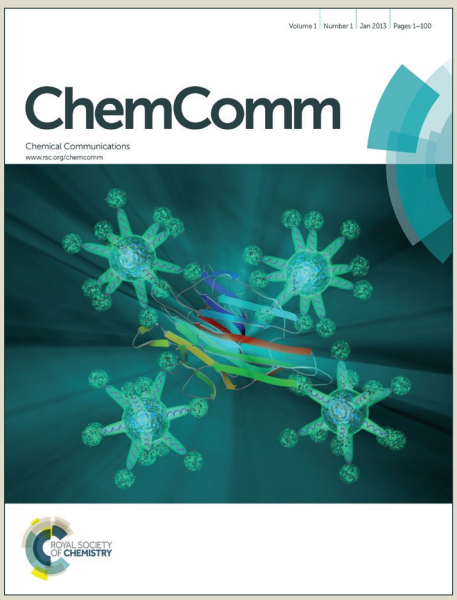
ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: R. Caporaso, S. Manna, S. Zinken, A. Kochnev, E. Lukyanenko, A. V. Kurkin and A. P. Antonchick, *Chem. Commun.*, 2016, DOI: 10.1039/C6CC07196A.



Journal Name

View Article Online
DOI: 10.1039/C6CC07196A

COMMUNICATION

Radical Trideuteromethylation with Deuterated Dimethyl Sulfoxide in the Synthesis of Heterocycles and Labelled Building Blocks

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

DOI: 10.1039/x0xx00000x

www.rsc.org/

Roberta Caporaso,[a,b,c] Srimanta Manna,[a,b] Sarah Zinken,[a,b] Alexander R. Kochnev,[d] Evgeny R. Lukyanenko,[d] Alexander V. Kurkin,[d] and Andrey P. Antonchick*[,a,b]

The potential of deuterated pharmaceuticals is being widely demonstrated. Here we describe the first trideuteromethylation under radical reaction conditions using deuterated dimethyl sulfoxide as reagent for the synthesis of labelled heterocycles and trideuteromethylated compounds. A broad scope of developed method for the synthesis of various scaffolds was demonstrated.

Deuterium, the stable, non-radioactive isotope of hydrogen, is known to medicinal chemists for its widespread range of applications in pharmaceutical discovery and development.[1] Deuterium is broadly employed in organic and organometallic chemistry, spectroscopy and medicine.[2] Recent emphasis on the incorporation of deuterium into small-molecule drugs underlined the potential benefits on the pharmacokinetic and toxicological properties of drugs.[3] Indeed, one common reason for therapeutic failure in drug development is the metabolism of drugs.[4] Although no deuterated compound has been approved as a human medicine yet, some of them have already reached clinical trials (Fig. 1).[3,5]

Very notable is the introduction of deuterium atoms instead of hydrogen which improved the inhibition of gastric acid secretion while introduction of fluorine atoms at the same positions led to dramatic reduction in activity (Fig. 1).[6] The introduction of the trideuteromethyl group in pyridine derivatives led to the development of a potent corticotropin releasing factor (CRF-1) receptor antagonist.[7] The presence of trideuteromethyl groups in β-position to carbonyl groups is important for the development of drugs. In an extreme case, the development of a very potent azapeptide with antiviral activity by introduction of 3 trideuteromethyl groups in β-position to carbonyl groups was demonstrated (Fig 1).[8]

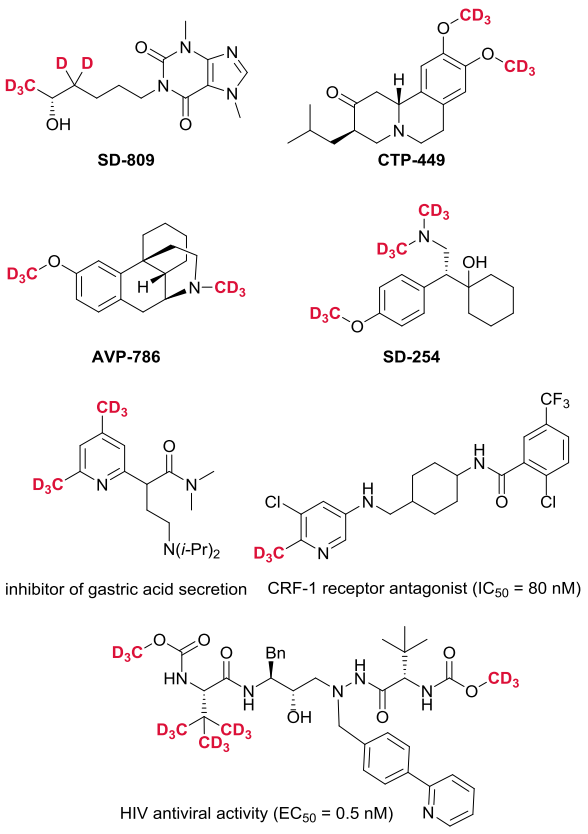
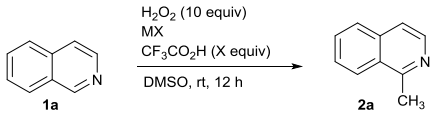


Fig. 1. Selected trideuteromethylated drugs.

Nowadays, the introduction of a methyl group is the subject of intense research, since the methyl group is one of the most commonly occurring functional groups in bioactive compounds.[9] Methylation is important in medicinal chemistry, while biological and physical properties of drugs can be positively affected due to introduction of the methyl group. This effect is called a "magic methyl effect".[10] Therefore, the development of novel methods of introduction of trideuteromethyl groups is highly demanded. Traditionally, deuterated iodomethane is used as source of trideuteromethyl

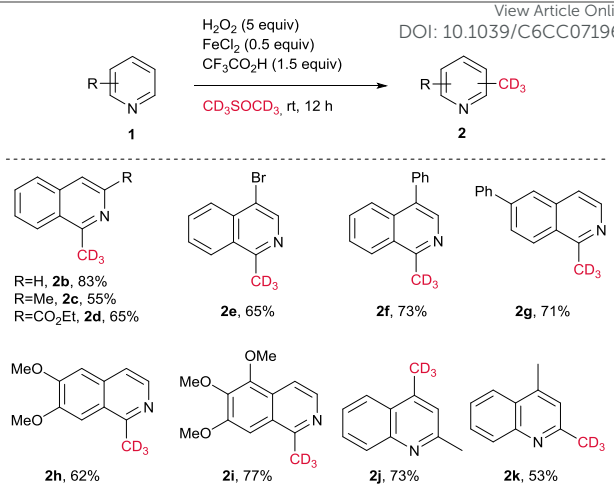
[a] Chemical Biology, Max Planck Institute of Molecular Physiology, Otto-Hahn-Straße 11, 44227 Dortmund, Germany. E-mail: andrey.antonchick@mpi-dortmund.mpg.de
[b] Chemical Biology, Department of Chemistry and Chemical Biology, Technical University Dortmund, Otto-Hahn-Straße 4a, 44227 Dortmund, Germany.
[c] Department of Pharmacy and Biotechnology, University of Bologna, Via Belmeloro 6, 40126 Bologna, Italy
[d] Department of Chemistry, Lomonosov Moscow State University, 1/3 Leninskie Gory, 119991 Moscow, Russia
Electronic Supplementary Information (ESI) available. See DOI: 10.1039/x0xx00000x

Table 1. Screening of reaction conditions[a]



entry	CF_3CO_2H (equiv)	MX (equiv)	yield (%)[b]
1	2	$Mn(OAc)_3$ (0.3)	10
2	1	$FeCl_2$ (1)	72
3[c]	1	FeS (0.5)	0
4	1	FeS (1)	70
5	2	$FeCl_2$ (0.5)	50
6	2	FeS (0.25)	60
7	2	$FeSO_4$ (0.5)	40
8	1.5	$FeCl_3$ (0.5)	traces
9	1.5	$FeCl_2$ (0.5)	88[c]
10	1.5	$FeCl_2$ (0.5)	90[d,e]

[a]Reaction conditions: **1a** (0.5 mmol) in DMSO (0.25 M) at rt for 24 h. [b]GC yield. [c]At 0°C. [d]Isolated yield after column chromatography. [e]Reaction performed using 5 equiv of H_2O_2.



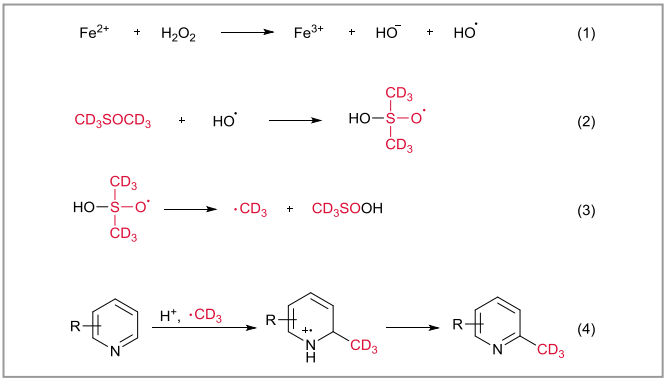
Scheme 1. Substrate Scope for Trideuteromethylation of Isoquinoline and Quinoline Derivatives. Reaction conditions: **1** (0.5 mmol) in CD_3SOCD_3 (0.5 M) at rt for 12 h. Yields are given for isolated products.

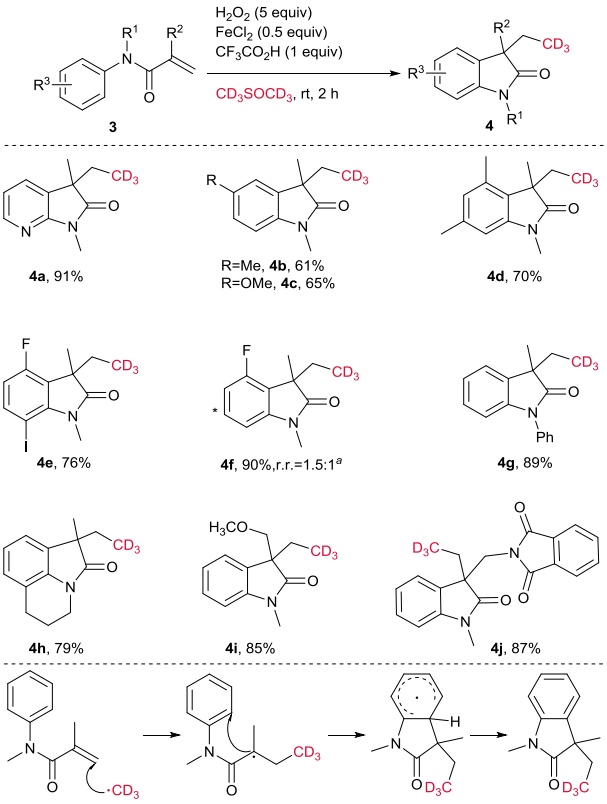
groups.[11] Furthermore, deutero exchange at acidic positions[12] and multistep methods based on application of deuterated reducing reagents[13] were reported for installation of trideuteromethyl groups. Having continuous interest in synthesis and functionalization of heterocycles under oxidative reaction conditions[14] we envisioned to develop a novel straightforward method for the introduction of trideuteromethyl groups using common chemicals. Based on the successful application of dimethyl sulfoxide in organic chemistry, herein we proposed deuterated dimethyl sulfoxide as source of trideuteromethyl radicals.[15] Deuterated dimethyl sulfoxide is a stable, non-toxic, cheap and widely available chemical in laboratories. Here we demonstrated the development of the first and efficient methodology of radical trideuteromethylation in the synthesis of heterocycles and valuable synthetic blocks.

As a preliminary experiment, isoquinoline in dimethylsulfoxide was treated with an aqueous solution of hydrogen peroxide in presence of trifluoroacetic acid as additive and various metal salts (Table 1). Only trace amounts of product **2a** were obtained using $Mn(OAc)_3$ (entry 1).[16] The yield of **2a** was dramatically improved using iron (II) salts, while the application of iron (III) chloride was not successful (entries 2-8). The loading of trifluoroacetic acid is important for the high yield of desired product. The best result was obtained using 1.5 equivalents of trifluoroacetic acid (entries 5 and 9). The amount of hydrogen peroxide can be reduced to 5 equivalents with no effect on the product yield. In result, it was found that the application of $FeCl_2$ in presence of 1.5 equiv of TFA and 5 equiv of H_2O_2 were the best reaction conditions leading to the formation of **2a** in 90% yield. Desired product **2a** was not formed in absence of CF_3CO_2H or $FeCl_2$.

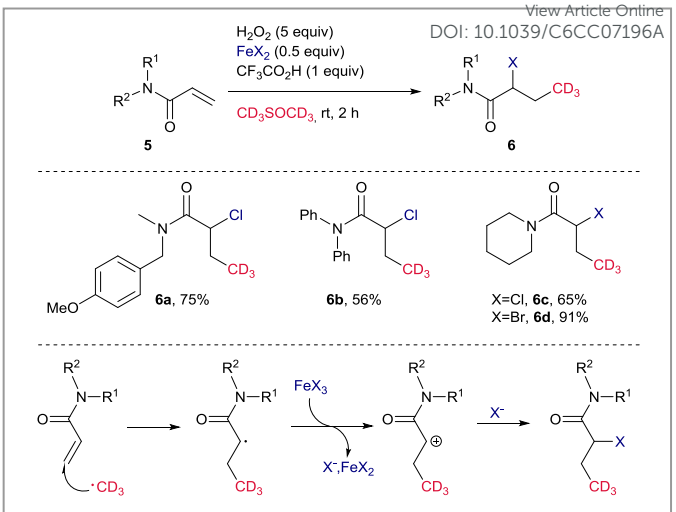
With the optimized conditions in hand, we turned on to investigate the substrate scope of this method. First, we evaluated isoquinoline derivatives using deuterated dimethyl sulfoxide (Scheme 1). Various isoquinolines bearing electron-donating and withdrawing groups as well as polysubstituted derivatives react smoothly under the developed reaction conditions (Scheme 1, **2b**-**2i**). Trideuterated natural products (**2b** and **2h**) and their derivatives were obtained in yields of 55-83% for the first time. Quinaldine reacts selectively at position C4 giving **2j** in 73% yield. Trideuteromethylation of lepidine led to C2-functionalizated product **2k** in 53% yield.

The mechanism of trideuteromethylation is described by equations 1-4. Initially, an iron (II) salt reacts with hydrogen peroxide which leads to the formation of iron (III) salt, hydroxide ion and hydroxyl radical (eqn (1)). In the next step, the hydroxyl radical is added to deuterated dimethyl sulfoxide (eqn (2)). The formed adduct is fragmented under the developed reaction conditions which leads to the formation of trideuteromethyl radical and deuterated methanesulfinic acid (eqn (3)). The trideuteromethyl radical possesses a nucleophilic character. In the following step, isoquinoline or quinoline are protonated and react with trideuteromethyl radicals under formation of radical cations (eqn (4)). The reaction occurs at the most electron deficient position which explains the selectivity of the trideuteromethylation. A similar regioselectivity was reported before.[16h,16j] The radical cation is oxidized under the reaction conditions to give the deuterated product after deprotonation (eqn (4)).

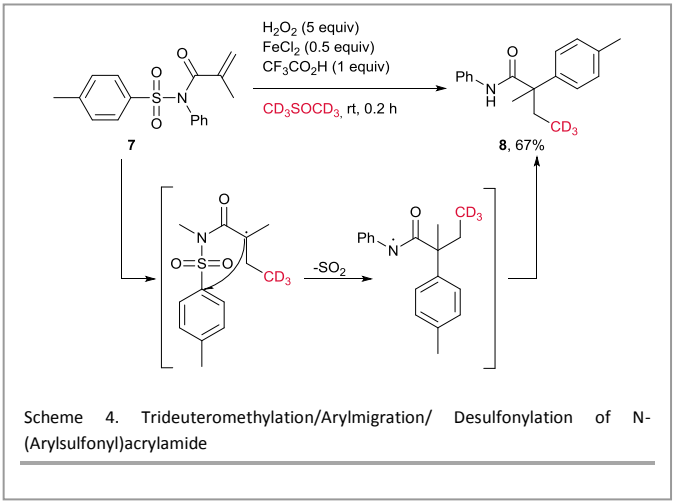




Scheme 2. Substrate Scope for *N*-Arylmethacrylamides. Reaction conditions: **3** (0.2 mmol) in CD_3SOCD_3 (0.2 M) at rt for 2h. Yields are given for isolated products. [a]Major isomer is shown, minor is indicated with star, and the yield was reported for mixture of isomers.



Scheme 3. Substrate Scope for Acrylamides. Reaction conditions: 5 (0.2 mmol) in CD_3SOCD_3 (0.2 M) at rt for 10 min. Yields are given for isolated products after column chromatography.



Scheme 4. Trideuteromethylation/Arylmigration/ Desulfonylation of N-(Arylsulfonyl)acrylamide

Encouraged by the successful application of this strategy in preparing trideuteromethylated quinoline and isoquinoline derivatives, we investigated the possibility to access different scaffolds. We decided to test a variety of *N*-methyl-*N*-arylmethacrylamides in order to obtain a product of difunctionalization of alkenes that would lead to trideuteromethylated oxindole derivatives (Scheme 2).[17] Deuterated 7-aza-2-oxidole derivative **4a** was obtained in 91% yield from the corresponding methacrylamide. A variety of substitutions were tolerated in the aniline part of methacrylamide giving desired products in 61-90% yields (**4b-4f**). However, electron donating groups gave products in lower yields in comparison to electron withdrawing groups. Functional groups in *ortho*-, *para*- and *meta*-position of the *N*-aryl moiety were tolerated (**4a-4f**). Gratifyingly, various substituents on the nitrogen atom as well as in α-position to the carbonyl group were allowed and led to the corresponding products in 79-89% yields (**4g-4j**). The reaction is initiated by addition of trideuteromethyl radical to methacrylamide derivative (**3**) at the β-position. The formed carbon centred radical undergoes cyclization and afterwards rearomatization to provide product **4**.[17e]

Afterwards, we examined the functionalization of acrylamides for the synthesis of α-haloamides which are valuable building blocks in the synthesis of various complex products (Scheme 3).[18] In this case, iron(II) salts promote the formation of trideuteromethyl radicals and provide halogen anions which are incorporated in the final products. Various acrylamides were converted to α-chloroamides using the developed reaction conditions (Scheme 3, **6a**-**6c**). Furthermore, using $FeBr_2$, α-bromoamide **6d** was obtained regioselectively in 91% yield. The addition of trideuteromethyl radical to acrylamide led to the formation of a carbon centred radical. The oxidation of formed radical by iron (III) salt provided a carbocation intermediate. An attack of the halide anion on carbocation led to formation of product **6**.

Recently, Nevado and co-workers reported an arene-migration incorporation strategy to build α-aryl-β-trifluoromethyl amides bearing a α-quaternary stereocenter in a regioselective manner by means of Togni's reagent through a copper-catalyzed aryl migration process.[19] To investigate the limitations of our method, we tested this reaction using *N*-(arylsulfonyl)acrylamide (Scheme 4, **7**). α-Aryl-β-functionalized amide bearing a quaternary stereocenter was obtained in moderate yield (**8**, 67%) through a tandem process that

involves radical addition, 1,4-aryl migration and desulfonylation.[19]

In conclusion, the first method of trideuteromethylation for the synthesis of labelled heterocycles and building blocks was developed. Using deuterodimethyl sulfoxide as source of radicals, various labelled products were obtained. The transformations occur under radical reaction conditions which are also suitable for cascade and tandem processes initiated by trideuteromethyl radicals. The developed strategy allows convenient and selective access to a wide range of deuterated heterocycles.

We gratefully acknowledge the University of Bologna for PhD internship program and Prof. Dr. H. Waldmann (Max-Planck-Institut für molekulare Physiologie Dortmund) for his generous support. This work was supported by the Max-Planck-Gesellschaft.

Notes and references

1 T. G. Gant, *J. Med. Chem.*, 2014, **57**, 3595-3611.
2 (a) I. Kheterpal and R. Wetzel, *Acc. Chem. Res.*, 2006, **39**, 584-593; (b) I. Lee, *Chem. Soc. Rev.*, 1995, **24**, 223-229; (c) H. H. Mantsch, H. Saito and I. C. P. Smith, *Prog. Nucl. Magn. Reson. Spectrosc.*, 1977, **11**, 211-271; (d) M. I. Blake, H. L. Crespi and J. J. Katz, *J. Pharm. Sci.*, 1975, **64**, 367-391; (e) F. H. Westheimer, *Chem. Rev.*, 1961, **61**, 265-273; (f) K. B. Wiberg, *Chem. Rev.*, 1955, **55**, 713-743.
3 (a) A. Mullard, *Nat. Rev. Drug Discovery*, 2016, **15**, 219-221; (b) G. S. Timmins, *Expert Opin. Ther. Pat.*, 2014, **24**; (c) L. M. Shao and M. C. Hewitt, *Drug News Perspect.*, 2010, **23**, 398-404; (d) C. O'Driscoll, *Chem. Ind.*, 2009, 7-7.
4 A. Katsnelson, *Nat. Med.*, 2013, **19**, 656-656.
5 (a) D. A. Stamler, F. Brown and M. Bradbury, *Mov. Disord.*, 2013, **28**, S271-S272; (b) C. Testa, *Neurotherapeutics*, 2016, **13**, 242-242; (c) C. Testa, D. Stamler and S. Frank, *Neurotherapeutics*, 2014, **11**, 222-223.
6 J. M. Hoffman, C. N. Habecker, A. M. Pietruszkiewicz, W. A. Bolhofer, E. J. Cragoe, M. L. Torchiana and R. Hirschmann, *J. Med. Chem.*, 1983, **26**, 1650-1653.
7 Organic compounds. US2010/35898, 2010.
8 Azapeptide derivatives as HIV protease inhibitors. EP2003120, 2008.
9 (a) T. Uemura, M. Yamaguchi and N. Chatani, *Angew. Chem. Int. Ed.*, 2016, **55**, 3162-3165; (b) R. Shang, L. Ilies and E. Nakamura, *J. Am. Chem. Soc.*, 2015, **137**, 7660-7663; (c) J. Jin and D. W. C. MacMillan, *Nature*, 2015, **525**, 87-90; (d) X. Chen, J. J. Li, X. S. Hao, C. E. Goodhue and J. Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 78-79.
10 H. Schonherr and T. Cernak, *Angew. Chem. Int. Ed.*, 2013, **52**, 12256-12267.
11 (a) S. Komarapuri, K. Krishnan and D. F. Covey, *J. Labelled Compd. Radiopharm.*, 2008, **51**, 430-434; (b) R. G. Gillis, *Tetrahedron Lett.*, 1968, 1413-1414.
12 G. Y. Iranzo and J. Elguero, *J. Labelled Compd. Radiopharm.*, 1990, **28**, 967-970.
13 (a) J. H. Gui, Q. H. Zhou, C. M. Pan, Y. Yabe, A. C. Burns, M. R. Collins, M. A. Ornelas, Y. Ishihara and P. S. Baran, *J. Am. Chem. Soc.*, 2014, **136**, 4853-4856; (b) V. A. Khripach, V. N. Zhabinskii, A. P. Antonchick, O. V. Konstantinova and B. Schneider, *Steroids*, 2002, **67**, 1101-1108; (c) A. P. Antonchick, B. Schneider, V. N. Zhabinskii and V. A. Khripach, *Steroids*, 2004, **69**, 617-628; (d) M. Adamczyk, J. R. Fishpaugh and D. Johnson, *J. Labelled Compd. Radiopharm.*, 1993, **33**, 153-155.
14 (a) Z. Q. Song and A. P. Antonchick, *Org. Biomol. Chem.*, 2016, **14**, 4804-4808; (b) S. Manna and A. P. Antonchick, *Angew. Chem. Int. Ed.*, 2016, **55**, 5290-5293; (c) R. Samanta, R. Narayan, J. O. Bauer, C. Strohmann, S. Sievers and A. P. Antonchick, *Chem. Commun.*, 2015, **51**, 925-928; (d) S. Manna, P. O. Serebrennikova, I. A. Utepova, A. P. Antonchick and O. N. Chupakhin, *Org. Lett.*, 2015, **17**, 4588-4591; (e) S. Manna, R. Narayan, C. Golz, C. Strohmann and A. P. Antonchick, *Chem. Commun.*, 2015, **51**, 6119-6122; (f) S. Manna and A. P. Antonchick, *Org. Lett.*, 2015, **17**, 4300-4303; (g) S. Manna and A. P. Antonchick, *Angew. Chem. Int. Ed.*, 2015, **54**, 14845-14848.
15 (a) E. Jones-Mensah, M. Karki and J. Magolan, *Synthesis*, 2016, **48**, 1421-1436; (b) X. F. Wu and K. Natte, *Adv. Synth. Catal.*, 2016, **358**, 336-352; (c) X. Jiang, C. Wang, Y. W. Wei, D. Xue, Z. T. Liu and J. L. Xiao, *Chem. Eur. J.*, 2014, **20**, 58-63; (d) K. Kawai, Y. S. Li, M. F. Song and H. Kasai, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 260-265; (e) S. W. Peabody, B. Breiner, S. V. Kovalenko, S. Patil and I. V. Alabugin, *Org. Biomol. Chem.*, 2005, 3, 218-221.
16 (a) M. Wan, H. X. Lou and L. Liu, *Chem. Commun.*, 2015, **51**, 13953-13956; (b) R. J. Tang, L. Kang and L. Yang, *Adv. Synth. Catal.*, 2015, **357**, 2055-2060; (c) S. Paul and J. Guin, *Chem. Eur. J.*, 2015, **21**, 17618-17622; (d) J. Kan, S. J. Huang, J. Lin, M. Zhang and W. P. Su, *Angew. Chem. Int. Ed.*, 2015, **54**, 2199-2203; (e) J. Jin and D. W. C. MacMillan, *Angew. Chem. Int. Ed.*, 2015, **54**, 1565-1569; (f) R. Xia, M. S. Xie, H. Y. Niu, G. R. Qu and H. M. Guo, *Org. Lett.*, 2014, **16**, 444-447; (g) Y. Siddaraju, M. Lamani and K. R. Prabhu, *J. Org. Chem.*, 2014, **79**, 3856-3865; (h) K. Matcha and A. P. Antonchick, *Angew. Chem. Int. Ed.*, 2013, **52**, 2082-2086; (i) T. Hoshikawa and M. Inoue, *Chem. Sci.*, 2013, **4**, 3118-3123; (j) A. P. Antonchick and L. Burgmann, *Angew. Chem. Int. Ed.*, 2013, **52**, 3267-3271.
17 (a) A. Ulmer, C. Brunner, A. M. Arnold, A. Pothig and T. Gulder, *Chem. Eur. J.*, 2016, **22**, 3660-3664; (b) D. J. Li, T. H. Yang, H. L. Su and W. Yu, *Adv. Synth. Catal.*, 2015, **357**, 2529-2539; (c) C. C. Li and S. D. Yang, *Org. Lett.*, 2015, **17**, 2142-2145; (d) X. Y. Duan, X. L. Yang, P. P. Jia, M. Zhang and B. Han, *Org. Lett.*, 2015, **17**, 6022-6025; (e) K. Matcha, R. Narayan and A. P. Antonchick, *Angew. Chem. Int. Ed.*, 2013, **52**, 7985-7989; (f) D. C. Fabry, M. Stodulski, S. Hoerner and T. Gulder, *Chem. Eur. J.*, 2012, **18**, 10834-10838.
18 (a) M. Y. Fu, L. Chen, Y. P. Jiang, Z. X. Jiang and Z. G. Yang, *Org. Lett.*, 2016, **18**, 348-351; (b) X. J. Tang and W. R. Dolbier, *Angew. Chem. Int. Ed.*, 2015, **54**, 4246-4249; (c) T. Yajima and H. Nagano, *Org. Lett.*, 2007, **9**, 2513-2515.
19 (a) W. Q. Kong, M. Casimiro, N. Fuentes, E. Merino and C. Nevado, *Angew. Chem. Int. Ed.*, 2013, **52**, 13086-13090; (b) W. Kong, M. Casimiro, E. Merino and C. Nevado, *J. Am. Chem. Soc.*, 2013, **135**, 14480-14483.