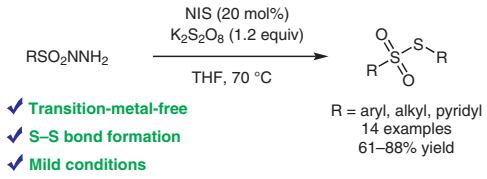
Synlett G. Zhou et al. Letter

Transition-Metal-Free Synthesis of Thiosulfonates through Radical Coupling Reaction

Guodong Zhou[a◊]
Xu-Dong Xu[a◊]
Gan-Ping Chen[a]
Wen-Ting Wei*[a,b]
Zhiyong Guo*[a]

[a] School of Materials Science and Chemical Engineering, Ningbo University, Ningbo 315211, P. R. of China
weiwenting@nbu.edu.cn
guozhiyong@nbu.edu.cn
[b] State Key Laboratory of Chemo/Biosensing and Chemometrics, Hunan University, Changsha 410082, P. R. of China

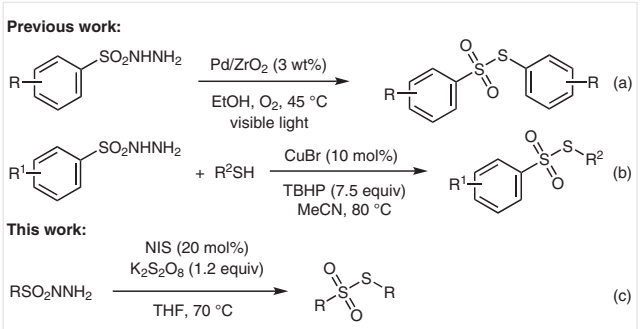
◊ These authors contributed equally to this work



Received: 03.06.2018
Accepted after revision: 03.07.2018
Published online: 02.08.2018
DOI: 10.1055/s-0037-1610649; Art ID: st-2018-w0336-l

Abstract An efficient and practical transition-metal-free radical coupling reaction of sulfonyl hydrazides mediated by NIS/$K_2S_2O_8$ has been developed to afford a variety of biological activity thiosulfonates in moderate to excellent yields. Compared to a known approach for the synthesis of thiosulfonates from sulfonyl hydrazides, this strategy features high yields, mild reaction conditions, and broad substrate scope. The mechanistic studies revealed that the procedure undergoes *via* a radical cross-coupling process for the construction of S–S bonds.

Keywords transition-metal-free, radical coupling reaction, S–S bonds, thiosulfonates



Scheme 1 Synthesis of thiosulfonates using sulfonyl hydrazides

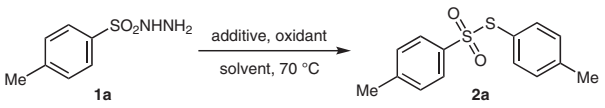
Thiosulfonates constitute the pivotal core of a wide variety of pharmaceutical molecules that exhibit antimicrobial and antiviral activities.[1] On the other hand, they are also important synthetic building blocks in organic synthesis.[2] The most common methods for building the thiosulfonates framework generally rely on the direct oxidation of disulfides[3] or mercaptans[4] and the sulfuration of sulfinic acid salts.[5] In 2017, Guo and co-workers used sulfonyl hydrazides as reagent for the preparation of thiosulfonates under Pd/ZrO_2/O_2/visible light conditions (Scheme 1, a).[6] In the same year, the Zou group described a copper-catalyzed *tert*-butyl hydroperoxide (TBHP) mediated cross-coupling of sulfonyl hydrazides with thiols for the synthesis of thiosulfonates (Scheme 1, b).[7] In spite of these advances, further exploration of more efficient and greener approach to enrich the synthesis of thiosulfonates is still highly desirable.

As an ideal alternative to transition-metal-catalytic oxidation system, the [I]/$K_2S_2O_8$ system has been increasingly explored.[8] Iodine sources (e.g., iodine, *N*-iodosuccinimide, tetrabutylammonium iodide, and potassium iodide) are low cost, nontoxic, and they can apply to a wide variety of transformations.[9] Recently, we have reported the C–hetero bonds formation under transition-metal-free conditions *via* radical coupling reaction.[10] As part of our continuous efforts in this strategy, we report a radical coupling reaction of sulfonyl hydrazides mediated by *N*-iodosuccinimide (NIS) with $K_2S_2O_8$ as the oxidant for the synthesis of thiosulfonates (Scheme 1, c). The most important features of the present method are the mild reaction conditions, high efficiency, and broad substrate scope.

We commenced our studies with the reaction of 4-methylbenzenesulfonohydrazide (**1a**) in the presence of tetrabutylammonium iodide (TBAI, 20 mol%), and TBHP (1.2 equiv) in tetrahydrofuran (THF) under air at 70 °C for 8 h. Gratifyingly, the desired radical coupling product S-(*p*-tolyl) 4-methylbenzenesulfonothioate (**2a**) was obtained in 53% yield (Table 1, entry 1).

When the reaction was performed at 60 °C, only 36% yield of **2a** was generated from the reaction, and a homo-coupling product 1,2-di-*p*-tolyldisulfane (**3a**) was obtained in 15% yield (Table 1, entry 2). Further increasing the temperature to 80 °C gave an identical yield to that of 70 °C (Table 1, entry 3). The controlled experiments showed that

Table 1 Optimization of Reaction Conditions[a]



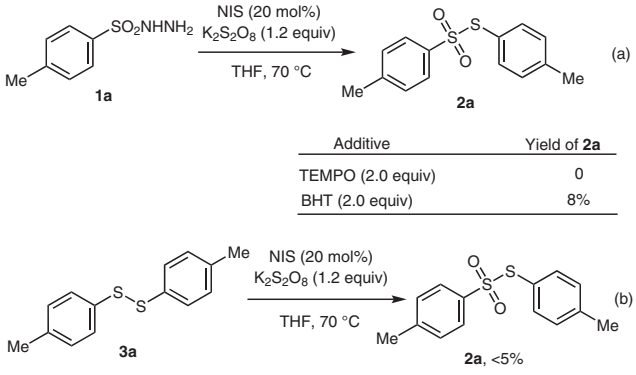
Entry	Additive (mol%)	Oxidant (equiv)	Solvent	Yield (%)
1	TBAI (20)	TBHP (1.2)	THF	53
2[b]	TBAI (20)	TBHP (1.2)	THF	36
3[c]	TBAI (20)	TBHP (1.2)	THF	55
4	TBAI (20)	–	THF	0
5	–	TBHP (1.2)	THF	0
6	I_2 (20)	TBHP (1.2)	THF	50
7	KI (20)	TBHP (1.2)	THF	10
8	NIS (20)	TBHP (1.2)	THF	81
9	NIS (20)	DTBP (1.2)	THF	82
10[d]	NIS (20)	$K_2S_2O_8$ (1.2)	THF	87
11	NIS (20)	$PhI(OAc)_2$ (1.2)	THF	trace
12	NIS (20)	H_2O_2	THF	0
13	NIS (20)	$K_2S_2O_8$ (1.2)	1,4-dioxane	43
14	NIS (20)	$K_2S_2O_8$ (1.2)	toluene	12
15	NIS (20)	$K_2S_2O_8$ (1.2)	DMF	7

[a] Reaction conditions: **1a** (0.3 mmol), additive (0.06 mmol, 20 mol%), oxidant (0.36 mmol, 1.2 equiv), and solvent (2 mL) open in air at 70 °C for 8 h.
[b] At 60 °C, and 1,2-di-*p*-tolyldisulfane (**3a**) was obtained in 15% yield.
[c] At 80 °C.
[d] 1,2-Di-*p*-tolyldisulfane (**3a**) was obtained in 5% yield.

the reaction did not take place in the absence of either an oxidant or an additive (Table 1, entries 4 and 5). Different additives, such as I_2, KI, and NIS, were further tested for the reaction (Table 1, entries 6–8), and the best yield was obtained with NIS (81%, Table 1, entry 8). Subsequently, further optimization was done with the oxidants di-*tert*-butyl peroxide (DTBP), $K_2S_2O_8$, $PhI(OAc)_2$ or H_2O_2, and $K_2S_2O_8$ was proved to be most effective for this transformation (Table 1, entries 8–12). It is worth noting that the $PhI(OAc)_2$ and H_2O_2nearly have no reactivity for this radical coupling. Several solvents including 1,4-dioxane, toluene, and *N*,*N*-dimethylformamide (DMF) were then examined but were inferior to THF (Table 1, entry 10 *vs* entries 13–15). Therefore, the optimal reaction conditions are as follows: 4-methylbenzenesulfonohydrazide (0.3 mmol), NIS (20 mol%), $K_2S_2O_8$ (1.2 equiv), and THF (2 mL) under air at 70 °C for 8 h.

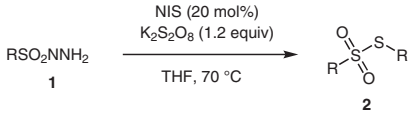
Using the optimal conditions described in Table 1, we next explored the scope of this transformation.[11] This reaction displayed high functional group tolerance and proved to be an efficient methodology for the preparation of thiosulfonates. Sulfonyl hydrazides with *para*-substituted electron-donating groups on aryl rings, such as methyl, *tert*-butyl, and methoxy, all gave the corresponding radical coupling product in 84–88% yields (Table 2, 2a–c). Benzenesulfonohydrazide (**1d**) was also applied to this reaction and furnished the desired product in 80% yield (**2d**). In comparison, slightly lower yields (70–76%) were observed having sulfonyl hydrazides with *para*-substituted electron-withdrawing groups (fluoro, chloro, bromo, and nitro) on aryl rings (**2e**–**h**). It was worth mentioning that the *ortho*- or *meta*-chloro-substituted sulfonyl hydrazides still exhibited high reactivity, affording the corresponding products in 72% and 73% yields, respectively (**2i**,**j**). In addition, polysubstituted sulfonyl hydrazide 2,4,6-trimethylbenzenesulfonohydrazide (**1k**) also proceeded smoothly to give the desired product in 88% yield (**2k**).

Polycyclic aromatic sulfonyl hydrazide (**1l**) also reacted efficiently and produced the corresponding thiosulfonate in good yield (**2l**). However, no reaction occurred when heteroaromatic sulfonyl hydrazide that contain pyridine (**1m**) was used as the substrate (**2m**). To our satisfaction, alkyl-substituted sulfonyl hydrazide methanesulfonohydrazide (**1n**), successfully went through this protocol, giving the corresponding product in 61% yield (**2n**). The known methodology that require Pd/ZrO_2 nanocomposite catalyst is not compatible with such type of substrate.[6]



Scheme 2 Control experiments

Table 2 Scope of Sulfonyl Hydrazides[a]



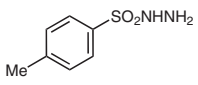
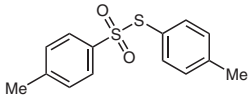
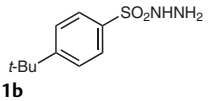
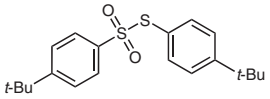
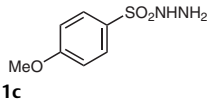
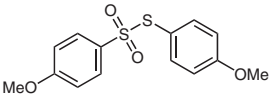
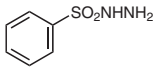
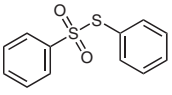
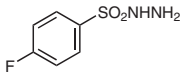
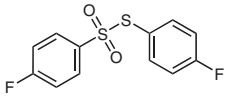
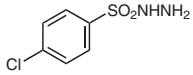
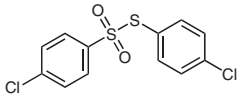
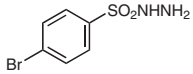
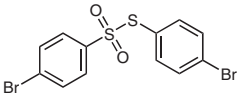
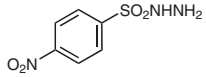
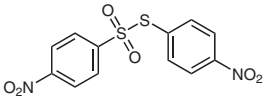
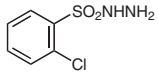
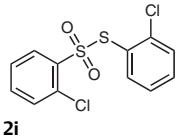
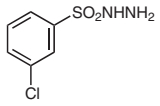
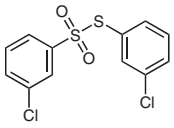
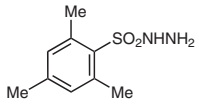
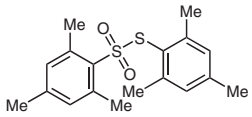
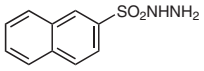
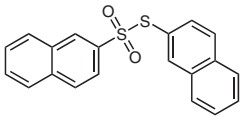
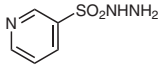
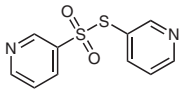
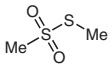
Entry	Substrate **1**	Product **2**	Yield (%)
1	 **1a**	 **2a**	87
2	 **1b**	 **2b**	84
3	 **1c**	 **2c**	88
4	 **1d**	 **2d**	80
5	 **1e**	 **2e**	76
6	 **1f**	 **2f**	71
7	 **1g**	 **2g**	73
8	 **1h**	 **2h**	70
9	 **1i**	 **2i**	72

Table 2 (continued)

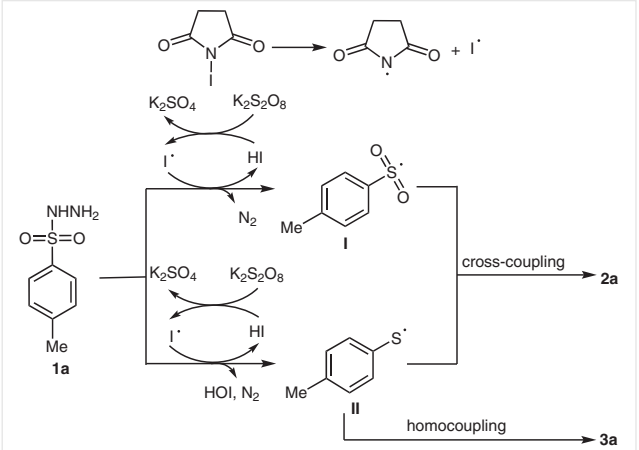
Entry	Substrate **1**	Product **2**	Yield (%)
10	 **1j**	 **2j**	73
11	 **1k**	 **2k**	88
12	 **1l**	 **2l**	84
13	 **1m**	 **2m**	trace
14	$MeSO_2NHNH_2$ **1n**	 **2n**	61

[a] Reaction conditions: **1** (0.3 mmol), NIS (0.06 mmol, 20 mol%), $K_2S_2O_8$ (0.36 mmol, 1.2 equiv), and THF (2 mL) open in air at 70 °C for 8 h.

To gain insight into the reaction mechanism, two control experiments were performed under the standard conditions (Scheme 2). We found that radical scavengers, such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT), significantly suppressed the reaction progress, indicating that the transformation occurred *via* a radical process (Scheme 2, a). Motivated by the result in Table 1, entry 2 and the literature precedents,[12] we speculated that the 1,2-di-*p*-tolyldisulfane (**3a**) might be an intermediate for this reaction. However, the designed reaction was inert under the standard conditions (Scheme 2, b).

Lastly, a hypothetical mechanism for the radical coupling reaction is outlined in Scheme 3 on the basis of the above results and previously reports.[6,13,14] At first, the iodine radical was generated from NIS.[13] Subsequently, sulfonyl hydrazide **1a** can transfer to sulfonyl radical **I** and **II** with the aid of iodine radical under the oxidative conditions.[13,14] The generation of sulfonyl radical **II** is supported by the isolation of **3a**. Finally, the cross-coupling reaction between radical **I** and **II** forms the desired thiosulfonate **2a**.[6]

In conclusion, we have demonstrated a novel and environmentally benign method for the efficient synthesis of thiosulfonates *via* NIS/$K_2S_2O_8$-promoted radical coupling reaction of sulfonyl hydrazides. The reaction proceeds through a radical cross-coupling process, in which one new S–S bond was formed. A possible reaction mechanism was



Scheme 3 Plausible reaction mechanism

proposed to explain the product formation. Further studies of this strategy, focusing on the synthesis of other *S*-heterocyclic compounds *via* a radical coupling process, is underway in our laboratory.

Funding Information

This research is sponsored by the Natural Science Foundation of Zhejiang Province (No. LQ18B020002), State Key Laboratory of Analytical Chemistry for Life Science (No. SKLACLS1804), the Open Subject of State Key Laboratory of Chemo/Biosensing and Chemometrics (2017016), Education Foundation of Zhejiang Province (No. Y201737123), and the K. C. Wong Magna Fund in Ningbo University. Prof. Z.Y. Guo also thank the Natural Science Foundation of China (Grants 41576098, 81773483).

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610649.

References and Notes

(1) For selected book and papers, see: (a) Acton, A. *Pharmaceuticals – Advances in Research and Application*; Scholarly editions: Atlanta, GA, **2012**. (b) Natarajan, P. *Tetrahedron Lett.* **2015**, *56*, 4131. (c) Iranpoor, N.; Mohajer, D.; Rezaeifard, A.-R. *Tetrahedron Lett.* **2004**, *45*, 3811.

(2) For selected book and paper, see: (a) Andrushko, V.; Andrushko, N. *Stereoselective Synthesis of Drugs and Natural Products*; John Wiley and Sons: New York, **2013**. (b) Zefirov, N. S.; Zyk, N. V.; Beloglaskina, E. K.; Kutateladze, A. G. *Sulfur Rep.* **1993**, *14*, 223.

(3) For selected papers, see: (a) Kirihara, M.; Naito, S.; Ishizuka, Y.; Hanai, H.; Noguchi, T. *Tetrahedron Lett.* **2011**, *52*, 3086. (b) Abdo, M.; Knapp, S. *J. Org. Chem.* **2012**, *77*, 3433. (c) Xu, Y.; Peng, Y.; Sun, J.; Chen, J.; Ding, J.; Wu, H. *J. Chem. Res.* **2010**, *41*, 358.

(4) For selected papers, see: (a) Iranpoor, N.; Mohajer, D.; Rezaeifard, A. R. *Tetrahedron Lett.* **2004**, *45*, 3811. (b) Iranpoor, N.; Firouzabadi, H.; Pourali, A. *Phosphorus, Sulfur Silicon Relat. Elem.* **2006**, *181*, 473. (c) Bahrami, K.; Khodaei, M. M.; Khaledian, D. *Tetrahedron Lett.* **2012**, *53*, 354. (d) Nair, V.; Augustine, A. *Org. Lett.* **2003**, *4*, 543. (e) Sobhani, S.; Aryanejad, S.; Maleki, M. F. *Synlett* **2011**, 319.

(5) For selected papers, see: (a) Liang, G. A.; Chen, J.; Chen, J.; Li, W.; Chen, J.; Wu, H. *Tetrahedron Lett.* **2012**, *53*, 6768. (b) Taniguchi, N. *J. Org. Chem.* **2015**, *80*, 1764. (c) Tranquilino, A.; Andrade, S. R. C. P.; Silva, A. P. M.; Menezes, P. H.; Roberta, A. O. *Tetrahedron Lett.* **2017**, *58*, 1265.

(6) Li, X.-J.; Zhou, C.; Diao, P.-H.; Ge, Y.-Q.; Guo, C. *Tetrahedron Lett.* **2017**, *58*, 1296.

(7) Zhang, G.-Y.; Lv, S.-S.; Shoberu, A.; Zou, J.-P. *J. Org. Chem.* **2017**, *82*, 9801.

(8) For selected papers, see: (a) Liu, Y.-W.; Badsara, S. S.; Liu, Y.-C.; Lee, C.-F. *RSC Adv.* **2015**, *5*, 44299. (b) Zhang, X.-S.; Jiao, J.-Y.; Zhang, X.-H.; Hu, B.-L.; Zhang, X.-G. *J. Org. Chem.* **2016**, *81*, 5710. (c) Chen, J. C.; Wang, T. Y.; Wang, T.; Lin, A. J.; Yao, H. Q.; Xu, J. Y. *Org. Chem. Front.* **2016**, *4*, 130. (d) Ji, P.-Y.; Zhang, M.-Z.; Xu, J.-W.; Liu, Y.-F.; Guo, C.-C. *J. Org. Chem.* **2016**, *81*, 5181. (e) Sen, C.; Sahoo, T.; Ghosh, S. C. *ChemistrySelect* **2017**, *2*, 2745. (f) Wu, Y.-D.; Huang, B.; Zhang, Y.-X.; Wang, X.-X.; Dai, J.-J.; Xu, J.; Xu, H.-J. *Org. Biomol. Chem.* **2016**, *14*, 5936.

(9) Finkbeiner, P.; Nachtsheim, B. J. *Synthesis* **2013**, *45*, 979.

(10) (a) Wei, W.-T.; Zhu, W.-M.; Shao, Q. J.; Bao, W.-H.; Chen, W.-T.; Chen, G.-P.; Luo, Y.-J.; Liang, H. Z. *ACS Sustainable Chem. Eng.* **2018**, *6*, 8029. (b) Wei, W.-T.; Zhu, W.-M.; Ying, W.-W.; Wang, Y.-N.; Bao, W.-H.; Gao, L.-H.; Luo, Y.-J.; Liang, H. Z. *Adv. Synth. Catal.* **2017**, *359*, 3551. (c) Wei, W.-T.; Zhu, W.-M.; Ying, W.-W.; Wu, Y.; Huang, Y.-L.; Liang, H. Z. *Org. Biomol. Chem.* **2017**, *15*, 5254. (d) Wei, W.-T.; Zhu, W.-M.; Liang, W. D.; Wu, Y.; Huang, H.-Y.; Huang, Y.-L.; Luo, F.-J.; Liang, H. Z. *Synlett* **2017**, *28*, 2153. (e) Ying, W.-W.; Zhu, W.-M.; Gao, Z.-H.; Liang, H. Z.; Wei, W.-T. *Synlett* **2018**, *29*, 663.

(11) **General Procedure**

To a Schlenk tube were added sulfonyl hydrazides (0.3 mmol), NIS (0.06 mmol), $K_2S_2O_8$ (0.36 mmol), and THF (2 mL). Then the tube was stirred open in air at 70 °C for the indicated time until complete consumption of starting material as monitored by TLC analysis. After the reaction was finished, the solution was concentrated under reduced pressure, and the mixture was purified by flash column chromatography over silica gel (hexane/ethyl acetate) to afford the desired product **2** and was analyzed by ^{1}H NMR and ^{13}C NMR spectroscopy (see Supporting Information).

Typical Data for Representative Compound: *S*-(*p*-Tolyl)4-methylbenzenesulfonothioate (2a)

Yellow oil (36.3 mg, 87% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.45 (d, *J* = 7.6 Hz, 2 H), 7.38 (d, *J* = 7.6 Hz, 2 H), 7.26–7.20 (m, 4 H), 2.40 (s, 3 H), 2.34 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 145.6, 142.6, 140.1, 136.5, 130.9, 130.3, 127.6, 124.2, 21.6, 21.4.

(12) Singh, R.; Allam, B. K.; Singh, N.; Kumari, K. K.; Singh, S. K.; Singh, K. N. *Org. Lett.* **2015**, *17*, 2656.

(13) Cao, X.; Cheng, X.; Xuan, J. *Org. Lett.* **2018**, *20*, 449.

(14) For selected papers, see: (a) Liu, Y.; Zheng, G. F.; Zhang, Q.; Li, Y.; Zhang, Q. *J. Org. Chem.* **2017**, *82*, 2269. (b) Wang, S. C.; Huang, X. H.; Wang, Q.; Ge, Z. M.; Wang, X.; Li, R. T. *RSC Adv.* **2016**, *6*, 11754. (c) Zhao, W. N.; Xie, P.; Bian, Z. G.; Zhou, A. H.; Ge, H. B.; Zhang, M.; Ding, Y. C.; Zheng, L. *J. Org. Chem.* **2015**, *80*, 9167. (d) Wang, F.-X.; Tian, S.-K. *J. Org. Chem.* **2015**, *80*, 12697. (e) Bao, Y.; Yang, X. Q.; Zhou, Q. F.; Yang, F. L. *Org. Lett.* **2018**, *20*, 1966. (f) Liang, G. G.; Liu, M. C.; Chen, J. X.; Ding, J. C.; Gao, W. X.; Wu, H. Y. *Chin. J. Chem.* **2012**, *30*, 1611. (g) Liang, G. G.; Chen, J.; Chen, J. L.; Li, W. M.; Chen, J. X.; Wu, H. Y. *Tetrahedron Lett.* **2012**, *53*, 6768. (h) Taniguchi, N. *Eur. J. Org. Chem.* **2014**, 5691.