Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: Y. Li, S. Huang, C. Liao, Y. Shao and L. Chen, *Org. Biomol. Chem.*, 2018, DOI: 10.1039/C8OB02129E.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C8OB02129E

Journal Name

COMMUNICATION

Transition-metal-free access to 2-aminopyridine derivatives from 2-fluoropyridine and acetamidine hydrochloride

Received 00th January 20xx,
Accepted 00th January 20xx

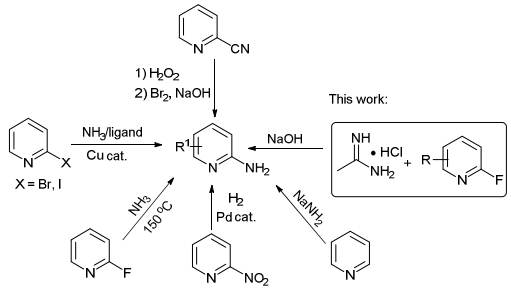
DOI: 10.1039/x0xx00000x

www.rsc.org/

Yibiao Li*[a], Shuo Huang[a], Chunshu Liao[a], Yan Shao[a] and Lu Chen[a]

Under catalyst-free conditions, an efficient method for the synthesis of 2-aminopyridine derivatives through the nucleophilic substitution and hydrolysis of 2-fluoropyridine and acetamidine hydrochloride has been developed. This amination uses inexpensive acetamidine hydrochloride as the ammonia source and has the advantages of a high yield, high chemoselectivity and wide substrate adaptability. The results suggest that other N-heterocycles containing fluorine substituents can also complete the reaction via these reaction conditions and yield the target products.

The formation of C–N bonds constitutes one of the most important transformations in organic synthesis, primarily due to the large proportion of medicinally relevant structures, dyes, and materials that contain amines.[1] 2-Aminopyridine derivatives have attracted much attention because of their wide application in heterocyclic synthesis. 2-Aminopyridine is a ubiquitous structural element in the synthesis of natural products, pharmaceutical and medicinal compounds, and fine chemicals such as luminescent materials. [2] Therefore, the development of a highly chemoselective method for the synthesis of 2-aminopyridine derivatives has both research significance and application value. Among the many methods for the synthesis of 2-aminopyridine, the copper-catalysed amination of 2-halogenopyridine is the most commonly used method, which has advantages such as high yield and mild reaction conditions. [3] The Pd-catalysed amination of 2-bromopyridine and $(Me_3Si)_2NHLi$ results in an 88% yield of the product 2-aminopyridine. [4] 2-Aminopyridine can also be prepared from the ammonolysis of 2-fluoro-pyridine and ammonia. However, high pressure and a sealed reaction vessel are required for the use of ammonia at high temperature. [5] Singarama and co-worker reported that lithium amides promote the amination of 2-fluoropyridine under mild conditions and providing 2-aminopyridines in good yields. [6] In addition, this reaction has low chemoselectivity and substrate adaptability. 2-Aminopyridine can also be obtained from the hydrolysis and Hofmann degradation of 2-cyanopyridine. [7] However, this method requires the use of a large amount of oxidants and toxic bromine and is therefore not suitable for large-scale production because of the difficulty in controlling the reactivity. 2-Aminopyridine can be obtained from the Pd/H_2-catalysed reduction of 2-nitropyridine[8]. The preparation of 2-aminopyridine through the Chichibabin reaction of pyridine compounds and sodium amide has very high atom economy. [9] However, the substrate of this reaction has very narrow applicability. In addition, the reaction suffers from many side reactions and strict reaction conditions. Although many methods for the synthesis of 2-aminopyridine exist, the continuous development of synthetic methods for 2-aminopyridine that have mild and controllable conditions and high chemoselectivity is extremely important.



Scheme 1 Synthesis of 2-aminopyridine

One important characteristic of more environmentally benign synthesis is to avoid the use of expensive transition metals and to use water as the surrogate solvent. While investigating the synthesis of haloimidazoles through the copper-catalysed reaction of 1,1-dibromoalkenes and amidines,[10] we found that in the synthesis of amidine compounds, small amounts of aniline by-products can be obtained from the copper-catalysed reaction of iodobenzene and acetamidine hydrochloride. Fu et al. also reported the preparation of primary aromatic amine derivatives from the

[a]School of Biotechnology and Health Sciences, Wuyi University, Jiangmen, Guangdong Province 529090, China, E-mail: leeyib268@126.com

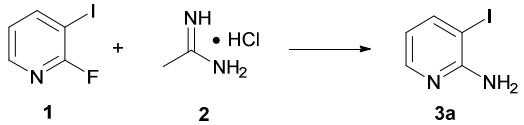
†Electronic Supplementary Information (ESI) available: General Experimental information, experimental procedure for product synthesis, full characterization data, ^1H and ^{13}C NMR spectra of all products. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C8OB02129E

copper-catalysed coupling and hydrolysis of iodobenzene and acetamidine hydrochloride; the results showed that catalysts and ligands are crucial to the reaction.[11] In the preparation of benzofuran, benzothiophene, thienopyridine and other heterocycles through cyclization from the oxygen and sulfur nucleophilic substitution of the C-F bond in 2-fluorophenylacetylene derivatives, we found that the reactivity of nucleophilic substitution on halogen atoms follows the descending order of F>Br>Cl>I.[12] In particular, the C-F bond close to the C-C triple bond is highly reactive and prone to nucleophilic substitution. In the present paper, we found that the C-F bond in the 2-position of pyridine also has high reactivity and chemoselectivity in nucleophilic substitution. Herein, we report an efficient transition-metal-free method for the synthesis of 2-aminopyridine derivatives with high yields from 2-fluoropyridine and acetamidine hydrochloride by using water as the mixing solvent.

At first, 2-fluoro-3-iodopyridine and acetamidine hydrochloride were chosen as the model substrates to optimize the reaction conditions. In lieu of transition metals as catalysts, Cs_2CO_3 was chosen as the base, and dimethyl sulfoxide (DMSO) was chosen as the solvent. After reacting for 24 hours at 120 °C, we found that this reaction can proceed to give a 23% yield of the target product (Table 1, entry 1). We found through the solvent screening that DMSO is the optimal solvent (Table 1, entries 2-5), whereas when toluene was used as the solvent, no target product was detected. Next, we further screened the base and found that carbonates and K_3PO_4 exhibited no apparent promotion effect (Table 1, entries 6-8). However, moderate yields were obtained when ^{t}BuOLi and sodium tert-butoxide were used (Table 1, entries 9-10). Surprisingly, when inexpensive NaOH was used, the yield can be significantly improved to 88%. When the reaction time was shortened to 12 hours, the yield decreased to 69%. However, when the reaction time was extended to 36 hours, the yield improved slightly to 91% (Table 1, entries 12-13). Lastly, we found that when the temperature was 130 °C, the reaction yield can reach 95% (Table 1, entry 14). This is likely because the amination requires nucleophilic substitution and hydrolysis; low temperature is unfavourable for the hydrolysis of amidine intermediates, thus resulting in the incomplete hydrolysis of the intermediate N-(3-iodopyridin-2-yl)acetamidine in the reaction. Lastly, we tested the ammonolysis by replacing acetamidine hydrochloride with pentanimidamide hydrochloride and cyclobutane carboxamide hydrochloride. The results suggest that acetamidine hydrochloride exhibited the best ammonolysis effect (Table 1, entries 15-16). It was found that the presence of glycerol or H_2O as solvent does not facilitate the reaction (Table 1 entries 17-18).

Table 1. Optimization of the Reaction Conditions[a]



1 **2** **3a**

Entry	Base	Solvent	Yield[b](%)
1	Cs_2CO_3	DMSO	23
2	Cs_2CO_3	DMF	13
3	Cs_2CO_3	DMAC	16
4	Cs_2CO_3	NMP	0
5	Cs_2CO_3	Toluene	0
6	K_2CO_3	DMSO	25
7	Na_2CO_3	DMSO	44
8	K_3PO_4	DMSO	63
9	^{t}BuOLi	DMSO	76
10	^{t}BuONa	DMSO	79
11	NaOH	DMSO	88
12[c]	NaOH	DMSO	69
13[d]	NaOH	DMSO	91
14[e]	**NaOH**	**DMSO**	**95**
15[f]	NaOH	DMSO	82
16[g]	NaOH	DMSO	79
17	NaOH	glycerol	24
18	NaOH	H_2O	<5

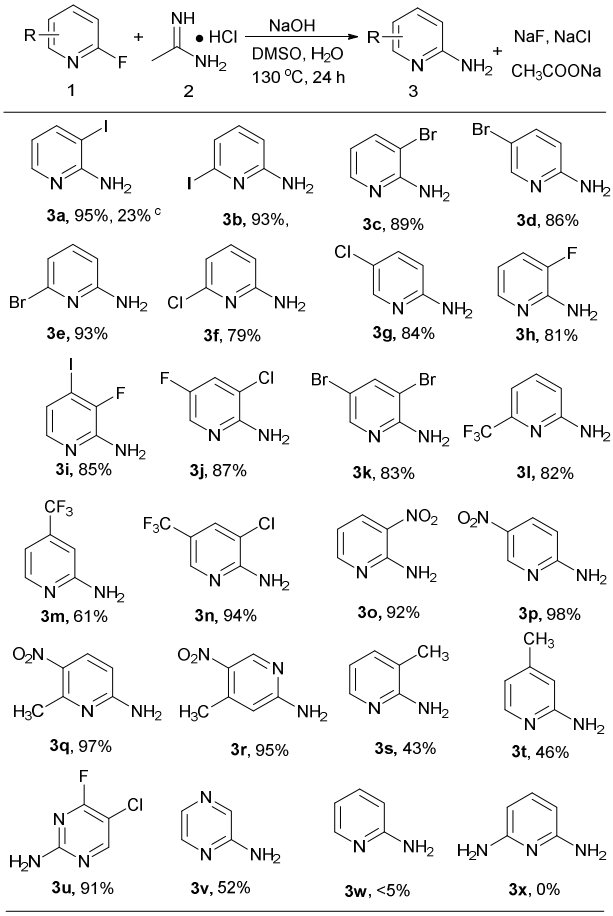
[a]Reaction conditions: 2-fluoro-3-iodopyridine (1.0 mmol), acetamidine hydrochloride (1.2 mmol), base (2.5 mmol), H_2O (0.5 mL) in solvent (2.5 mL) at 120 °C for 24 h; [b]Yields of isolated products; [c]Reaction was carried out at 120 °C for 12 h; [d]Reaction was carried out at 120 °C for 36 h; [e]Reaction was carried out at 130 °C for 24 h; [f]Pentanimidamide hydrochloride was used instead of acetamidine hydrochloride; [g]carboxamide hydrochloride was used instead of acetamidine hydrochloride.

By using the best conditions screened for the transition metal-free synthesis of 2-aminopyridine derivatives from 2-fluoropyridine derivatives and acetamidine hydrochloride (Table 1, entry 14), the development of substrates for this amination with high chemoselectivity was performed. The results suggest that when the pyridine ring has electron-withdrawing groups, the amination can be completed smoothly with a high yield of the target product. This reaction is tolerant to substituent groups such as iodine, bromine, chlorine, trifluoromethyl, nitro, and methyl. When fluorine is at the 2-position of pyridine, this fluorine atom has high reactivity, thus leading to high yields of the target products. The co-existing iodine substituents are not affected (Scheme 2, **3a**-**3b**). When the fluorine and chlorine or bromine substituents are at the 2-position and 6-position, the reaction takes priority at the fluorine to give 6-chloropyridin-2-amine and 6-bromopyridin-2-amine in a high yield (Scheme 2, 3e and **3f**). Interestingly, when fluorine substituents are present at different locations on the pyridine ring, the reaction takes priority on the fluorine at the 2-position to give 2-aminopyridine, while the fluorine atoms at other positions are not affected (Scheme 2, **3h**-**3j**). It can be seen from the substrate development that steric hindrance has little impact on this amination reaction, while the electronegativity of the pyridine substituent is the most important influencing factor. When the pyridine ring is joined by the strong electron-withdrawing nitro group, the reaction can proceed at low temperature and result in excellent yields (Scheme 2, **3o**-**3r**). In addition, when the pyridine ring is combined with electron-

View Article Online
DOI: 10.1039/C8OB02129E

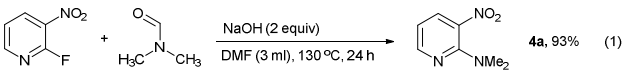
donating groups such as a methyl group, the reaction can be completed, resulting in moderate yields of the target products (Scheme 2, **3s**-**3t**). It is worth noting that when pyrimidine was used as the raw material for the amination, the reaction can also proceed smoothly, and the sole target product **3u** was obtained. Lastly, 2-fluoropyrazine was used as the raw material for the amination reaction under standard reaction conditions; a 52% yield of the target product pyrazin-2-amine **3v** was obtained. Unfortunately, the reaction with 2-fluoropyridine failed in the reactions under the standard reaction conditions. Increasing the reaction temperature can slightly increase the yield. When use 2,6-difluoropyridine as the substrate, only afforded a complex mixture and no product was detected. In addition, when using normal pyridine (C_5H_5N) as the substrate, the reaction does not work.

Scheme 2 Transition-metal-free synthesis of pyridin-2-amine derivatives[a]

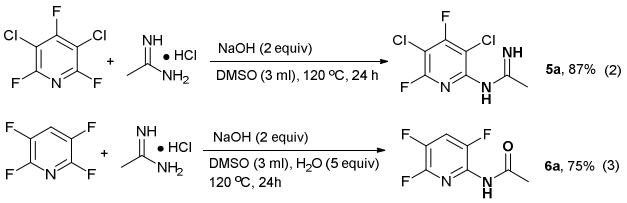


[a]Reaction conditions: 2-fluoropyridine (1.0 mmol), acetamid ine hydrochloride (1.2 mmol), NaOH (2.5 mmol), H_2O (0.5 mL) in DMSO (2.5 mL) at 130 °C for 24 h; [b] Yields of isolated products. [c]2-chloro-3-iodopyridine was used as substrate.

Interestingly, when we investigated the amination, we found that when dimethylformamide (DMF) was used as the raw material and acetamidine hydrochloride was not added, NaOH promoted the degradation of DMF. The amination then proceeded, and a high yield of *N,N'*-dimethylaminopyridine **4a** was obtained [Eq. (1)].[13]

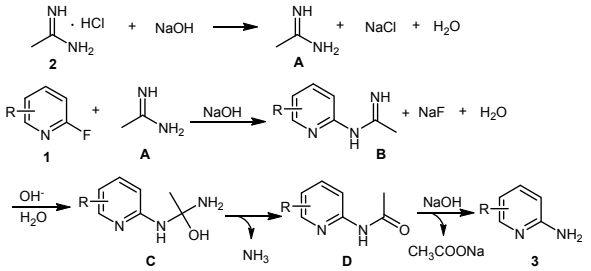


To further verify the reaction mechanism and expand the practicability of this reaction, we chose a few pyridine derivatives with multiple substituents that have high steric hindrance for the amination with acetamidine hydrochloride to synthesize amidine substituent derivatives [Eq. (2)]. We successfully obtained N-(3,5-dichloro-4,6-difluoropyridin-2-yl) acetamidine (**5a**, 87%), which can be used to prepare 2-aminopyridine derivatives through hydrolysis. More importantly, amidine derivatives are important intermediates for medicinal and organic synthesis.[14] Interestingly, under a H_2O (5 equiv) condition, 2,3,5,6-tetrafluoropyridine reaction with acetamidine hydrochloride gave the N-(3,5,6-trifluoropyridin-2-yl)acetamide product **6a** in 75% yield [Eq. (3)].



The plausible reaction mechanism for this amination reaction is as follows (Scheme 3): [11, 14a] acetamidine hydrochloride **2** first reacts with NaOH to yield acetamidine **A**, which reacts with 2-fluoropyridine **1** *via* nucleophilic substitution under the assistance of NaOH to yield N-(pyridin-2-yl)acetamidine intermediate **B**. Then, in the presence of water, NaOH provides -OH groups for the nucleophilic attack of intermediate **B** to yield **C**. Intermediate **C** may be conversion into amide **D** according to the revelation of [Eq. (3)]. Finally, the hydrolysis of amide **D** under interaction with water yields the target product 2-aminopyridine derivatives **3** and sodium acetate.

Scheme 3 Possible mechanism for the synthesis of pyridin-2-amines.



In conclusion, we reported an efficient and transition-metal-free method for the synthesis of 2-aminopyridine derivatives from 2-fluoropyridine derivatives and acetamidine hydrochloride. The reaction uses inexpensive and more safe

View Article Online
DOI: 10.1039/C8OB02129E

acetamidine hydrochloride as the ammonium source to yield 2-aminopyridine with high chemoselectivity. This method provides a convenient option for the synthesis of 2-aminopyridine and primary aromatic amines, important intermediates for medicinal and organic synthesis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the National Natural Science Foundation of China (21302146), the Foundation of the Department of Education of Guangdong Province (2016KTSCX144, 2017KZDXM085) and Science Foundation for Young Teachers of Wuyi University (2015td01) and Chemical Industry Collaborative Innovation Center of Yueshan Town 2017(368) for financial support.

Notes and references

1 (*a*) A. Klapars, J. C. Antilla, X.-H. Huang and S. L. Buchwald, *J. Am. Chem. Soc*. 2001, **123**, 7727-7729; (*b*) E. R. Strieter, B. Bhayana, S. L. Buchwald, *J. Am. Chem. Soc*. 2009, **131**, 78-88; (*c*) D. Ma, Q. Cai, H. Zhang, *Org. Lett*, 2003, **5**, 2453-2455; (d) P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev*., 2016, **116**, 12564-12649; (*d*) A. K. Mailyan, J. A. Eickhof, A. S. Minakova, Z. Gu, P. Lu, A. Zakarian, *Chem. Rev*., 2016, **116**, 4441-4557; (*e*) Y. Park, Y. Kim, S. Chang, *Chem. Rev*., 2017, **117**, 9247-9301; (*f*) V. Samantha, W. H. Joshua, M. J. Adam, *J. Org. Chem*., 2015, **80**, 2545-2553; (g) R. Wang, W. Guan, Z. Han, F. Liang, T. Suga, X. Bi, H. Nishide, *Org. Lett*., 2017, **19**, 358–2361.

2 (*a*) M. R.Chapman, M. H. T. Kwan, G. E. King, B. A. Kyffin, A. J. Blacker, C. E. Willans, B. N. Nyuyen, *Green Chem*., 2016, **18**, 4623-4627; (*b*) D. Zhou, H. Lee, J. M. Rothfuss, D. L. Chen, D. E. Ponde, M. J. Welch, R. H. Mach, *J. Med. Chem*., 2009, **52**, 2443–2453; (*c*) C. He, J. Hao, H. Xu, Y. Mo, H. Liu, J. Han, A. Lei, *Chem. Commun*., 2012, **48**, 11073–11075; (*d*) Y. Gao, M. Yin, W. Wu, H. Huang, H. Jiang, *Adv. Syn. Catal*., 2013, **355**, 2263-2273; (*e*) R. Yan, H. Yan, C. Ma, Z. Ren, X. Gao, G. Huang, R. Liang, *J. Org. Chem*. 2012, **77**, 2024–2028; (*f*) N. Chernyark, V. Gevorgyan, *Angew. Chem. Int. Ed*., **2010**, **49**, 2743-2746; (*g*) H. Cao, X. Liu, L. Zhao, J. Cen, J. Lin, Q. Zhu, M. Fu, *Org. Lett*., 2014, **16**, 146–149.

3 (*a*) B-S. Liao, S-T. Liu, *Catal Commun.*, 2013, **32**, 28-31; (*b*) M. K. Elmkaddem, C. Fischmeister, C. M. Thomas, J-L. Renaud, *Chem Commun.*, 2010, **46**, 925-927; (*c*) Z. Wu, Z. Jiang, D. Wu, H. Xiang, X. Zhou, *Eur. J. Org. Chem*, 2010, 1854-1857; (*d*) H. Xu, Y. Liang, Z. Cai, H. Qi, C. Yang, Y. Feng, *J. Org. Chem*. 2011, **76**, 2296-2300; (*e*) S. Fantasia, J. Windish, M. Scalone, *Adv. Syn. Catal*., 2013, **355**, 627-631.

4 (*a*) M. Gray, V. Snieckus, H. Lebel, *e-EROS Encyclopedia of Reagents for Organic Synthesis*, 2014, 1-12; (*b*) M. Nikoorazm, A. Ghorbani-Choghamarani, N. Noori, B. Tahmasbi, *Applied Organometallic Chemistry*, 2016, **30**, 843-851; (*c*) N. Noori, M. Nikoorazm, A. Ghorbani-Choghamarani, *Catal Lett.*, 2017, **147**, 204-214.

5 (*a*) D. Blomberg, K. Brickmann, J. Kihlberg, *Tetrahedron*, 2006, **62**, 10937-10944; (*b*) L. Estel, F. Marsais, G. Queguiner, *J. Org. Chem*., 1988, **53**, 2740-2744.

6 L. Pasumansky, A. R. Hernandez, S. Gamsey, C. T. Goralski, B. Singaram, *Tetrahedron Lett.*, 2004, **45**, 6417-6420.

7 M. D. Vera, J. T. Lundquist IV, M. V. Chengalvala, J. E. Cottom, I. B. Feingold, L. M. Garrick, D. M. Green, D. B. Hauze, C. W. Mann, J. F. Mehlmann, J. F. Rogers, L. Shanno, J. E. Wrobel, J. C. Pelletier, *Bioorg. Med. Chem. Lett*, 2010, **20**, 2512-2515.

8 (*a*) M. Orlandi, F. Yosi, M. Bonsognore, M. Benaglia, *Org. Lett*., 2015, **17**, 941–3943; (*b*) S. M. Baghbanian, M. Farhang, S. M. Vahdat, M. J. Tajbakhsh, *J. Mol. Catal. A: Chem.* 2015, **407**, 128-136; (*c*) D. Nandi, S. Siwal, M. Choudhary, K. Mallick, *Appl Catal., A,* 2016, **523**, 31-38; (*d*) S. S. Kotha, N. Sharma, G. Sekar, *Tetrahedron Lett,* 2016, **57**, 1410-1413; (*e*) K. Abiraj, G. R. Srinivasa, D. C. Gowda, *Syn Commun*, 2005, **35**, 223-230.

9 (*a*) F. W. Bergstrom, W. C. Fernelius, *Chem. Rev*., 1937, **20**, 413–487; (*b*) C. K. Mcgill, A. Rappa, *Advances in heterocyclic chemistry. Academic Press*, 1988, **44**, 1-79; (*c*) A. E. Chichibabin, O. A. Zeide, *Zhurnal Russkago Fiziko-Khimicheskago Obshchestva*, 1914, **46**, 1216-1236.

10 Y. Li, L. Cheng, Y. Shao, S. Jiang, J. Cai, N. Sun, *Eur. J. Org. Chem*. 2015, 4325–4329.

11 X. Gao, H. Fu, R. Qiao, Y. Jiang, Y. Zhao, *J. Org. Chem*. 2008, **73**, 6864–6866.

12 (*a*) Y. Li, X. Luo, Y. Shao, L. Chen, *J. Org. Chem*., 2018, **83**, 8768-8774; (*b*) J Cai, S. Huang, R He, L. Chen, D. Chen, S. Jiang, B. Li, Y. Li, *Org. Biomol. Chem.,* 2017, **15**, 333-337; (*c*) Y. Li, L. Cheng, L. Chen, B. Li, N. Sun, N. Qing. *Chin. J. Org. Chem*., 2016, **36**, 2426-2436; (*d*) Y. Li, L. Cheng, B. Li, S. Jiang, L. Chen, Y. Shao, *ChemSelect*, 2016, **1**, 1092-1095; (*d*) Y. Li, L. Cheng, X. Liu, B. Li, N. Sun, *Beilstein J. Org. Chem*. 2014, **10**, 2886–2891.

13 J. Garcia, J. Sorrentino, E. J. Diller, D. Chapman, Z. R. Woydziak, *Syn. Commun.* 2016, **46**, 475-481.

14 (*a*) M. Cortes-Salva, C. Garvin, J. C. Antilla, *J. Org. Chem*. 2011, **76**, 1456–1459; (*b*) B. Li, L. Samp, J. Sagal, C. M. Hayward, C. Yang, Z. Zhang, *J. Org. Chem*., 2013, **78**, 1273–1277; (*c*) D. Zhao, J. Hu, N. Wu, X. Huang, X. Qin, J. Lan, J. You, *Org. Lett*, 2011, **13**, 6516-6519; (*d*) X. Wei, M. Zhao, Z. Du, X. Li, *Org. Lett*, 2011, **13**, 4636-4639; (*e*) Y. Wang, X. Zhu, S. Chiba. *J. Am. Chem. Soc.* 2012, **134**, 3679−3682.