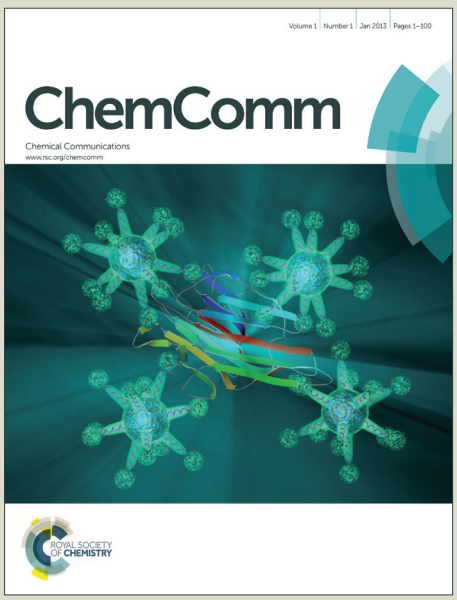
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal NameChemcomm

COMMUNICATION

CFBSA: A Novel and Practical Chlorinating Reagent

Zehai Lu,[a] Qingwei Li,[a] Minghua Tang,[a] Panpan Jiang,[a] Hao Zheng*[b] and Xianjin Yang*[ac]

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

DOI: 10.1039/x0xx00000x

www.rsc.org/

A structurally simple, highly reactive chlorinating reagent, N-chloro-N-fluorobenzenesulfonylamine (CFBSA), was conveniently prepared from inexpensive Chloramine B in high yield. A wide range of substrates were chlorinated with it in good to high yields and proper selectivity.

Chlorine exists widely in biologically active pesticides, pharmaceuticals and natural products, such as Tidopidine, Hakquino, Azintamide, Axinellamine, etc[1] (Figure 1). It also plays a great role in organic synthesis, since the introduction of chlorine confers molecules with functionalizability, especially in cross-coupling chemistry.[2] It is also reported that chlorination is a useful method to modulate conjugated polymers.[3] Accordingly, high effective chlorination attracts increasing interests of chemists in relevant areas.[4] However, the research pace for new chlorinating reagents is rather slow and practical chlorinating reagents were rarely reported.

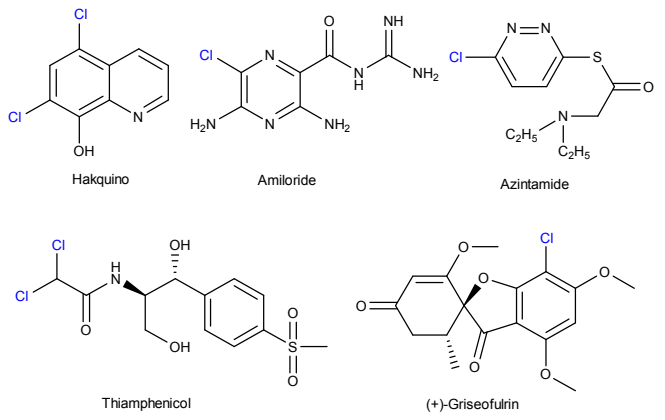
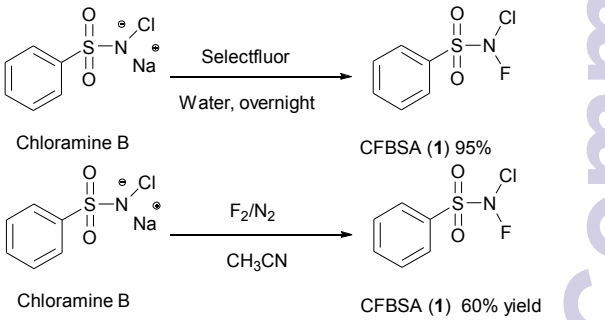


Fig 1. Classical chlorine-containing medicines and pesticides.

The reactivity and practicality of traditional chlorinating reagent such as N-chlorosuccinimide (NCS), Cl_2, SO_2Cl_2, HCl, $POCl_3$, 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) and t-BuOCl were discussed below. NCS[5] and DCDMH[6] have high stability and good operating convenience, but their reactivity is not satisfying and substrates scope is limited. SO_2Cl_2[7] and Cl_2[8] are not stable in storage and their reactivity is too aggressive, which result in their severe operating conditions and low selectivity. Although t-BuOCl[9] has moderate reactivity and operating convenience, the substrates are limited to aromatic compounds and it is too sensitive for its storage. In spite of its lowest cost, HCl[10] has limited substrate scope and low chlorinating reactivity. $POCl_3$[11] has satisfying reactivity and substrate scope, but the high toxicity limited its further application.

Thus, a practical chlorinating reagent is worthy for further exploration. In this communication, we report a novel chlorinating reagent, *N*-chloro-*N*-fluorobenzenesulfonylamide (CFBSA), which has characters of simple structure, high reactivity, easy availability, wide substrate range and stable storage.

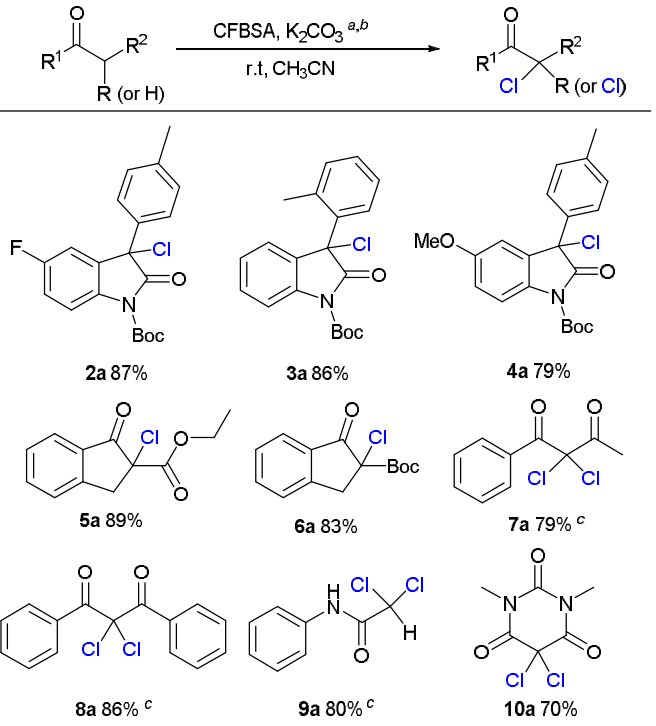


Scheme 1. The preparation of CFBSA.

As showed in Scheme 1, CFBSA can be easily prepared from the inexpensive Chloroamine B (one normal industrial disinfectant) by the reaction with Selectfluor or 20% F_2/N_2 gas in 95% and 60% yield respectively. Both synthetic routes of CFBSA can be used in laboratory or industry.

[a] *Key lab for Advanced Material &Institute of Fine Chemicals,East China University of Science and Technology, 130 Meilong Road, Shanghai 200231 (China) E-mail: yxj@ecust.edu.cn*
[b] *College of Chemistry and Biology, Donghua University, 2999 Renmin Road, Shanghai 201620 (China)*
[c] *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Science, 345 Ling-Ling Road, Shanghai 200232 (China) E-mail: zhenghao@dhu.edu.cn*
† *Electronic Supplementary Information (ESI) available. See DOI: 10.1039/x0xx00000x*

Table 1. The chlorination of carbonyl compounds



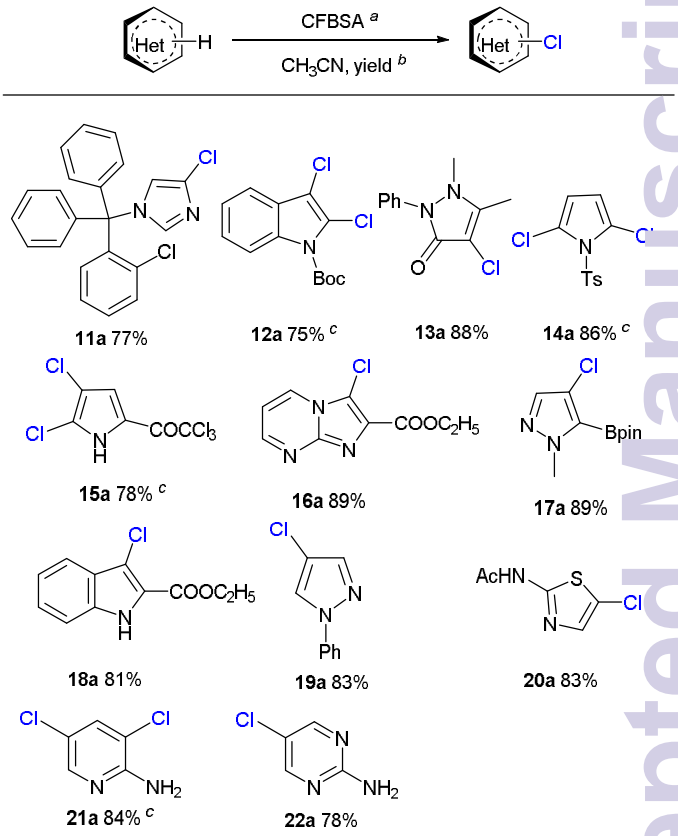
[a] The reaction conditions were as follows: 3-aryl-2-oxindoles or 1,3-dicarbonyl compounds (1.0 equiv), CFBSA (1.2 equiv) and K_2CO_3 (1.5 equiv) for the formation of compounds (**2a~6a**), or CFBSA (2.4 equiv) and K_2CO_3 (2.5 equiv) for the formation of compounds (**7a~10a**), CH_3CN (3 mL), r.t., overnight. [b] Isolated yields based on carbonyl compounds. [c] Deacetylated product from 3-oxo-N-phenylbutanamide.

In our lab, we found that the N-F bond in N-fluorobenzenesulfonylamide is very strong and hard to cleavage,[12a] thus we speculated that, with the existence of electron-withdrawing N-sulfonyl groups, the introduced N-Cl bond in CFBSA would be more reactive than the N-F bond and would result in chlorination occurrence.

The chlorination was verified by the reaction of *N*-Boc-5-fluoro-3-(p-tolyl)-2-oxoindole (**2**)[12] with CFBSA. In this reaction, chlorinated product **2a** was surprisingly afforded in 87% yield, and no fluorinated product was detected. Through further investigation, the optimal reaction conditions were determined as follows: CFBSA (1.2 equiv), potassium carbonate (1.5 equiv, if needed to accelerate reaction rate), acetonitrile and room temperature, etc.

Some other *N*-Boc-3-aryl-2-oxindoles were tested with the optimal conditions, the corresponding chlorination products were obtained in good to high yields (Table 1, **2a~4a**). Under similar conditions, some 1,3-dicarbonyl compounds were also tested. For 2-carboxyl-substituted 1-oxoindanes, **5a** and **6a** were afforded in 89% and 83% yields, respectively. Notably, as the 1,3-diketone activated methylene substrate, it can be dichlorinated when adequate CFBSA was used, 2.4 equiv of CFBSA and 2.5 equiv of base were essential in order to ensure a rapid and complete dichlorination. For example, **7a**, **8a**, **10a** were obtained in good to high yields. As for 3-oxo-*N*-phenylbutanamide, the dichlorinated product was further deacetylated to afford **9a** in 80% yield, which is reported to have great academic and industrial significance and this kind motifs exist in many biologically active compounds.[13]

Table 2. The chlorination of nitrogen-containing aromatic heterocyclic compounds.

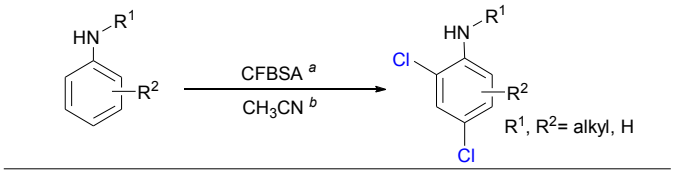


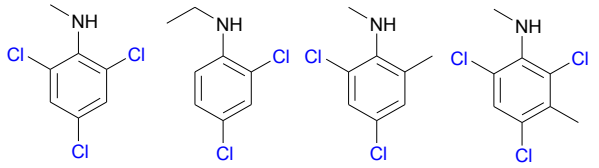
[a] The reaction conditions were as follows: heterocycle (1.0 equiv), CFBSA (1.2 equiv), CH_3CN (3 mL), room temperature, overnight. [b] Isolated yields were based on starting material. [c] CFBSA (2.4 equiv) for the formation of single dichlorinated products.

Recently, Baran's group[2a] reported a guanidine-based chlorinating reagent, CBMG, with good chlorinating reactivity and monochlorinated selectivity to nitrogen-containing aromatic heterocyclic compounds and others. As a comparison, we studied the chlorination reaction of CFBSA with various nitrogen-containing aromatic heterocyclic compounds, the results were showed in Table 2. CFBSA has almost identical reactivity and selectivity as CBMG when 1.2equiv CFBSA was used, the reaction showed good regioselectivity and monochlorinated products **11a**, **13a**, **16a**, **17a**, **18a**, **19a**, **20a** and **22a** were obtained in good yields respectively. For some more reactive substrates, the use of more than 2.0 equiv chlorinating reagent would lead to dichlorination. The chlorination of N-Boc-protected indole gave 2,3-dichlorinated product N-Boc-2,3-dichloroindole **12a** in 75% yield, while CBMG gave N-Boc-3-chloroindole in 73% yield as reported.[2a]

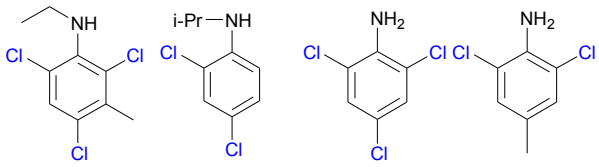
For N-Ts-protected pyrrole, 2,5-dichlorinated product **14a** was afforded in 86% yield with 2.4 equiv of CFBSA, while 60% yield was afforded with 2.2 equiv CBMG in anhydrous chloroform as reported.[2a] For the cases of **12a**, **14a**, **15a** and **21a**, with 2.4 equiv CFBSA, single dichlorinated product was formed without observa

Table 3. Chlorination of anilines and N-alkyl-anilines.





23a 78% **24a** 81% **25a** 83% **26a** 83%



27a 80% **28a** 89% **29a** 70% **30a** 62% [c]

[a] The reaction conditions: *N*-alkyl aniline (1.0 equiv), CFBSA (2.4 equiv for the formation of the compounds **24a**, **25a**, **28a**, **30a** and 3.6 equiv for the formation of the compounds **23a**, **26a**, **27a**, **29a**), CH_3CN (3 mL), room temperature, overnight. [b] Isolated yields were based on the substrates. [c] Reaction temperature at 0 ^{0}C.

-on of monochlorinated product, while, with 2.2 equiv of CBMG, a mixture of mono- and dichlorinated and products were usually obtained as reported.[2a] So, we can conclude that CFBSA is more reactive chlorinating reagent than CBMG in some cases.

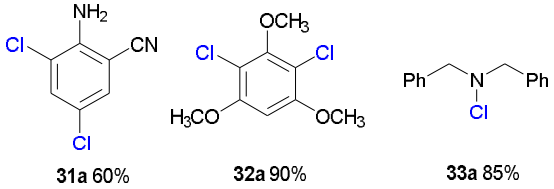
Although the chlorination of aniline was widely reported,[14, 5e] rare reports were found for the direct chlorination of *N*-alkylaniline, possibly for the latter high reactivity leads to the difficulty of selective chlorination. Our investigation in the chlorination reaction of anilines and *N*-alkylanilines with CFBSA gave much better results, majorly affording trichlorinated or *o*, *p*-dichlorinated products in high yields (Table 3).

In addition to carbonyl compounds, heteroarenes and anilines, other compounds, such as methoxybenzene, alkylamine, thiazole, naphthol, pyridine, pyrimidine can also be chlorinated in moderate to good yields by CFBSA under mild reaction conditions (**31a~35a**, Table 3). The reaction showed good *o*- or *p*-site selectivity consistent with expectations to give one major product, which brings convenience for its separation. These results indicated that CFBSA was a versatile and effective chlorinating reagent.

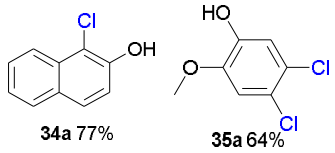
As for the chlorination mechanism, from the *o*- or *p*-site selectivity of electron-rich aromatic substrates, it is reasonable to suppose that the reaction proceeds via electrophilic process similar to other kinds of N-chloro chlorinating reagents. In the presence of radical inhibitors butylated hydroxyl toluene (BHT) and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), chlorination of carbonyl compounds **6** gave **6a** in 80% and 84% yields respectively (Scheme 2), which indicated that the chlorination may not go through a radical process.

Under our reaction conditions, various chlorinating reagents were chosen to chlorinate carbonyl compounds 1,3-dimethylbarbituric acid (**10**) and aniline (**26**), the results are

Table 4. Chlorinationof other kind of substrates. [a,b]

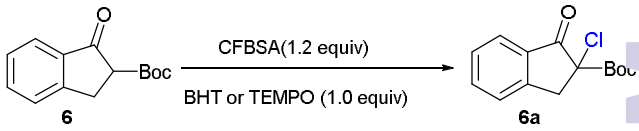


31a 60% **32a** 90% **33a** 85%



34a 77% **35a** 64%

[a] Products obtained with standard procedure. [b] 1.2 equiv CFBSA for the formation of **33a** and **34a**, 2.4equiv for the formation of **31a**, **32a** and **35a**.



over 80% yield

Scheme 2. The mechanism exploration.

listed in Table 5. For trichloroisocyanuric acid gave **10a** in 90% yield and gave **26a** in 36% yield (Entry 1 in Table 5). What's more, for 1,3-dichloro-5,5-dimethylhydantoin and t-BuOCl, **10a** and **26a** were formed in moderate yields, respectively (Entries 2 and 5 in Table 5). With cyanuric chloride and N-chlorosuccinimide as chlorinating reagent, zero or very low yields were obtained (Entries 3 and 4 in Table 5). When CBMG was used in the reaction, mixtures of products were got with **10a** and **26a** in lower yields (Entry 6 in Table 5). As for CFBSA, it gave **10a** and **26a** in 75% and 86% yields, respectively (Entry 7 in Table 5).

Table 5. The test of chlorinating reagents on 1,3-dimethylbarbituric acid (**10**) and aniline (**26**).

Entry [a]	Chlorinating reagents	**10a**	**26a**
1	Trichloroisocyanuric acid	90% [b]	36%
2	1,3-Dichloro-5,5-dimethylhydantoin	69%	71%
3	Cyanuric chloride	0%	0%
4	N-Chlorosuccinimide	8%	7%
5	t-BuOCl	32%	62%
6	CBMG	27%	19%
7	CFBSA	75%	86%

[a] The reaction conditions are as follows: compounds **10** and **26** (1.0 equiv), various chlorinating reagents (2.4 equiv for **10** and 3.6 equiv for **26**), CH_3CN, room temperature, 5 hrs. [b] The yields were obtained from ^{1}H NMR with 1,2,4-trimethylbenzene as the internal standard.

The stability of CFBSA was examined by some experiments. CFBSA is pale yellow liquid at room temperature. The TLC-monitoring experiment confirmed that no decomposition occurred by exposing it to air for several months or heating it to 100 ^{0}C overnight. DSC experiment indicated that there was no thermal

event below 130 ^{0}C with a maximum exotherm temperature at 192 ^{0}C (100 ^{0}C for CBMG as reported). [2a]

In conclusion, a novel chlorinating reagent CFBSA was developed. It has properties of high reactivity, easy availability, wide substrate range and stable storage in comparison of the classical chlorinating reagents, such as NCS, chlorine gas, etc. Chlorination with CFBSA can selectively give single monochlorinated, dichlorinated or trichlorinated products in terms of the substrates and prevent the formation of mixtures of various chlorinated products by controlling reaction conditions. Simple availability from Selectfluor and Chloromine B in water means eco-friendliness and its low-cost preparation from fluorine gas make it to be a potential industrial material. In addition, the reagent has been patented by us, and further study on the synthetic application of CFBSA is underway in our laboratory.

We are grateful to the National Natural Science Foundation of China (NSFC) (grant number 21372077) for financial support.

Notes and References

1 (*a*) J. Q. Martin, J. F. Desmond. *Circulation*., 1999, **100**, 1667; (*b*) D. Anthony, C. P. Nick. *Clinical Therapeutics*., 2004, **26**, 649; (*c*) R. A. Rodriguez, D. B. Steed, P. S. Baran. *J. Am. Chem. Soc*., 2014, **136**, 15403; (*d*) H. R. Mads, S. R. Marc, A. Simon, B. Sven, K. Alwin, O. L. Thomas, H. C. Mads. *J. Med. Chem*., 2012, **55**, 652; (*e*) I. B. Seiple, J. A. M. Mercer, R. J. Sussman, Z-Y. Zhang, A. G. Myers. *Angew. Chem. Int. Ed.*, 2014, **53**, 4642.

2 (*a*) R. A. Rodrigo, C.-M. Pan, Y. Yabe, Y. Kawamata, M. D. Eastgate, P. S. Baran. *J. Am. Chem. Soc*., 2014, **136**, 6908; (*b*) T. Vlaar, E. Ruijter, Bert U. W. Maes, Romano V. A. Orru. *Angew. Chem. Int. Ed*., 2013, **52**, 7084; (*c*) M. Aufiero, F. Proutiere, F. Schoenebeck. *Angew. Chem. Int. Ed*., 2012, **51**, 7226; (*d*) F. Popowycz, E. Me´tay, M. Lemaire. *C. R. Chimie*., 2011, **14**, 621; (*e*) B. Tim, C. Julie, B. James, Z. Serguei, D. Jeff, M. James, C. Alfredo. *Org. Lett*., 2006, **8**, 104; (*f*) B. Tim, G. A. David, A. M. George, M. James, C. Alfredo. *J. Org. Chem*., 2004, **69**, 7635.

3 (*a*) T. Lei, J.-H. Dou, J. Pei. *Chem. Sci*., 2013, **4**, 2447; (*b*) Y. Li, B. Meng, H. Tong, Z.-Y. Xie, L.-X. Wang. *Polym. Chem.,* 2014, **5**, 1848; (*c*) Yu. G. Kryazhev, V. S. Solodovnichenko. *Solid Fuel Chemistry*., 2012, **46**, 330; (*d*) M. Kijima, S. Mukai, K. Ohmura, H. Shirakawa, M. Kyotani. *Synthetic Metals.*, 1999, **101**, 59.

4 (*a*) N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru, S. Kanemasa. *Angew. Chem. Int. Ed*., 2005, **44**, 4204; (*b*) M. Marigo, S. Bachmann, N. Halland, A. Braunton. *Angew. Chem. Int. Ed*., 2004, **43**, 5507; (*c*) G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, N. Melchiorre, L. Sambri. *Angew. Chem. Int. Ed*., 2005, **44**, 6219; (*d*) K. Shibatomi, A. Narayama. *Eur. J. Org. Chem*., 2013, **2**, 812.

5 (*a*) J. A. Tunge, S. R. Mellegaard. *Org. Lett*., 2004, **6**, 1205; (*b*) X.-Y. Sun, Y.-H. Sun, C. Zhang, Y. Rao. *Chem. Commun*., 2014, **50**, 1262; (*c*) S. R. Whitfield, M. S. Sanford. *J. Am. Chem Soc*., 2007, **129**, 15142; (*d*) M. Candy, C. Guyoon, S. Mersmann, J.-R. Chen, C. Bolm. *Angew. Chem. Int. Ed*., 2012, **51**, 4440. (*e*) A. Zanka, A. Kubota. *Synlett.*, 1999, 1984.

6 (*a*) A. Khazaei, F. Abbasi, M. Kianiborazjani, S. Saednia. *J. Braz. Chem. Soc*., 2014,**25**, 361; (*b*) T. E. Nickson, C. A.Roche-Dolson, Synthesis 1985, 669.

7 (*a*) P. W. Donaldp, R. K. Paulr. *J .Org. Chem*., 1964, **29**, 1956; (*b*) B. B. Burg, M. K. Ross. *J. Am. Chem Soc*., 1943, **65**, 1637; (*c*) N. . Saper, B. B. Snider. *J. Org. Chem*., 2014, **79**, 809.

8 (*a*) D. W. William, E. H. Henry. *J .Org. Chem*., 1979, **44**, 1155 (*b*) M. Ballester, C. Molinet, J. Castañer. *J. Am. Chem Soc.,* 1960, **8.** 4254; (*c*) T. H. Chao, L. P. Cipriani. *J .Org. Chem*., 1961, **26**, 1079.

9 (*a*) Z.-T. Wang, L. Zhu, F. Yin, Z.-Q. Su, Z.-D. Li, C.-Z.Li. *J. Am. Chem. Soc*., 2012, **134**, 4258; (*b*) D. S. Matteson. *J. Org. Chem*., 1964, **29**, 3399; (*c*) T. J. Donohoe, P. D. Johnson, A. Cowley, M. Keenan. *J. Am. Chem. Soc*., 2002, **124**, 12934; (*d*) T. J. Donohoe, W. Gattrell, J. Kloesges, E. Rossignol. *Org. Lett*., 2007, **9**, 1725; (*e*) H. Baganz, H.-J. May. *Angew. Chem. Int. Ed*., 1966, **5**, 420.

10 (*a*) F. Kakiuchi, T. Kochi, H. Mutsutani, N. Kobayashi, . Nishiyama, T. Tanabe. *J. Am. Chem Soc*., 2009, **131**, 11310; (*b*) A. Senaratne, F. M. Orihuela, A. J. Malcolm, K. G. Anderson *Organic Process Research & Development*., 2003, **7**, 1856; (*c*) M. C. Cabaleiro, C. J. Cooksey, M. D. Johnson. *J. Chem. Soc*., 1960, 565; (*d*) F. A. Luzzio, J. Chen. *J. Org. Chem*., 2008, **73**, 5621.

11 (*a*) E. A. Arnott, L.-C. Chan, B. G. Cox, B. Meyrick, A. J. Phil *Org. Chem*., 2011, **76**, 1653; (*b*) C.-G. Duan, J. Jia, R. X. Zhu, J. W. Wang. *J. Heterocyclic Chem*., 2012, **49**, 865; (*c*) C. Venkatesh, P. Singh, P. K. Mahata, H. Ila, H. Junjappa, *Org. Lett*., 2005, **7**, 216 (*d*) X.-H. Deng, A. Roessler, I. Brdar,; R. Faessler, N. S. Mani. *J. Org Chem*., 2011, **76**, 8262; (*e*) K.-W. Wang,D.-X. Xiang, J.-Y. Liu, Y. Pan, D.-W. Dong. *Org. Lett*., 2008, **10**, 1691.

12 (*a*) F.-J. Wang, Q.-Y. Hu, X.-J. Yang. *Eur. J. Org. Chem*., 2014, **1**, 3607; (*b*) M.-X. Zhao, Z.-W. Zhang, M.-X. Chen, W.-H. Tang, M. S . *Eur. J. Org. Chem*., 2011, **16**, 3001.

13 (*a*) J. Wang, H.-T. Li, D.-W. Dong. *Eur. J. Org. Chem.,* 2013, **2**, 5376; (*b*) B. Staskun, P. C. Meltzer. *Tetrahedron*., 1977, **3**, 2429; (*c*) W.-B. Liu, L.-Q. Tan, P. Zhou, C. Chen, Q. Zhan *Synthesis*., 2013, **45**, 2600; (*d*) W.-Bi. Liu,C. Chen,Q, Zhang, Z. -L Zhu. *Beilstein J. Org. Chem*., 2012, **8**, 344.

14 (*a*) H. Wang, Y.-J. Shen, Z.-H. Sun. *Beilstein J. Org. Chem*., 2012, 744; (*b*) I. Rosen, J. P. Stallings, *J. Org. Chem.*, 1960, **25** (9), 1484.