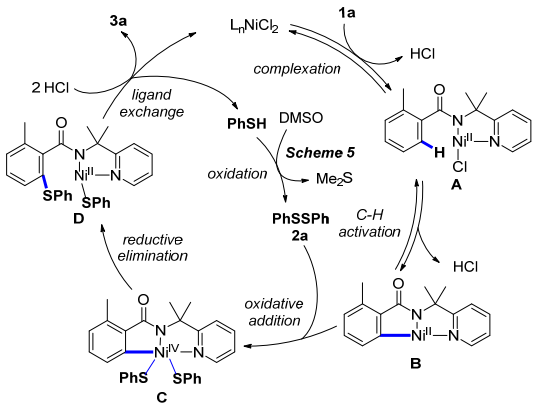
When 4-methylbenzenethiol **6** was reacted with benzamide **1a** under the standard conditions, the thiolated product **5b** was obtained in 45% yield, which was consistent with Pd-catalyzed C-H thiolation by Nishihara (Scheme 5a). It has been reported that thiols could be oxidized to disulfides mediated by DMSO.[17] As expected, a control experiment showed that benzenethiol **6** was oxidized to disulfide **4b**, which was unambiguously confirmed by the GC-MS analysis of the reaction mixtures (Scheme 5b).[18]

Scheme 5 Thiolation with thiol 6 and its oxidation



On the basis of these mechanistic studies and previous reports,[10,12,14b,14h-i] a plausible mechanism was proposed in Scheme 6. Precomplexation to the PIP directing group is followed by a reversible C-H activation step to form Ni(II)-pincer complex **B**. Oxidative addition of disulfide **2a** followed by reductive elimination provides complex **D**. Subsequent protonation releases the desired thiolation product **3a** and benzenethiol with the regeneration of Ni(II) catalyst. As shown in Scheme 5, benzenethiol can be oxidized to dilsulfide by DMSO and merged into the catalytic cycle. A detailed mechanism remained to be elucidated.[19]

Scheme 6 Plausible reaction mechanism



In conclusion, we have developed the first nickel-catalyzed thiolation of aromatic C-H bonds with disulfides.[20] Catalytic nickel catalyst is used and no metallic oxidants or cocatalysts are required. This catalytic system tolerates various important and useful functional groups, providing an efficient protocol for the synthesis of diaryl sulfides. This novel process constitutes a significant extension to the recently reported thiolation reactions and benefits the development of new catalytic system to diverse synthesis of aryl sulfides.

Acknowledgements

Financial support from the National Basic Research Program of China (2015CB856600), the NSFC (21422206, 21272206), the Fundamental Research Funds for the Central Universities (2014QNA3008), and Qianjiang Project (2013R10033) is gratefully acknowledged.

Notes and references

Department of Chemistry, Zhejiang University, Hangzhou 310027, China. E-mail: bfshi@zju.edu.cn

† Electronic Supplementary Information (ESI) available: Experimental details and characterization data for new compounds. See DOI: 10.1039/b000000x/

‡ These authors contributed equally to this work.

1 (a) T. Kondo, and T. Mitsudo, *Chem. Rev.* 2000, **100**, 3205; (b) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.* 2003, **42**,5400; (c) A. Thuillier and P. Metzner, Sulfur Reagents in Organic Synthesis, Academic Press, New York, 1994.

2 E. A. Ilardi, E. Vitaku and J. T. Njardarson, *J. Med. Chem.* 2014, **57**, 2832.

3 C. Shen, P. Zhang, Q. Sun, S. Bai, T. S. A. Hor, and X. Liu, *Chem. Soc. Rev.* DOI: 10.1039/c4cs00239c.

4 For selected recent reviews, see: (a) G. Rouquet and N. Chatani, *Angew. Chem. Int. Ed.*, 2013, **52**, 11726; (b) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem. Int. Ed.* 2012, **51**, 8960; (c) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord and F. Glorius, *Angew. Chem. Int. Ed.* 2012, **51**, 10236; (d) K. Engle, T.-S. Mei, M. Wasa

and J.-Q. Yu, *Acc. Chem. Res*. 2012, **45**, 788; (e) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev*. 2012, **112**, 5879; (f) C. Zhang, C. Tang, N. Jiao, *Chem. Soc. Rev.* 2012, **41**, 3464; (g) L. Ackermann, *Chem. Rev*. 2011, **111**, 1315; (h) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev*. 2011, **111**, 1293; (i) O. Baudoin, *Chem. Soc. Rev.* 2011, **40**, 4902; (j) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev*. 2010, **110**, 624; (k) T. W. Lyons, M. S. Sanford, *Chem. Rev.* 2010, **110**, 1147; (l) O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074.

5 (a) X. Chen, X.-S. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.* 2006, **128**, 6790; (b) L. Chu, X. Yue and F.-L. Qing, *Org. Lett.* 2010, **12**, 1644; (c) S. Zhang, P. Qian, M. Zhang, M. Hu and J. Cheng, *J. Org. Chem.* 2010, **75**, 6732; (d) L. D. Tran, I. Popov and O. Daugulis, *J. Am. Chem. Soc.* 2012, **134**, 18237; (e) X.-B. Yan, P. Gao, H.-B. Yang, Y.-X. Li, X.-Y. Liu and Y.-M. Liang, *Tetrahedron* 2014, **70**, 8730.

6 For Cu-catalyed C–H activation/C–S bond formation of activated C–H bonds, see: (a) S. Fukuzawa, E. Shimizu, Y. Atsuumi, M. Hagac and K. Ogata, *Tetrahedron Lett.* 2009, **50**, 2374; (b) S. Ranjit, R. Lee, D. Heryadi, C. Shen, J. Wu, P. Zhang, K.-W. Huang and X. Liu, *J. Org. Chem*. 2011, **76**, 8999; (c) A.-X. Zhou, X.-Y. Liu, K. Yang, S.-C. Zhao and Y.-M. Liang, *Org. Biomol. Chem.* 2011, **9**, 5456-5462; (d) C. Chen, X.-H. Xu, B. Yang and F.-L Qing,. *Org. Lett.* 2014, **16**, 3372; (e) X. Li, Y. Xu, W. Wu, C. Jiang, C. Qi and H. Jiang, *Chem. Eur. J*. 2014, **20**, 7911.

7 For selected examples of intramolecular C-H thiolation, see: (a) K. Inamoto, Y. Arai, K. Hiroya and T. Doi, *Chem. Commun.* 2008, 5529; (b) K. Inamoto, C. Hasegawa, K. Hiroya and T. Doi, *Org. Lett.* 2008, **10**, 5147; (c) L. L. Joyce and R. A. Batey, *Org. Lett.* 2009, **11**, 2792; (d) X.-L. Fang, R.-Y. Tang, P. Zhong and J.-H. Li, *Synthesis* 2009, **24**, 4183; (e) H. Wang, L. Wang, J. Shang, X. Li, H. Wang, J. Gui and A. Lei, *Chem. Commun.* 2012, **48**, 76; (e) S. K. Sahoo, A. Banerjee, S. Chakraborty and B. K. Patel, *ACS Catal.* 2012, **2**, 544.

8 F.-J. Chen, G. Liao, X. Li, J. Wu and B.-F. Shi, *Org. Lett.* 2014, **16**, 5644.

9 Y. Yang, W. Hou, L. Qin, J. Du, H. Feng, B. Zhou and Y. Li, *Chem. Eur. J*. 2014, **20**, 416.

10 (a) M. Iwasaki, M. Iyanaga, Y. Tsuchiya, Y. Nishimura, W. Li, Z. Li and Y. Nishihara, *Chem. Eur. J*. 2014, **20**, 2459; (b) M. Iwasaki, W. Kaneshika, Y. Tsuchiya, K. Nakajima and Y. Nishihara, *J. Org. Chem.* DOI: 10.1021/jo502274t; (c) Selenation: M. Iwasaki, Y. Tsuchiya, K. Nakajima and Y. Nishihara, *Org. Lett.* 2014, **16**, 4920; (d) P. Saravanan and P. Anbarasan, *Org. Lett.* 2014, **16**, 848; (e) For a Pd-catalyzed sulfonylation: X. Zhao, Dimitrijević, V. M. Dong, *J. Am. Chem. Soc.* 2009, **131**, 3466; (b) X. Zhao, V. M. Dong, *Angew. Chem. Int. Ed.* 2011, **50**, 932.

11 For reviews on Ni-catalyzed C-H activation of electronically biased arenes and heteroarenes, see: a) J. Yamaguchi, K. Muto and K. Itami, Eur. *J. Org. Chem*. 2013, **19**; b) Y. Nakao, *Chem. Rec.* 2011, ***11***, 242. And references therein.

12 Y. Aihara, N. Chatani, *J. Am. Chem. Soc.* 2013, ***135***, 5308.

13 For pioneer work of the use of bidentate auxiliary, see: a) V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.* 2005, **127**, 13154; b) D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.* 2010, **132**, 3965; C) B. D. Dangel, K. Godula, S. W. Youn, B. Sezen and D. Sames, *J. Am. Chem. Soc.* 2002, **124**, 11856. For a review, see ref 4a.

14 (a) H. Shiota, Y. Ano, Y. Aihara, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.* 2011, **133**, 14952; (b) Y. Aihara and N. Chatani, *J. Am. Chem. Soc.* 2014, **136**, 898; (c) M. Li, J. Dong, X. Huang, K. Li, Q. Wu, F. Song and J. You, *Chem. Commun.* 2014, **50**, 3944; (d) W. Song, S. Lackner and L. Ackermann, *Angew. Chem. Int. Ed.* 2014, **53**, 2477; (e) X. Wu, Y. Zhao and H. Ge, *J. Am. Chem. Soc.* 2014, **136**, 1789; (f) X. Wu, Y. Zhao and H. Ge, *Chem. Eur. J.* 2014, **20**, 9530; (g) X. Cong, Y. Li, Y. Wei and X. Zeng, *Org. Lett.* 2014, **16**, 3926. (h) M. Iyanaga, Y. Aihara and N. Chatani, *J. Org. Chem.* 2014, **79**, 11933; (i) A. Yokota, Y. Aihara and N. Chatani, *J. Org. Chem.* 2014, **79**, 11922; (j) Y. Aihara, M. Tobisu, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.* 2014, **136**, 15509.

15 (a) F.-J. Chen, S. Zhao, F. Hu, K. Chen, Q. Zhang, S.-Q. Zhang and B.-F. Shi, *Chem. Sci.* 2013, **4**, 4187; (b) Q. Zhang, K. Chen, W.-H. Rao, Y.-J. Zhang, F.-J. Chen and B.-F. Shi, *Angew. Chem. Int. Ed*. 2013, **52**, 13588; (c) Q. Zhang, X.-S. Yin, S. Zhao, S.-L. Fang and B.-F. Shi, *Chem. Commun.* 2014, **50**, 8353; (d) X. Li, Y.-H. Liu, W. J. Gu, B. Liu, F.-J. Chen and B.-F. Shi, *Org. Lett.* 2014, **16**, 3904; (e) Y.-J. Liu, Y.-H. Liu, X.-S. Yin, W.-J. Gu and B.-F. Shi, *Chem. Eur. J.* 2015, **21**, 205.

16 However, dialkyl disulfides did not react under the standard conditions, probably due to the less oxidizing ability of dialkyl disulfides.

17 (a) C. N. Yiannios and J. V. Karabinos, *J. Org. Chem.* 1963, **28**, 3246; (b) T. J. Wallace, *J. Am. Chem. Soc.* 1964, **86**, 2018; (c) W. E. Fristad and J. R. Peterson, *Synth. Commun.* 1985, **15**, 1.

18 See the Supporting Information for details.

19 A Ni(I)/Ni(III) catalytic cycle cannot be ruled out, see: (a) A. T. Higgs, P. J. Zinn, S. J. Simmons and M. S. Sanford, *Organometallics* 2009, **28**, 6142. And ref 14e - 14f.

20 During the revision of our manuscript, a related Ni-catalyzed thiolation directed by PIP was reported, see: K. Yang, Y. Wang, X. Chen, A. A. Kadi, H.-K. Fun, H. Sun, Y. Zhang, H. Lu, *Chem. Commun.* DOI: 10.1039/C4CC10431E.