ChemComm

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Chem. Commun.*, 2023, 59, 3707

Received 2nd November 2022, Accepted 27th February 2023

DOI: 10.1039/d2cc05934g

rsc.li/chemcomm

Photo/Ni dual-catalyzed radical defluorinative sulfonylation to synthesize *gem*-difluoro allylsulfones†

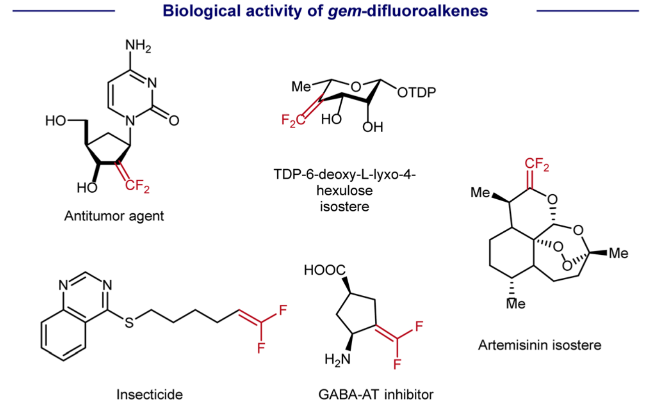
Yiran Xu, Shengchun Wang, Zhao Liu, Mian Guo* and Aiwen Lei *

Radical defluorinative functionalization of α-trifluoromethyl styrenes represents an effective way toward *gem*-difluoroalkenes. There are general interests in developing novel synthetic protocols for defluorinative functionalization with various types of radicals. However, reports on the preparation of *gem*-difluoro allylsulfones *via* an *S*-centered radical pathway are limited. Herein, we developed a photo/nickel dual-catalyzed defluorinative sulfonylation that rapidly and reliably synthesizes *gem*-difluoro allylsulfones. The merit of this protocol is exhibited by its mild conditions and wide scope, thus providing a novel strategy for the sulfonyl radical participating in radical defluorinative coupling.

As a type of carbonyl isostere, *gem*-difluoroalkenes are usually of unique metabolic stability, bioactivity, and target specificity, thus providing more opportunities for drug discovery (Scheme 1).[1] Therefore, the synthesis of *gem*-difluoroalkenes has recently been an emerging goal in organic and medicinal chemistry. Until now, several strategies have been developed for the preparation of *gem*-difluoroalkenes. Classic methods, such as Wittig-type and Reformatsky decarboxylation reactions, usually involve highly reactive species and/or harsh conditions, and result in a limited compatibility of functional groups. As a convergent approach, S_N2-type reactions, in which fluoride is lost by nucleophilic attack on CF_3, require strong nucleophiles and may limit their substrate scope.[2] Distinctive in mechanisms, the revival of radical chemistry has provided new opportunities to prepare *gem*-difluoroalkenes, in which the defluorination of CF_3 is achieved by a Ni/Cr-promoted β-F elimination[3] (Scheme 2A) or a photo-/electro-induced radical/polar cross-cover[4] (Scheme 2B). However, most studies of radical defluorinative coupling are focused on *C*-centered radicals or *B*-centered radicals (Scheme 2B). The exploration of other types of radicals to synthesize diversified *gem*-difluoroalkenes is in crucial demand, yet challenging.

Due to the unique properties of the C–S bond, the construction of *S*-containing compounds has drawn much attention from synthetic chemists over recent decades.[5] Among these organic sulfur compounds, allylsulfones serve as versatile synthetic blocks and can be effectively transformed to other value-added chemicals.[6] Thus, we became interested in the synthesis of *gem*-difluoro allylsulfones which have the potential to integrate the nature of both *gem*-difluoro alkenes and allylsulfones. However, the synthesis of *gem*-difluoro allylsulfones *via* an *S*-centered radical pathway remains elusive. Challenges still exist in such desired transformations. Defluorinative sulfonylation to synthesize *gem*-difluoro allylsulfones is endergonic by 17.9 kcal mol^{-1}, which is thermodynamically unfeasible. In addition, an aerobic difunctionalization to produce functionalized CF_3-substituted tertiary alcohol is exergonic by −1.2 kcal mol^{-1}, which is thermodynamically spontaneous (see the detailed DFT calculation in Fig. S1, ESI†).

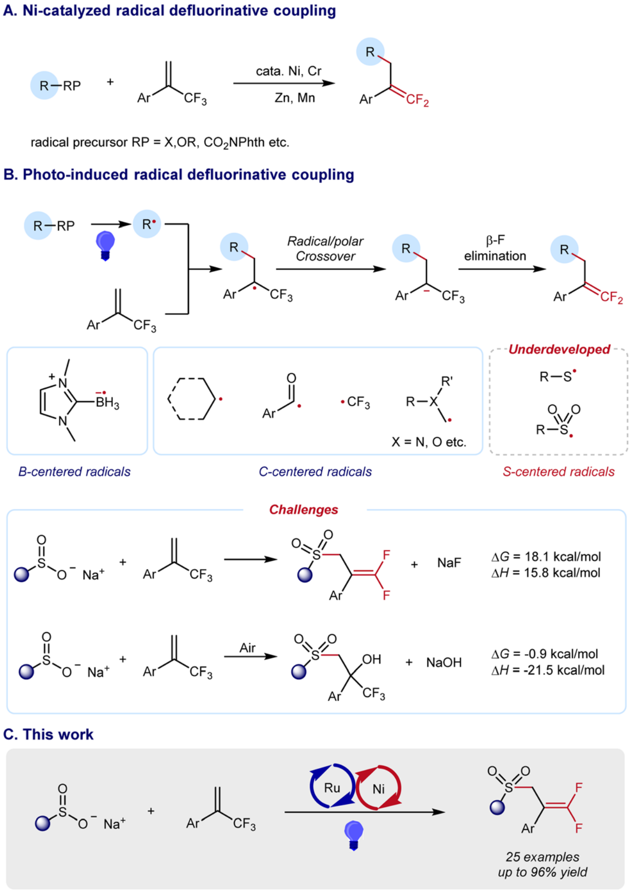
To address such a thermodynamic challenge, we focused our attention to the photocatalytic organic reaction that utilizes visible light as energy input, providing a green and sustainable



Scheme 1 Representative *gem*-difluoroalkenes with biological activity.

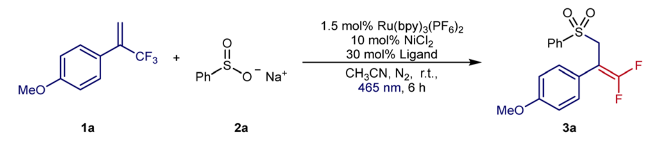
College of Chemistry and Molecular Sciences, The Institute for Advanced Studies (IAS), Wuhan University, Wuhan 430072, P. R. China.
E-mail: aiwenlei@whu.edu.cn, whguomian@whu.edu.cn

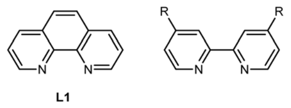
† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d2cc05934g



Scheme 2 Recent advances in radical defluorinative functionalization to synthesize gem-difluoroalkenes. (A) Ni catalyzed radical defluorinative coupling. (B) Photo-induced radical defluorinative coupling. (C) Outline of this work.

Table 1 Optimization of reaction conditions[a]





L2: R = H
L3: R = ^{t}Bu
L4: R = COOMe

Entry	Variation from the standard conditions[a]	Yield[b] [%]
1	**L1** was used	21
2	**L2** was used	93
3	**L3** was used	65
4	**L4** was used	36
5	10 mol% $Ni(bpy)_3Cl_2$ was used	96 (90)
6	Without ligand	39
7	Without $Ru(bpy)_3(PF_6)_2$	n.d.
8	Without $Ni(bpy)_3Cl_2$	Trace
9	Without irradiation	n.d.
10	Eosin Y as photocatalyst	n.d.
11	$[Ir(dFCF_3ppy)_2((4,4'-dCF_3bpy))](PF_6)$ as photocatalyst	12
12	DCE as solvent	21
13	THF as solvent	n.d.
14	Air instead of N_2	n.d.

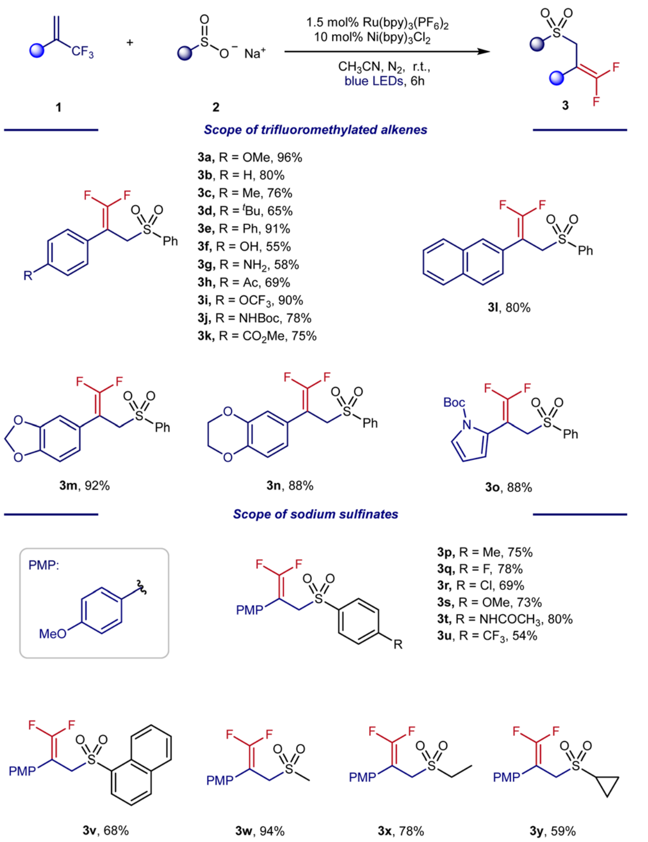
[a] Conditions: **1a** (0.15 mmol, 1.0 equiv.), **2a** (0.20 mmol, 1.33 equiv.), $Ru(bpy)_3(PF_6)_2$ (1.5 mol%), $NiCl_2$ (10 mol%), ligand (30 mol%) in MeCN (2.0 mL) under N_2 atmosphere and irradiation with blue LED (465 nm) for 6 h. [b] Yields were determined by GC-FID with decane as the internal standard; isolated yield is shown in parentheses.

synthetic protocol. Merging photocatalysis and nickel catalysis, we considered that a radical defluorinative coupling could be achieved based on the addition of a sulfonyl radical to α-(trifluoromethyl)-styrenes, where the subsequent β-F elimination could be effectively promoted by a nickel catalyst (Scheme 2C). This dual-catalyzed process would offer a solution to avoid a fast side reaction that leads to α-trifluoromethyl-β-sulfonyl tertiary alcohols with trace air. Herein, we report the successful execution of this design plan.

At the outset of our investigation, we chose 1-methoxy-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene **1a** as the radical acceptor and inexpensive sodium benzenesulfinate **2a** as the sulfonyl radical precursor (Table 1). The initial examination was focused on the ligands with $Ru(bpy)_3(PF_6)_2$ as the photocatalyst and $NiCl_2$ as the metal catalyst (entries 1–4). To our delight, the desired transformation was successfully realized in 93% isolated yield with 30 mol% **L2** as ligand. By merging $Ru(bpy)_3(PF_6)_2$ and $Ni(bpy)_3Cl_2$, the best results were found in MeCN under blue LED irradiation at room temperature to obtain **3a** in 96% GC yield and 90% isolated yield. Control experiments (entries 6–9) proved that $Ru(bpy)_3(PF_6)_2$, $Ni(bpy)_3Cl_2$ and irradiation were essential for this organic transformation. Without the nickel catalyst, only a trace amount of product could obtain and the yield was lowered to 39% without the bipyridine ligand. When using eosin Y or an iridium complex as photocatalysts instead of $Ru(bpy)_3(PF_6)_2$, lower yields of **3a** were found (entries 10 and 11). This transformation exhibited a much lower yield with DCE as the solvent and failed with THF as the solvent (entries 12 and 13). Similar to other radical defluorinative couplings, the synthesis of *gem*-difluoro allylsulfones failed in air (entry 14).

With the optimal conditions in hand, we turned our attention to exploring the generality of our photo/Ni dual-catalyzed radical defluorinative coupling of α-trifluoromethyl styrene. As shown in Scheme 3, the scope was largely insensitive to electronic changes at the *para* and *meta* positions of trifluoromethylated alkenes (**3a–3k**). However, this defluorinative coupling failed with *otho*-substituted trifluoromethylated alkenes (see the ESI†). Interestingly, other cyclic motifs of CF_3-substituted alkenes were also suitable radical acceptors for this organic transformation, including naphthalene (**3l**), benzodioxole (**3m**), benzodioxan (**3n**), and *N*-Boc pyrrole (**3o**).

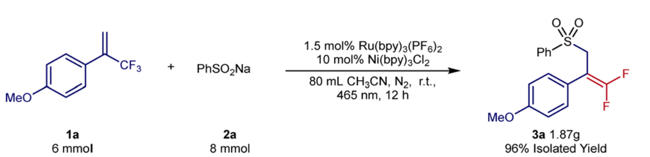
Next, the scope of the sodium sulfinates was examined. A series of *para*-substituted sodium benzenesulfinates, including halides (**3q** and **3r**), amides (**3t**), and trifluoromethyl (**3u**), were all well tolerated, forming the desired products in 54–80% yield. In addition, 2-naphthylsulfinic acid sodium (**3v**) was also a suitable sulfonyl radical precursor for this transformation, providing 64% yield. Pleasingly, sodium alkylsulfinates (**3w–3y**) were also well-tolerated under the reaction conditions and provided yields of 59–94%. To further explore the potential applications of this synthetic



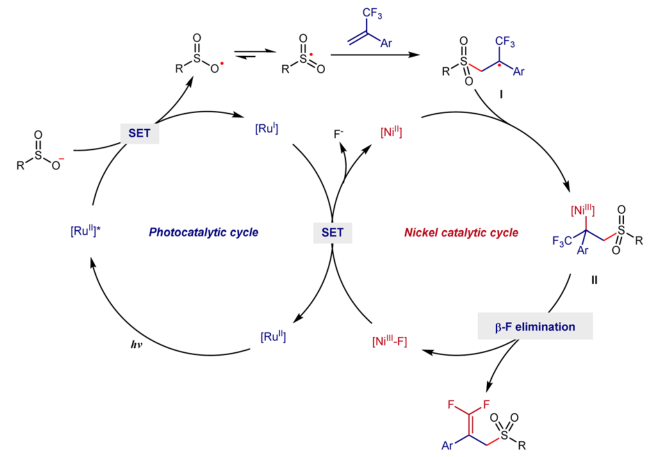
Scheme 3 Scope of substrates. Reaction conditions: **1** (0.15 mmol, 1.0 equiv.), **2** (0.2 mmol, 1.33 equiv.), $Ru(bpy)_3(PF_6)_2$ 1.5 mol%, $Ni(bpy)_3Cl_2$ 10 mol%, MeCN (2.0 mL), room temperature, N_2, 6 h. Yields of isolated products are shown.

method, we carried out a gram-scale experiment (Scheme 4). The gram-scale reaction between **1a** and **2a** afforded the corresponding gem-difluoroalkenes **3a** in 96% isolated yield.

Based on previous reports,[4h,7] a plausible mechanism of this radical defluorinative sulfonylation is shown in Scheme 4. Firstly, sodium benzenesulfonate is preferentially oxidized by photo-excited $Ru^{II}(bpy)_3$ to generate the corresponding sulfonyl radical and Ru^{I} complex. Then, radical addition occurs between the sulfonyl radical and **2a** to form a benzyl carbon radical **I**, which can further react with Ni^{II} to form alkyl-Ni^{III} species **II**. Next, the final product **3a** is obtained *via* a β-F elimination from **II**, and at the same time Ni^{III}-F is generated. Finally, $Ru^{II}(bpy)_3$ and Ni^{II} are regenerated *via* a single electron transfer between the Ru^{I} complex and Ni^{III}-F and the catalytic cycle is completed (Scheme 5).



Scheme 4 Gram-scale experiment. **1a** (6 mmol, 1.0 equiv.), **2a** (8 mmol, 1.33 equiv.), $Ru(bpy)_3(PF_6)_2$ (0.09 mmol, 1.5 mol%), $Ni(bpy)_3Cl_2$ (0.6 mmol, 10 mol%), 80 mL CH_3CN, r.t., 465 nm, 12 h.



Scheme 5 Proposed mechanism.

We have demonstrated that a radical defluorinative sulfonyla-tion, consisting of the addition of a sulfonyl radical to alkenes and a nickel-promoted β-F elimination, leads to a challenging coupling of sodium sulfinates and CF_3-substituted alkenes to synthesize a series of *gem*-difluoro allylsulfones. This protocol features mild conditions, a facile synthesis, and a wide scope of substrates. We believe that this method not only provides a rare example of a sulfonyl radical participating in the synthesis of *gem*-difluoro allylsulfones, but also represents a new strategy of photo/nickel dual-catalyzed defluorinative functionalization.

This work was supported by the National Key R&D Program of China (No. 2021YFA1500104), the National Natural Science Foundation of China (No. 22031008 and No. 22171216), the Science Foundation of Wuhan (No. 2020010601012192), and the Postdoctoral Foundation of Hubei Province (No. 211000025). We thank Prof. Xiaotian Qi for his efforts in DFT calculations. The numerical calculations in this paper were performed on the supercomputing system at the Supercomputing Center of Wuhan University.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) M. Bobek, I. Kavai and E. De Clercq, *J. Med. Chem.*, 1987, **30**, 1494; (*b*) C. Leriche, X. He, C. W. Chang and H. W. Liu, *J. Am. Chem. Soc.*, 2003, **125**, 6348; (*c*) K. Fujii, Y. Nakamoto, K. Hatan and Y. Kanetsuki, JP2006016331 A, 2006; (*d*) Y. Pan, J. Qiu and R. B. Silverman, *J. Med. Chem.*, 2003, **46**, 5292; (*e*) G. Magueur, B. Crousse, M. Ourévitch, D. Bonnet-Delpon and J.-P. Bégué, *J. Fluorine Chem.*, 2006, **127**, 637.
2 (*a*) G. Chelucci, *Chem. Rev.*, 2012, **112**, 1344; (*b*) X. Zhang and S. Cao, *Tetrahedron Lett.*, 2017, **58**, 375; (*c*) M. Hu, Z. He, B. Gao, L. Li, C. Ni and J. Hu, *J. Am. Chem. Soc.*, 2013, **135**, 17302; (*d*) M. Wang, X. Pu, Y. Zhao, P. Wang, Z. Li, C. Zhu and Z. Shi, *J. Am. Chem. Soc.*, 2018, **140**, 9061; (*e*) P. H. S. Paioti, J. Del Pozo, M. S. Mikus, J. Lee, M. J. Koh, F. Romiti, S. Torker and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2019, **141**, 19917.
3 (*a*) Y. Lan, F. Yang and C. Wang, *ACS Catal.*, 2018, **8**, 9245; (*b*) Z. Lin, Y. Lan and C. Wang, *ACS Catal.*, 2018, **9**, 775; (*c*) X. Lu, X. X. Wang, T. J. Gong, J. J. Pi, S. J. He and Y. Fu, *Chem. Sci.*, 2019, **10**, 809;

(*d*) C. Zhu, Z. Y. Liu, L. Tang, H. Zhang, Y. F. Zhang, P. J. Walsh and C. Feng, *Nat. Commun.*, 2020, **11**, 4860; (*e*) C. Zhang, Z. Lin, Y. Zhu and C. Wang, *J. Am. Chem. Soc.*, 2021, **143**, 11602; (*f*) Y. Ping, Q. Pan, Y. Guo, Y. Liu, X. Li, M. Wang and W. Kong, *J. Am. Chem. Soc.*, 2022, **144**, 11626.

4 (*a*) T. Fujita, K. Fuchibe and J. Ichikawa, *Angew. Chem., Int. Ed.*, 2019, **58**, 390; (*b*) F.-L. Qing, X.-Y. Liu, J.-A. Ma, Q. Shen, Q. Song and P. Tang, *CCS Chem.*, 2022, **4**, 2518; (*c*) F. Tian, G. Yan and J. Yu, *Chem. Commun.*, 2019, **55**, 13486; (*d*) W. Xu, H. Jiang, J. Leng, H. W. Ong and J. Wu, *Angew. Chem., Int. Ed.*, 2020, **59**, 4009; (*e*) T. Xiao, L. Li and L. Zhou, *J. Org. Chem.*, 2016, **81**, 7908; (*f*) S. B. Lang, R. J. Wiles, C. B. Kelly and G. A. Molander, *Angew. Chem., Int. Ed.*, 2017, **56**, 15073; (*g*) J. P. Phelan, S. B. Lang, J. Sim, S. Berritt, A. J. Peat, K. Billings, L. Fan and G. A. Molander, *J. Am. Chem. Soc.*, 2019, **141**, 3723; (*h*) L.-H. Wu, J.-K. Cheng, L. Shen, Z.-L. Shen and T.-P. Loh, *Adv. Synth. Catal.*, 2018, **360**, 3894; (*i*) W. J. Yue, C. S. Day and R. Martin, *J. Am. Chem. Soc.*, 2021, **143**, 6395; (*j*) W. Chen, S. Ni, Y. Wang and Y. Pan, *Org. Lett.*, 2022, **24**, 3647; (*k*) X. Yan, S. Wang, Z. Liu, Y. Luo, P. Wang, W. Shi, X. Qi, Z. Huang and A. Lei, *Sci. China: Chem.*, 2022, **65**, 762; (*l*) C. Zhu, M. M. Sun, K. Chen, H. Liu and C. Feng, *Angew. Chem., Int. Ed.*, 2021, **60**, 20237; (*m*) Z. Cai, R. Gu, W. Si, Y. Xiang, J. Sun, Y. Jiao and X. Zhang, *Green Chem.*, 2022, **24**, 6830; (*n*) F. Li, C. Pei and R. M. Koenigs, *Angew. Chem., Int. Ed.*, 2022, **61**, e202111892; (*o*) B. Wang, C. T. Wang, X. S. Li, X. Y. Liu and Y. M. Liang, *Org. Lett.*, 2022, **24**, 6566; (*p*) X. Wang, C. Wang and C. Bolm, *Org. Lett.*, 2022, **24**, 7461.

5 (*a*) P. Chauhan, S. Mahajan and D. Enders, *Chem. Rev.*, 2014, **114**, 8807; (*b*) C. Shen, P. Zhang, Q. Sun, S. Bai, T. S. Hor and X. Liu, *Chem. Soc. Rev.*, 2015, **44**, 291; (*c*) H. Yi, G. Zhang, H. Wang, Z. Huang, J. Wang, A. K. Singh and A. Lei, *Chem. Rev.*, 2017, **117**, 9016; (*d*) P. Renzi, E. Azzi, A. Lanfranco, R. Moro and A. Deagostino, *Synthesis*, 2021, 3440.

6 (*a*) A. El-Awa, M. N. Noshi, X. M. du Jourdin and P. L. Fuchs, *Chem. Rev.*, 2009, **109**, 2315; (*b*) X. Chen, S. Hussain, S. Parveen, S. Zhang, Y. Yang and C. Zhu, *Curr. Med. Chem.*, 2012, **19**, 3578.

7 (*a*) Q. Liu and L.-Z. Wu, *Natl. Sci. Rev.*, 2017, **4**, 359; (*b*) A. Y. Chan, I. B. Perry, N. B. Bissonnette, B. F. Buksh, G. A. Edwards, L. I. Frye, O. L. Garry, M. N. Lavagnino, B. X. Li, Y. Liang, E. Mao, A. Millet, J. V. Oakley, N. L. Reed, H. A. Sakai, C. P. Seath and D. W. C. MacMillan, *Chem. Rev.*, 2022, **122**, 1485; (*c*) Z. Li, C. Li, Y. Ding and H. Huo, *Coord. Chem. Rev.*, 2022, **460**, 214479; (*d*) T. Ichitsuka, T. Fujita and J. Ichikawa, *ACS Catal.*, 2015, **5**, 5947; (*e*) F. Chen, X. Xu, Y. He, G. Huang and S. Zhu, *Angew. Chem., Int. Ed.*, 2020, **59**, 5398; (*f*) C. Yao, S. Wang, J. Norton and M. Hammond, *J. Am. Chem. Soc.*, 2020, **142**, 4793; (*g*) J. S. Lin, X. Y. Dong, T. T. Li, N. C. Jiang, B. Tan and X. Y. Liu, *J. Am. Chem. Soc.*, 2016, **138**, 9357.

