



Cite this: *Chem. Commun.*, 2015, 51, 7341

Received 16th February 2015,
Accepted 17th March 2015

DOI: 10.1039/c5cc01436k

www.rsc.org/chemcomm

Nickel-catalyzed direct thiolation of unactivated C(sp³)–H bonds with disulfides†

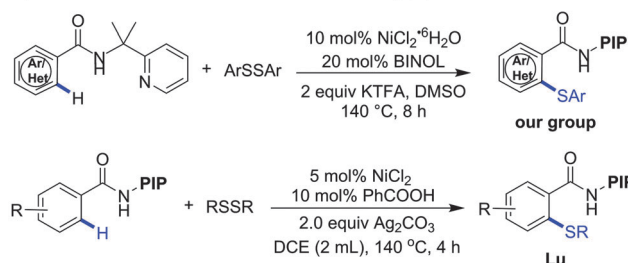
Sheng-Yi Yan,‡ Yue-Jin Liu,‡ Bin Liu, Yan-Hua Liu, Zhuo-Zhuo Zhang and Bing-Feng Shi*

The first nickel-catalyzed thiolation of unactivated C(sp³)–H bonds with disulfides was described. This transformation uses (dppp)NiCl₂ as a catalyst and BINOL as a ligand, which are efficient for the thiolation of β-methyl C(sp³)–H bonds of a broad range of aliphatic carboxamides. The reaction provides an efficient synthetic pathway to access diverse thioethers.

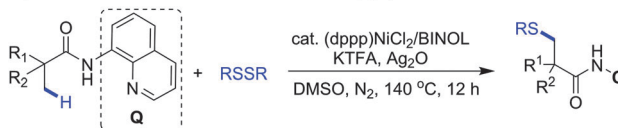
In recent years, transition-metal-catalyzed functionalization of C–H bonds to form C–C and C–heteroatom bonds has attracted significant attention.¹ So far, only a few examples of transition-metal-catalyzed thiolation of unactivated C(sp²)–H bonds have been reported.² Significant achievements on thiolation of arene C(sp²)–H bonds mediated by copper have been made by groups of Yu,^{3a} Qing,^{3b} Cheng,^{3c} Daugulis,^{3d} and Liang.^{3e} The synthesis of benzoisothiazolones *via* copper-mediated C–S/N–S formation using elemental sulfur has also been demonstrated by our group.⁴ The direct thiolation of aryl C–H bonds by using expensive second-row transition metal catalysts, such as Pd and Rh, has also been reported recently.^{5,6} More recently, our group^{7a} and Lu's group^{7b} independently reported the Ni(II)-catalyzed thiolation of aromatic C(sp²)–H bonds with disulfides by using our newly developed 2-(pyridine-2-yl)isopropylamine (PIP-amine) directing group (Scheme 1A). In comparison, the direct thiolation of unactivated C(sp³)–H bonds remains a great challenge, largely on account of the inherent low reactivity of aliphatic C(sp³)–H bonds⁸ and the competitive coordination of the sulfur species to interfere with the C–H functionalization reaction. Therefore, the development of a general and efficient method for the thiolation of unactivated C(sp³)–H bonds would be very challenging and extremely attractive.

Since the seminal work of Daugulis,⁹ elegant achievements have been made by using a bidentate directing group in the transformations of C(sp³)–H bonds.¹⁰ However, most of the

A) Previous Work: Thiolation of Unactivated C(sp²)–H Bonds



B) This Work: Thiolation of Unactivated C(sp³)–H Bonds



Scheme 1 Nickel-catalyzed unactivated C–H thiolation.

transformations of C(sp³)–H bonds reported are catalyzed by palladium catalysts. Recently, direct functionalization of C(sp³)–H bonds has been achieved using the bidentate directing group in conjunction with nickel catalysts,¹¹ which are abundant, inexpensive and relatively less toxic.¹² Though elegant studies on the direct C–C, C–N and C–O bond formation *via* Ni-catalyzed C–H functionalization have been made,^{13–16} the more challenging C–S bond formation *via* C(sp³)–H activation has not been realized.

Owing to their ubiquity in numerous biologically active compounds and pharmaceuticals,¹⁷ the construction of sulfur-containing compounds by chemical synthesis through transition metal-catalyzed/mediated sulfenylation of arylhalides has attracted tremendous attention.¹⁸ However, these traditional methods are largely restricted to the use of pre-functionalized precursors. Due to our continuous investigation of the functionalization of unactivated C(sp³)–H bonds,¹⁹ we are becoming interested in developing methods for the thiolation of unactivated C(sp³)–H bonds in consideration of the great challenges associated. Here we report the first example of nickel-catalyzed thiolation of β-methyl C(sp³)–H bonds of a broad range of aliphatic carboxamides and disulfides (Scheme 1B).

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

† Electronic supplementary information (ESI) available: Experimental details and characterization data for new compounds. See DOI: 10.1039/c5cc01436k

‡ These authors contributed equally to this work.

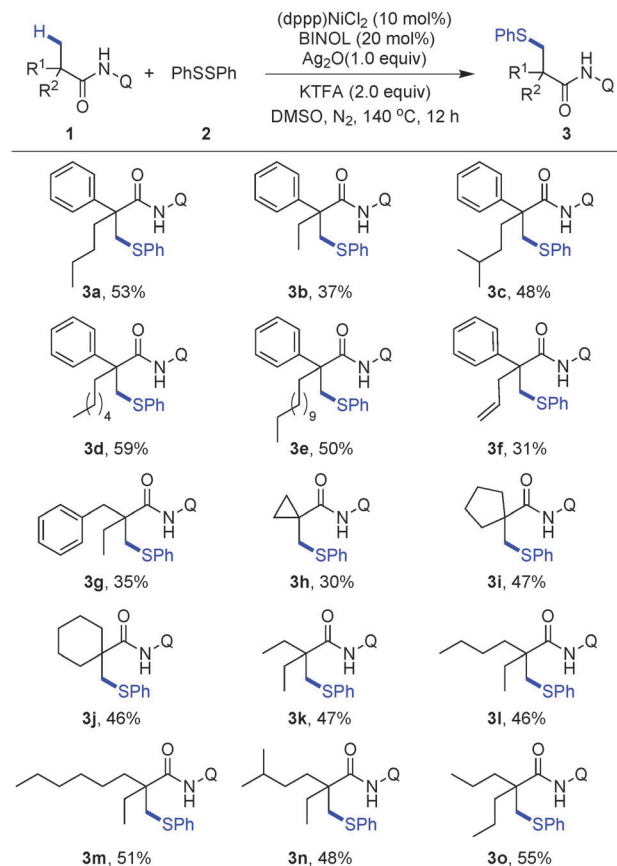
Table 1 Optimization of the reaction conditions^a

Entry	[Ni]	Base	Additive (equiv.)	Yield ^b (%)
1	NiCl ₂ ·6H ₂ O	KTFA	—	24
2	Ni(acac) ₂	KTFA	—	19
3	Ni(OTf) ₂	KTFA	—	20
4	NiI ₂	KTFA	—	24
5	NiCl ₂	KTFA	—	23
6	(dppp) NiCl ₂	KTFA	—	27
7	(dppp) NiCl ₂	KTFA	Cu(OAc) ₂ (2.0)	Trace
8	(dppp) NiCl ₂	KTFA	CuF ₂ (2.0)	N.R
9	(dppp) NiCl ₂	KTFA	CuO (2.0)	42
10	(dppp) NiCl ₂	KTFA	Cu(OH) ₂ (2.0)	40
11	(dppp) NiCl ₂	KTFA	Cu(OH) ₂ ·CO ₃ (2.0)	45
12	(dppp) NiCl ₂	KTFA	Ag ₂ O (2.0)	37
13	(dppp) NiCl ₂	KTFA	Ag ₂ CO ₃	20
14	(dppp) NiCl₂	KTFA	Ag₂O (1.0)	56 (53^c)
15	(dppp) NiCl ₂	Na ₂ CO ₃	Ag ₂ O (1.0)	39
16	(dppp) NiCl ₂	NaHCO ₃	Ag ₂ O (1.0)	23
17	(dppp) NiCl ₂	K ₂ CO ₃	Ag ₂ O (1.0)	20
18	(dppp) NiCl ₂	NaOAc	Ag ₂ O (1.0)	17
19	(dppp) NiCl ₂	NaTFA	Ag ₂ O (1.0)	44
20	(dppp) NiCl ₂	LiTFA	Ag ₂ O (1.0)	35
21	—	KTFA	Ag ₂ O (1.0)	N.R

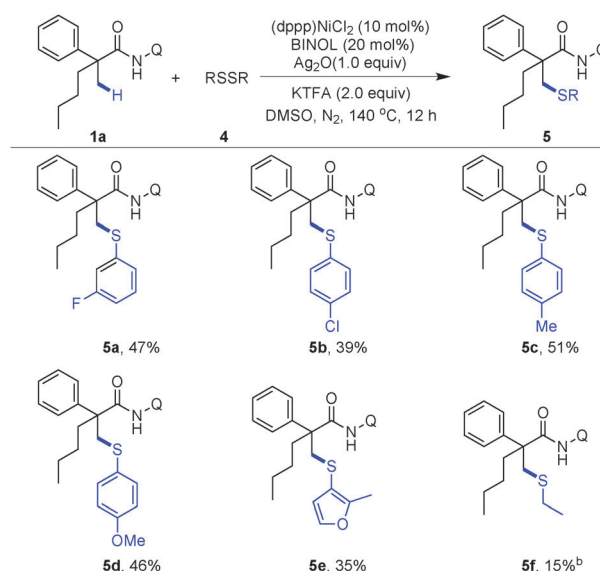
^a Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), [Ni] (10 mol%) BINOL (20 mol%), base (0.2 mmol) and additive (0.1 mmol) in DMSO (1 mL) at 140 °C for 12 h. ^b ¹H NMR yield using CH₂Br₂ as the internal standard. ^c Isolated yield.

Our exploration commenced by studying the reaction between amide **1a** and PhSSPh **2a** under the conditions which have been reported by our group recently.^{7a} To our delight, the desired product **3a** was obtained in 24% yield (Table 1, entry 1). (dppp) NiCl₂ was found to be the best after extensive screening of nickel catalysts (entry 6). To improve the efficiency of the reaction further, the influence of the additives was investigated. As shown in Table 1, the thiolated product **3a** was isolated in 53% yield when Ag₂O was employed (entry 14). Unfortunately, a number of bases were screened and found to reduce the yield of the desired product (entries 15–20). Controlled reaction in the absence of a nickel catalyst revealed that nickel was essential for the success of this reaction (entry 21).

With the optimized reaction conditions in hand, the scope of the reaction of aliphatic amides **1** with PhSSPh was investigated as shown in Scheme 2. In general, aliphatic amides substituted with a phenyl group at the α-position reacted exclusively at the methyl group, and the γ-aromatic C(sp²)-H bonds were not thiolated (**3a–3f**). In addition, 2,2-disubstituted propanamides bearing both the linear and cyclic chains proceeded smoothly to afford the corresponding thiolated products in medium yield (**3h–3o**). The methylene C(sp³)-H bonds were unreactive under present reaction conditions, even with the relatively more reactive benzylic and cyclopropyl methylene C(sp³)-H bonds (**3g**, **3h**). It is noteworthy that a vinyl functional group was tolerated and produced the desired product in 31% yield (**3f**). Notably, no other by-product was observed and the starting materials were recovered in all the case.

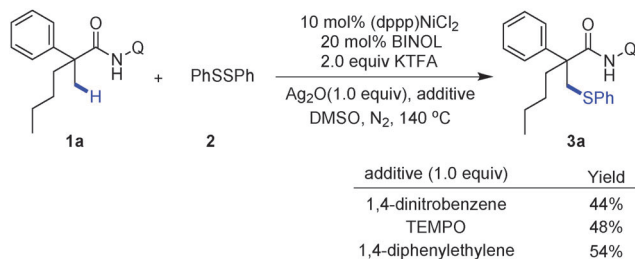


Scheme 2 Scope of amides^a. ^a Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), (dppp)NiCl₂ (10 mol%) BINOL (20 mol%), KTFA (0.2 mmol) and Ag₂O (0.1 mmol) in DMSO (1 mL) at 140 °C for 12 h. Isolated yield.

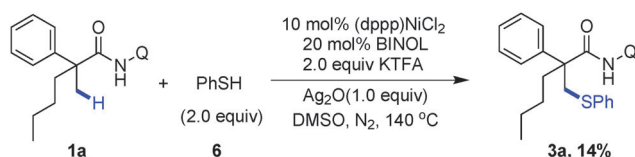


Scheme 3 Scope of disulfides^a. ^a Reaction conditions: **1** (0.1 mmol), **4** (0.2 mmol), (dppp)NiCl₂ (10 mol%) BINOL (20 mol%), KTFA (0.2 mmol) and Ag₂O (0.1 mmol) in DMSO (1 mL) at 140 °C for 12 h. Isolated yield. ^b Reaction was conducted on 0.3 mmol scale.

The results for thiolation of amide **1a** with various disulfides are shown in Scheme 3. Diaryl disulfides bearing either an



Scheme 4 Radical scavenger experiments.



Scheme 5 Thiolation with thiol 6.

electron-donating or electron-withdrawing group were evaluated and found to be compatible with the optimized reaction conditions (5a–5d). In addition, 2-methyl-3-furyl disulfide was employed and afforded the corresponding product 5e in 35% yield. Notably, dialkyl disulfide 4f also reacted with benzamide 1a, albeit with reduced yield (5f, 15%).

In order to gain insights into the mechanism for this transformation, radical trapping experiments were carried out to evaluate the possibility that a thiophenyl radical participates in the present reaction. As shown in Scheme 4, the addition of 1 equivalent of 1,4-dinitrobenzene (electron-transfer scavenger) had no effect on the reaction. Additionally, when radical inhibitors, such as TEMPO and 1,4-diphenylethylene, were added, the desired product 3a was obtained in 48% and 54% yield respectively. These results are in sharp contrast to the finding of the Lu group,^{7b} indicating that radical intermediates might not be involved in this transformation.

When benzenethiol 6 was employed,²⁰ the desired product 3a was isolated in 14% yield under standard conditions, which was consistent with Pd-catalyzed C–H thiolation by Nishihara (Scheme 5).^{5a–c}

Chatani proposed a Ni(II)/Ni(IV) catalytic cycle for the Ni-catalyzed C–H arylation and alkylation reactions.^{13b–e} More recently, Sanford reported that the formation of C(sp³)–sulfur bonds *via* the reductive elimination from Ni(IV) complexes is possible.²¹ On the basis of these results and precedents, we hypothesized that a high-valent Ni(IV) intermediate might be involved in this Ni-catalyzed thiolation reaction.^{7a} Further efforts to clarify the detailed mechanism are ongoing.

In summary, we have developed the first nickel-catalyzed thiolation of unactivated C(sp³)–H bonds of aliphatic acid derivatives with disulfides.²² Besides diaryl disulfides, dialkyl disulfides are also capable of undergoing the thiolation reactions moderately. This transformation uses (dppp)NiCl₂ as a catalyst and BINOL as a ligand, which are efficient for the thiolation of β-methyl C(sp³)–H bonds of a broad range of aliphatic carboxamides and disulfides. The reaction provides an efficient synthetic pathway to access diverse thioethers.

Financial support from the National Basic Research Program of China (2015CB856600), the NSFC (21422206 and 21272206), the Fundamental Research Funds for the Central Universities, and Zhejiang Provincial NSFC (LZ12B02001) is gratefully acknowledged.

Notes and references

- 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 and 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 and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (l) O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074.
- C. Shen, P. Zhang, Q. Sun, S. Bai, T. S. A. Hor and X. Liu, *Chem. Soc. Rev.*, 2015, **44**, 291.
- (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.
- F.-J. Chen, G. Liao, X. Li, J. Wu and B.-F. Shi, *Org. Lett.*, 2014, **16**, 5644.
- (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.*, 2014, **79**, 11330; (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.
- Y. Yang, W. Hou, L. Qin, J. Du, H. Feng, B. Zhou and Y. Li, *Chem. – Eur. J.*, 2014, **20**, 416.
- (a) S.-Y. Yan, Y.-J. Liu, B. Liu, Y.-H. Liu and B.-F. Shi, *Chem. Commun.*, 2015, **51**, 4069; (b) K. Yang, Y. Wang, X. Chen, A. A. Kadi, H.-K. Fun, H. Sun, Y. Zhang and H. Lu, *Chem. Commun.*, 2015, **51**, 3582.
- For selected reviews on C(sp³)–H activation, see: (a) G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, 2013, **52**, 11726; (b) C. Zhang, C. Tang and N. Jiao, *Chem. Soc. Rev.*, 2012, **41**, 3464; (c) O. Baudoin, *Chem. Soc. Rev.*, 2011, **40**, 4902; (d) J. F. Hartwig, *Chem. Soc. Rev.*, 2011, **40**, 1992; (e) H. Li, B.-J. Li and Z.-J. Shi, *Catal. Sci. Technol.*, 2011, **1**, 191; (f) M. Wasa, K. M. Engle and J.-Q. Yu, *Isr. J. Chem.*, 2010, **50**, 605; (g) K. Godula and D. Sames, *Science*, 2006, **312**, 67.
- For pioneering 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.
- For a selected review, see: (a) ref. 8a; for selected examples, see: (b) B. V. S. Reddy, L. R. Reddy and E. J. Corey, *Org. Lett.*, 2006, **8**, 3391; (c) R. Giri, N. Mangel, B. M. Foxman and J.-Q. Yu, *Organometallics*, 2008, **27**, 1667; (d) G. He and G. Chen, *Angew. Chem., Int. Ed.*, 2011, **50**, 5192; (e) N. Rodríguez, J. A. Romero-Revilla, M. A. Fernández-Ibáñez and J. C. Carretero, *Chem. Sci.*, 2013, **4**, 175; (f) F. Pan, P.-X. Shen, L.-S. Zhang, X. Wang and Z.-J. Shi, *Org. Lett.*, 2013, **15**, 4758; (g) R. Shang, L. Ilies, A. Matsumoto and E. Nakamura, *J. Am. Chem. Soc.*, 2013, **135**, 6030.
- For a review, see: L. C. Misal Castro and N. Chatani, *Chem. Lett.*, DOI: 10.1246/cl.150024.
- For selected reviews, see: (a) S. Z. Tasker, E. A. Standley and T. F. Jamison, *Nature*, 2014, **509**, 299; (b) X. Hu, *Chem. Sci.*, 2011, **2**, 1867; (c) A. A. Kulkarni and O. Daugulis, *Synthesis*, 2009, 408; (d) J. Yamaguchi, K. Muto and K. Itami, *Eur. J. Org. Chem.*, 2013, 19; (e) Q. Qian, Z. Zang, Y. Chen, W. Tong and H. Gong, *Mini-Rev. Med. Chem.*, 2013, **13**, 802.
- (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.*, 2013, **135**, 5308; (c) A. Yokota, Y. Aihara and N. Chatani,

- J. Org. Chem.*, 2014, **79**, 11922; (d) Y. Aihara and N. Chatani, *J. Am. Chem. Soc.*, 2014, **136**, 898; (e) M. Iyanaga, Y. Aihara and N. Chatani, *J. Org. Chem.*, 2014, **79**, 11933; (f) Y. Aihara, M. Tobisu, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.*, 2014, **136**, 15509; (g) X. Cong, Y. Li, Y. Wei and X. Zeng, *Org. Lett.*, 2014, **16**, 3926.
- 14 (a) X. Wu, Y. Zhao and H. Ge, *J. Am. Chem. Soc.*, 2014, **136**, 1789; (b) X. Wu, Y. Zhao and H. Ge, *Chem. – Eur. J.*, 2014, **20**, 9530.
- 15 M. Li, J. Dong, X. Huang, K. Li, Q. Wu, F. Song and J. You, *Chem. Commun.*, 2014, **50**, 3944.
- 16 (a) W. Song and L. Ackermann, *Chem. Commun.*, 2013, **49**, 6638; (b) W. Song, S. Lackner and L. Ackermann, *Angew. Chem., Int. Ed.*, 2014, **53**, 2477.
- 17 E. A. Ilardi, E. Vitaku and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 2832.
- 18 (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.
- 19 (a) Q. Zhang, K. Chen, W.-H. Rao, Y.-J. Zhang, F.-J. Chen and B.-F. Shi, *Angew. Chem., Int. Ed.*, 2013, **52**, 13588; (b) K. Chen, F. Hu, S.-Q. Zhang and B.-F. Shi, *Chem. Sci.*, 2013, **4**, 3906; (c) Q. Zhang, X.-S. Yin, S. Zhao, S.-L. Fang and B.-F. Shi, *Chem. Commun.*, 2014, **50**, 8353; (d) K. Chen and B.-F. Shi, *Angew. Chem., Int. Ed.*, 2014, **53**, 11950; (e) K. Chen, S.-Q. Zhang, J.-W. Xu, F. Hu and B.-F. Shi, *Chem. Commun.*, 2014, **50**, 13924; (f) K. Chen, S.-Q. Zhang, H.-Z. Jiang, J.-W. Xu and B.-F. Shi, *Chem. – Eur. J.*, 2015, **21**, 3264.
- 20 (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.
- 21 For a recent example of the synthesis and characterization of the organometallic Ni(IV) complex, see: N. M. Camasso and M. S. Sanford, *Science*, 2015, **347**, 1218.
- 22 During the submission of this manuscript, the Ni-catalyzed thiolation of the unactivated C(sp³)–H bond of propionamides was reported: C. Lin, W. Yu, J. Yao, B. Wang, Z. Liu and Y. Zhang, *Org. Lett.*, 2015, **17**, 1340.