Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201500943

Iodine-Mediated Synthesis of Aromatic Thioethers with Aromatic Amines and Sulfonyl Hydrazides in High Regioselectivity *via* C(sp^2)–H Bond Functionalization

Xiaobo Pang,[a] Likui Xiang,[a] Xiaodong Yang,[a] and Rulong Yan[a,*]

[a] State Key Laboratory of Applied Organic Chemistry, Key Laboratory of Nonferrous Metal Chemistry and Resources Utilization of Gansu Province, Department of Chemistry, Lanzhou University, Lanzhou, Gansu 730000, People's Republic of China
Fax: (+86)-931-891-2596; e-mail: yanrl@lzu.edu.cn

Received: October 6, 2015; Revised: October 29, 2015; Published online: January 12, 2016

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201500943.

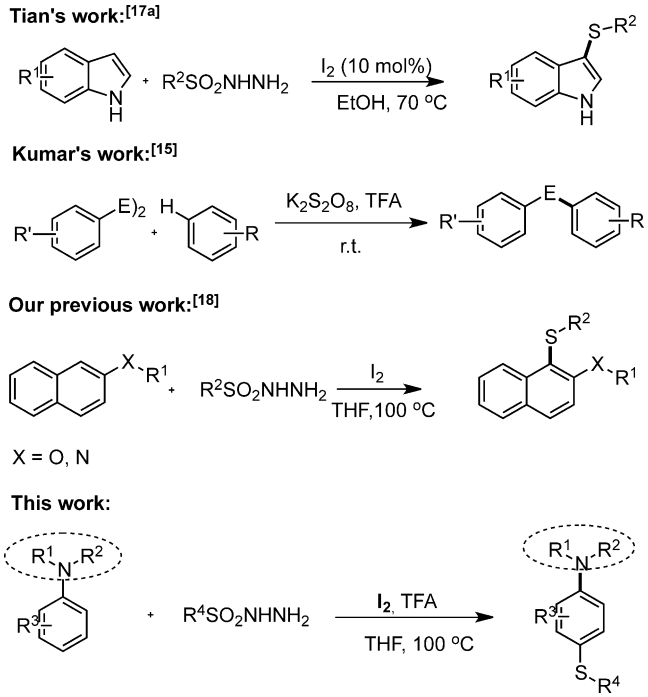
Abstract: An iodine-mediated synthesis of aromatic thioethers from aromatic amines and sulfonyl hydrazides *via* C(sp^2)–H bond functionalization and C–S bond formation has been developed. In this procedure, various substituents on the sulfonyl hydrazides, such as alkyl, methoxyl, chloro, bromo and fluoro groups, and aromatic amines are tolerated in the thiolation which generates the desired products in moderate to good yields.

Keywords: aromatic thioethers; C–S bond formation; hydrazines; iodine; regioselectivity; sulfur

Organic compounds containing C–S bond are widely present in many functional materials.[1] Furthermore, organosulfur compounds are important building blocks for the synthesis many bioactive[2] and pharmaceutical compounds.[3] Particularly, the structural unit of diaryl sulfides exists extensively in potential drug candidates with antifungal and anticancer activities as well as for HIV, Alzheimer's or Parkinson's diseases.[4] A number of transition metal-catalyzed approaches to synthesize diaryl sulfides has been developed.[5] Most of the transition metal-catalyzed strategies, such as Pd,[6] Cu,[7] Co,[8] Rh,[9] etc.[10] have similar drawbacks for extensive applications due to the expensive and toxic transition metal catalysts. With the increased concern about environmental issues, metal-free cross-coupling reactions for the construction of the C–S bond have been demonstrated as highly efficient protocols and have received much attentions. In the past several years, excellent and significant works on the construction of the C–S bond have been reported by the groups of Tian,[11] Jiang,[12] and others[13] through eco-friendly and economical methods. In those procedures, various thiolating/sulfenylating reagents had been applied for C–S bond formation.[14] In 2013, Kumar's group reported a transition metal-free synthetic method for unsymmetrical diaryl chalcogenides from arenes and diaryl dichalcogenides.[15] More recently, Wang's group reported an iodine-catalyzed arylthiation of substituted anilines with thiols to form the C–S bond.[16] Nevertheless, it is still a great challenge to synthesize diaryl sulfides from readily accessible substrates through metal-free oxidative reactions.

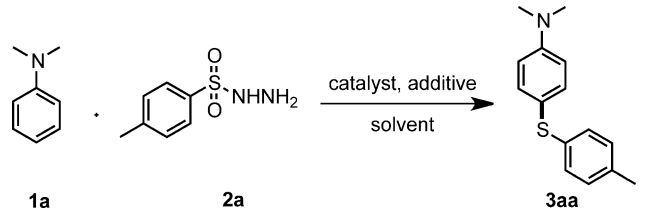
Sulfonyl hydrazide, as an ideal thiolating agent, has emerged as a candidate due to its ready accessibility and stability. To the best of our knowledge, there are as yet no examples concerning a method for the construction the C–S bond to a benzene ring directly uzsing sulfonyl hydrazides as sulfenylating agents under metal-free conditions. Inspired by previous works[17]and our experience in development of new and efficient methods for the construction of the C–S bond,[18] herein we have developed a direct C–S bond formation method between aromatic amines and sulfonyl hydrazides under I_2-mediated conditions with high regioselectivity (Scheme 1).

N,N-Dimethylaniline **1a** and *p*-toluenesulfonyl hydrazide **2a** were firstly chosen as model substrates in the presence of I_2 (0.5 equiv.) in THF at 100 °C, no reaction occurred under these conditions. It was gratifying that with the use of 0.5 equiv. 2,2,2-trifluoroacetic acid (TFA) as the additive, *N,N*-dimethyl-4-(*p*-tolylthio)aniline **3aa** was isolated in 52% (Table 1, entry 2). Extensive evaluating of other acids as additives, such as boron fluoride·diethyl etherate ($Et_2O{\cdot}BF_3$), trifluoromethanesulfonic acid (TfOH), $Sc(OTf)_3$, pivalic acid (PivOH) and $InBr_3$, lower or no yields of **3aa** were obtained (Table 1, entries 3–7). Then different amounts of TFA were used in the reaction (Table 1, entries 8–11) and 1.2 equiv. of TFA



Scheme 1. C–S bond formation reactions.

Table 1. Optimization of reaction condition.[a]



Entry	Catalyst (equiv.)	Additive (equiv.)	Yield [%][b]
1	I_2 (0.5)	–	–
2	I_2 (0.5)	TFA (0.5)	52
3	I_2 (0.5)	$Et_2O{\cdot}BF_3$ (0.5)	42
4	I_2 (0.5)	TfOH (0.5)	–
5	I_2 (0.5)	$Sc(OTf)_3$ (0.5)	–
6	I_2 (0.5)	PivOH (0.5)	–
7	I_2 (0.5)	$InBr_3$ (0.5)	–
8	I_2 (0.5)	TFA (0.2)	–
9	I_2 (0.5)	TFA (0.8)	60
10	I_2 (0.5)	TFA (1.0)	72
11	I_2 (0.5)	TFA (1.2)	88
12	–	TFA (1.2)	–
13	I_2 (0.2)	TFA (1.2)	43
14	I_2 (1.0)	TFA (1.2)	80
15[c]	I_2 (0.5)	TFA (1.2)	63

[a] *Reaction conditions:* **1a** (0.3 mmol), **2a** (0.6 mmol), additive, THF (2 mL), 100 °C, 12 h.
[b] Isolated yield.
[c] 0.36 mmol of **2a** was used in this process.

gave an excellent yield for this reaction. After screening the amount of I_2 for the transformation, the highest yield was achieved when 0.5 equiv. I_2 was used. Moreover, we found that I_2 was crucial for this reaction and no desired product was isolated in the absence of I_2 (Table 1, entries 12–14). After the reaction conditions had been screened, it could be concluded that the optimal reaction should be performed in the presence of I_2 (0.5 equiv.) and TFA (1.2 equiv.) in THF at 100 °C (Table 1, entry 11).

Under these optimal reaction conditions, a series of arylsulfonyl hydrazides was investigated for this reaction (Table 2). To our delight, various substituted sulfonyl hydrazides could react with *N,N*-dimethylaniline and generate the desired products in moderate to high yields. In this process, the electronic effect of the substituted sulfonyl hydrazides had mo major influence on the reaction and the sulfonyl hydrazides with electron-donating and electron-withdrawing groups gave the desired products in similar yields. Nevertheless, when **1a** reacted with 4-nitrobenzenesulfonohydrazide **2o** under the optimal reaction conditions, just only a trace of **3ao** was detected by TLC. Moreover, the thiophene-2-sulfonohydrazide **2n** was also tolerated in this process, furnishing the target compounds **3an** in excellent yield.

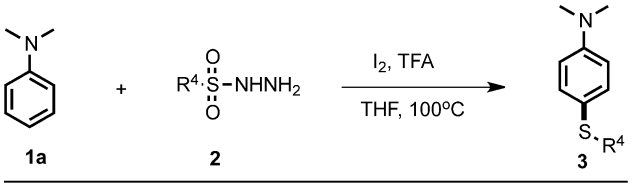
The success of C–S bond formations between substituted sulfonyl hydrazides and *N,N*-dimethylaniline inspired us to investigate a variety of substituted aromatic amines. Then, various aromatic amines were also investigated in the process (Table 3) and most of the aromatic amines could couple with **2a** in moderate yields. It was clearly observed that moderate yields were afforded when the aromatic amines with nitrogen heterocycles, such as 1-(*o*-tolyl)piperazine **1f**, 4-phenylmorphline **1g**, 1-phenylpyrrolidine **1h** were used. However, when 1-phenyl-1*H*-pyrrole **1i**, *N*-methylaniline **1j** and aniline **1k** were employed under the optimal reaction conditions, only trace amounts of **3ia**, **3ja** and **3ka** were obtained.

To gain further insights into this transformation, firstly, we performed experiments of coupling **1a** and **2a** at 100 °C with 0.5 equiv. I_2 in THF for 10 h, the by-products **4**, **5** and product **3aa** were detected in the reaction mixture. Next, the compounds **4** and **5** can both react with **1a** to give the desired product **3aa** in 70% and 74% yields, respectively (Scheme 2).

On the basis of previous relevant studies and experimental results, a proposed mechanism for this process is depicted in Scheme 3. First, sulfonyl hydrazide **2** was converted to intermediated **4** under the catalysis of iodine. At the same time, N_2, HOI and HI were generated in this process.[17a] Subsequently, intermediate **5** which was produced by reduction of **4** reacted with HI to form sulfenyl iodide **6**. Finally, the target compound **3** was accessed by electrophilic substitution between **6** and **1**.

In summary, we have developed a straightforward method for the synthesis of aromatic thioethers in

Table 2. Thiolation of substituted sulfonyl hydrazides and *N,N*-dimethylaniline.



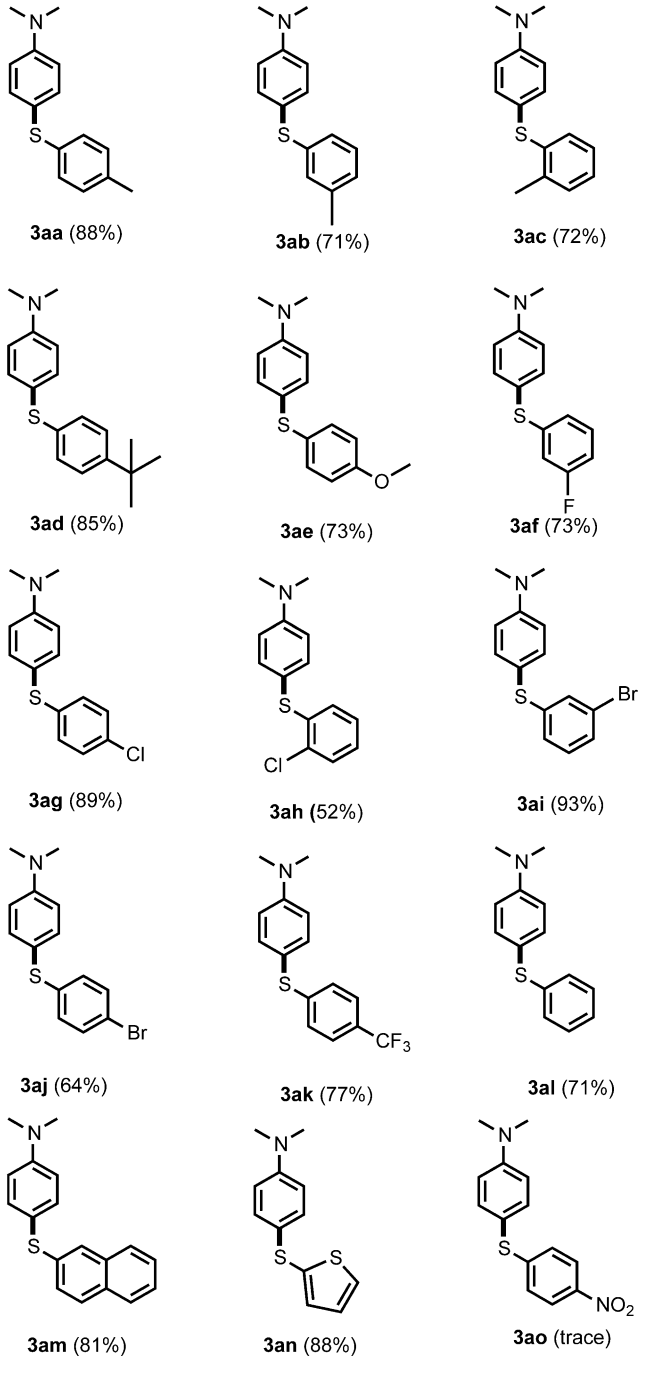
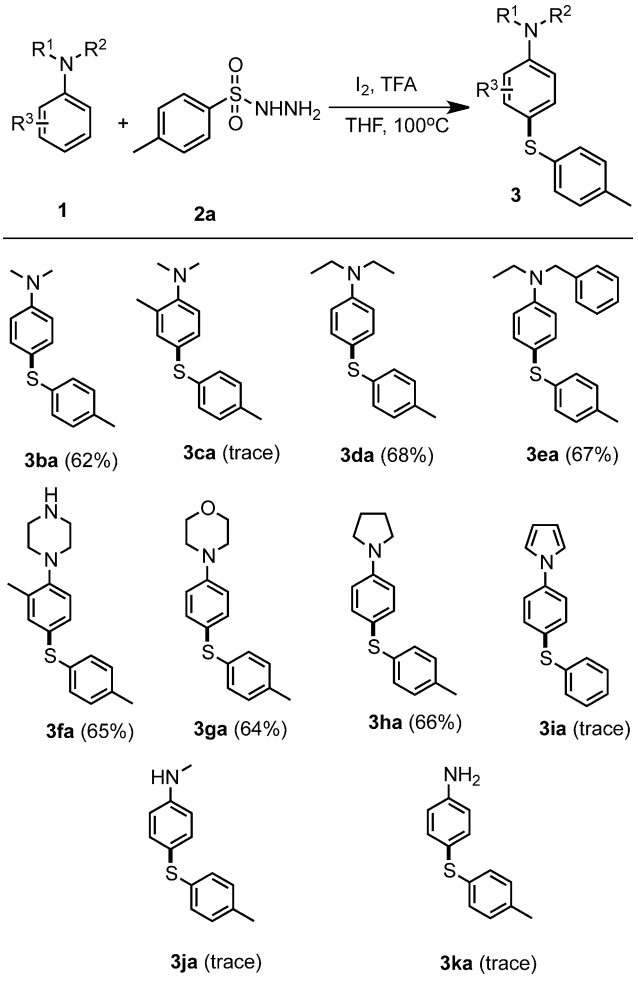
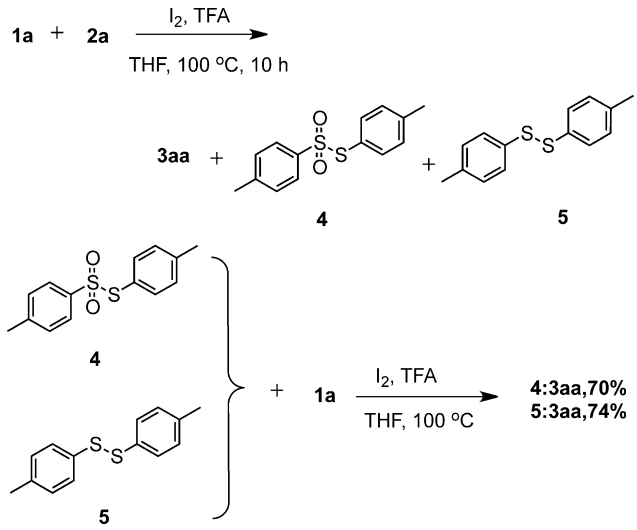


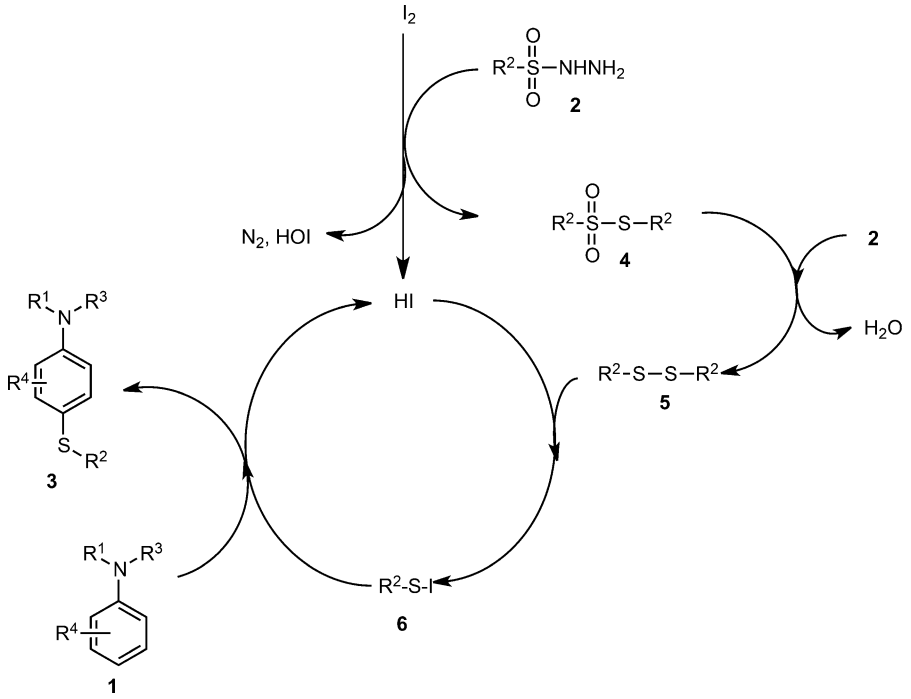
Table 3. Thiolation of substituted aromatic amines and *p*-toluenesulfonyl hydrazides.





Scheme 2. Control experiments.

high regioselectivity through C(sp^2)–H bond functionalization of aromatic amines. A series of aromatic amines and sulfonyl hydrazides were tolerated in this



Scheme 3. Proposed mechanism.

transformation and generated synthetically valuable aromatic thioethers in moderate to good yields when utilizing iodine and TFA.

Experimental Section

General Procedure for the Synthesis of the Desired Aromatic Thioethers

An oven-dried pressure tube was charged with aromatic amine **1** (0.3 mmol), arylsulfonyl hydrazide **2** (0.6 mmol), I_2 (0.15 mmol), TFA (0.36 mmol) and 2 mL of THF. Next, the mixture was stirred at 100 °C for 12 h. After cooling to room temperature, the mixture was diluted with ethyl acetate and washed with a solution of sodium thiosulfate. Then the solution was extracted with ethyl acetate and dried with anhydrous sodium sulfate. The combined organic phase was evaporated under vacuum, and the residues were purified by column chromatography. Finally, the product **3** was obtained.

Acknowledgements

This work was supported by National Natural Science Foundation of China (21202067) and the Fundamental Research Funds for the Central Universities (lzujbky-2014-71).

References

[1] H. Yamaguchi, Y. Minoura, *Appl. Polym. Sci.* **2003**, *15*, 1869.

[2] a) M. I. Konaklieva, B. J. Plotkin, *Recent Pat. Anti-Infect. Drug Discovery* **2006**, *1*, 177; b) J. Legors, J. R. Dehli, C. Bolm, *Adv. Synth. Catal.* **2005**, *347*, 19; c) H. Kumagai, *Aroma Res.* **2004**, *5*, 312; d) S. C. Mitchell, R. M. Nickson, R. H. Waring, *Sulfur Rep.* **1993**, *13*, 279.

[3] a) B. M. Trost, I. Fleming, (Eds.); *Comprehensive Organic Syntheses*, Vol. 6, Pergamon Press, Oxford, **1996**; b) I. P. Beletskaya, V. P. Ananikov, *Chem. Rev.* **2011**, *111*, 1596.

[4] a) S. Sciabola, E. Carosati, M. Baroni, R. Mannhol, *J. Med. Chem.* **2005**, *48*, 3756; b) L. Llauger, H. He, J. Kim, J. Aguirre, N. Rosen, U. Peters, P. Davies, G. J. Chiosis, *J. Med. Chem.* **2005**, *48*, 2892; c) T. Otzen, E. G. Wempe, B. Kunz, R. Bartels, G. Lehwark-Yvetot, W. Hansel, K. J. Schaper, J. K. Seydel, *J. Med. Chem.* **2004**, *47*, 240; d) Y. Wang, S. Chackalamannil, Z. Hu, J. W. Clader, W. Greenlee, W. Billard, H. Binch, G. Crosby, V. Ruperto, R. A. Duffy, R. McQuade, J. E. Lachowiz, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2247; e) Z. Y. Sun, E. Botros, A. D. Su, Y. Kim, E. J. Wang, N. Z. Baturay, C. H. Kwon, *J. Med. Chem.* **2000**, *43*, 4160; f) S. F. Nielsen, E. O. Nielsen, G. M. Olsen, T. Liljefors, D. Peters, *J. Med. Chem.* **2000**, *43*, 2217.

[5] a) X. H. Ye, J. L. Petersen, X. D. Shi, *Chem. Commun.* **2015**, *51*, 7863; b) Y. Zhang, Y. Li, X. Zhang, X. Jiang, *Chem. Commun.* **2015**, *51*, 941; c) P. Saravanan, P. Anbarasan, *Org. Lett.* **2014**, *16*, 848; d) P. F. Wang, X. Q. Wang, J. J. Dai, Y. S. Feng, H. J. Xu, *Org. Lett.* **2014**, *16*, 4586; e) S. R. Guo, W. M. He, J. N. Xiang, Y. Q. Yuan,

Chem. Commun. **2014**, *50*, 8578; f) H. Tian, C. J. Zhu, H. J. Yang, H. Fu, *Chem. Commun.* **2014**, *50*, 8875.
[6] a) T. Migita, T. Shimizu, Y. Asami, J. Shiobara, Y. Kato, M. Kosugi, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385; b) M. A. Fernandez-Rodriguez, Q. Shen, J. F. Hartwig, *Chem. Eur. J.* **2006**, *12*, 7782; c) M. Sayah, M. G. Organ, *Chem. Eur. J.* **2011**, *17*, 11719; d) V. Guilarte, M. A. Fernandez-Rodriguez, P. Garcia-Garcia, E. Hernando, R. Sanz, *Org. Lett.* **2011**, *13*, 5100.
[7] a) E. Sperotto, G. P. M. van Klink, J. G. de Vries, G. van Koten, *J. Org. Chem.* **2008**, *73*, 5625; b) F. Y. Kwong, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 3517; c) C. K. Chen, Y. W. Chen, C. H. Lin, H. P. Lin, C. F. Lee, *Chem. Commun.* **2010**, *46*, 282; d) C. G. Bates, P. Saejueng, M. Q. Doherty, D. Venkataraman, *Org. Lett.* **2004**, *6*, 5005; e) C. Uyeda, Y. Tan, G. C. Fu, J. C. Peters, *J. Am. Chem. Soc.* **2013**, *135*, 9548; f) X. Li, Y. Xu, W. Wu, C. Jiang, C. Qi, H. Jiang, *Chem. Eur. J.* **2014**, *20*, 7911.
[8] Y. C. Wong, T. T. Jayanth, C. H. Cheng, *Org. Lett.* **2006**, *8*, 5613.
[9] a) K. Ajiki, M. Hirano, K. Tanaka, *Org. Lett.* **2005**, *7*, 4193; b) M. Arisawa, T. Suzuki, T. Ishikawa, M. Yamaguchi, *J. Am. Chem. Soc.* **2008**, *130*, 12214.
[10] a) A. Correa, M. Carriland, C. Bolm, *Angew. Chem.* **2008**, *120*, 2922; *Angew. Chem. Int. Ed.* **2008**, *47*, 2880; b) J. R. Wu, C. H. Lin, C. F. Lee, *Chem. Commun.* **2009**, 4450; c) S. Jammi, P. Barua, L. Rout, P. Saha, T. Punniyamurthy, *Tetrahedron Lett.* **2008**, *49*, 1484; d) Y. G. Zhang, K. C. Ngeow, J. Y. Ying, *Org. Lett.* **2007**, *9*, 72, 3495; e) O. Baldovino-Pantaleon, S. Hernandez-Ortega, D. Morales-Morales, *Adv. Synth. Catal.* **2006**, *348*, 236.
[11] a) F. L. Yang, F. X. Wang, T. T. Wang, Y. J. Wang, S. K. Tian, *Chem. Commun.* **2014**, *50*, 2111; b) F. L. Yang, X. T. Ma, S. K. Tian, *Chem. Eur. J.* **2012**, *18*, 1582; c) T. T. Wang, F. X. Wang, F. L. Yang, S. K. Tian, *Chem. Commun.* **2014**, *50*, 3802.
[12] Y. Xu, X. Tang, W. Hu, W. Wu, H. Jiang, *Green Chem.* **2014**, *16*, 3720.
[13] a) S. R. Guo, Y. Q. Yuan, J. N. Xiang, *Org. Lett.* **2013**, *15*, 4654; b) R. Y. Tang, Y. X. Xie, Y. L. Xie, J. N. Xiang, J. H. Li, *Chem. Commun.* **2011**, *47*, 12867.
[14] a) X. Chen, X. S. Hao, C. E. Goodhue, J. Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 6790; b) K. Inamoto, Y. Arai, K. Hiroya, T. Doi, *Chem. Commun.* **2008**, 5529; c) X. Zhao, E. Dimitrijevic, V. M. Dong, *J. Am. Chem. Soc.* **2009**, *131*, 3466; d) S. I. Fukuzawa, E. Shimizu, Y. Atsuumi, M. Haga, K. Ogata, *Tetrahedron Lett.* **2009**, *50*, 2374; e) X. L. Fang, R. Y. Tang, P. Zhong, J. H. Li, *Synthesis* **2009**, 4183; f) S. H. Zhang, M. L. Hu, J. Cheng, *J. Org. Chem.* **2010**, *75*, 6732.
[15] C. D. Prasad, S. J. Balkrishna, A. Kumar, B. S. Bhakuni, K. Shrimali, S. Biswas, S. Kumar, *J. Org. Chem.* **2013**, *78*, 1434.
[16] D. S. Yang, K. L. Yan, W. Wei, J. Zhao, X. G. Sheng, G. Q. Li, S. L. Lu, H. Wang, *J. Org. Chem.* **2015**, *80*, 6083.
[17] a) F. L. Yang, S. K. Tian, *Angew. Chem. Int. Ed.* **2013**, *52*, 4929; b) V. G. Ricordi, S. Thurow, F. Penteado, R. F. Schumacher, G. Perin, E. J. Lenardao, D. Alves, *Adv. Synth. Catal.* **2015**, *357*, 933.
[18] X. Kang, R. L. Yan, G. Q. Yu, X. B. Pang, X. X. Liu, X. N. Li, L. K. Xiang, G. S. Huang, *J. Org. Chem.* **2014**, *79*, 10605.

