ChemComm
Chemical Communications

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: R. Nie, R. Lai, S. Lv, Y. Xu, L. Guo, Q. Wang and Y. Wu, *Chem. Commun.*, 2019, DOI: 10.1039/C9CC05804D.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/C9CC05804D

COMMUNICATION

Received 00th January 20xx,

Water-Mediated C-H Activation of Arenes with Secure Carbene Precursors: the Reaction and its Application

Ruifang Nie,† Ruizhi Lai,† Songyang Lv, Yingying Xu, Li Guo, Qiantao Wang* and Yong Wu*

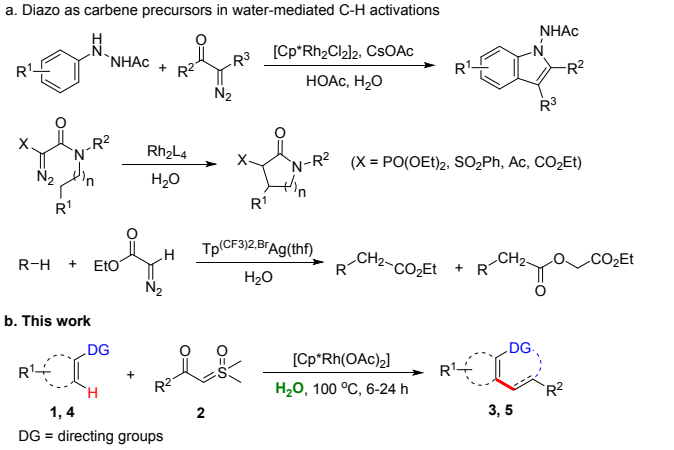
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

A water-mediated C-H activation using sulfoxonium ylides is reported, providing a general, green and step-economic approach to construct C-C bond and varieties of useful N-heterocycle scaffolds. Notably, the "water-mediated", in contrast to that of in organic solvent, shows a great potential in developing pharmaceutical, biochemistry and chemical industries.

Conventionally, organic synthesis relies heavily on organic solvents, which are usually used in vast quantity in comparison with that of the reactants. As a result, the bulk of chemical waste was the toxic organic solvents. Therefore, limiting or avoiding the use of organic solvents could effectively reduce the amount of chemical waste and meet the growing needs for sustainable chemistry across academic and industrial fields.[1] To achieve this goal, one way would be developing solvent-free processes, but solvents also play an immense role in bringing the reaction equilibrium and rates under control or even be a partner to improve the catalyst in many reactions.[2] Alternative solvents were also developed,[3] but none of them are as "green" as water given its abundance, cost-efficiency, environment compatibility, non-toxicity and non-flammability.

Transition-metal-catalysed successive activation and functionalization of C-H bonds is at the heart of synthetic innovations for the development of C-C bond cross-coupling processes because it does not require pre-functionalizing the substrate and is highly regioselective.[4] C-H activation/annulation represents one of the hottest topics in recent years,[5] because it does not only specifically functionalize the inert C-H bonds but also forms varieties of cyclic compounds by coupling and cyclization with the introduced functional groups. Unsurprisingly, most of C-H activations were reacted in organic solvents, with limited exceptions. Among the exceptions, diazo reagents as carbene precursors has been used in water-mediated C-H functionalization successfully (Scheme 1a).[6] The diazo reagents, however, can cause safety issues in large scale processes due to their instability and the risk of potential exothermic reactions linked releasing of nitrogen gas. This greatly limited its application. In recent years, α-carbonyl sulfoxonium ylides as safer alternative reagents to diazo compounds has been optimized in laboratory and industry scales.[7] Typically, these reagents are well-behaved crystalline solids that demonstrate high stability and serve as carbene precursors that do not generate gas by-products. In recent years, C-H activation of sulfoxonium ylides with different directing groups (DG) in organic solvents were independently reported by many groups.[8] These methodologies composed a powerful toolbox to afford N-heterocycles such as lactones, lactams, isoquinolines, azolopyrimidines, indazoles, indoles and etc. Despite the application of sulfoxonium ylides is constantly expanding, this secure carbene precursor has not detached



Scheme 1 Water-mediated C-H activation

Sichuan Engineering Laboratory for Plant-Sourced Drug and Research Center for Drug Industrial Technology, Key Laboratory of Drug-Targeting and Drug Delivery System of the Education Ministry, West China School of Pharmacy, Sichuan University, Chengdu, 610041, China.
Email: wyong@scu.edu.cn (Yong Wu); qwang@scu.edu.cn (Qiantao Wang)
† R.N. and R.L. contributed equally.
Electronic Supplementary Information (ESI) available: general information, experimental procedures, characterization data and spectra data. See DOI:10.1039/x0xx00000x

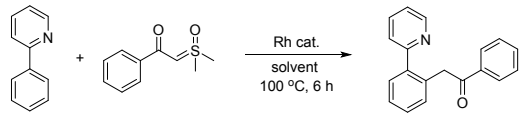
from the organic solvent system yet, and the study about non-organic solvent mediated reactions was underexploited. Thus, the study of sulfoxonium ylides in "green" solvents would be of great interest. Recently, our group were interested in the diversified reactivities of sulfoxonium ylides.[8d] Meanwhile, our group were committed to the study of non-organic solvent mediated C-H activation for a long time.[9] Herein, as a result, we reported our most recent work in water-mediated sp2 C-H activation of arenes with sulfoxonium ylides (Scheme 1b).

The reactions of 2-phenylpyridine **1a** and dimethyloxosulfonium benzoylmethylide **2a** in the presence of $[Cp^*RhCl_2]_2/AgSbF_6$ and non-organic solvents at 100 °C were initially investigated (Table S1 in ESI). Fortunately, the reaction proceeded smoothly in water providing the desired product **3a** with a 82% isolated yield (Table 1, entry 1). Notably, $[Cp^*Rh(OAc)_2]$ was obviously favoured as the catalyst to generate product **3a** with a 86% isolated yield, and more green without any additives (Table 1, entries 2-5). Excessive temperature will cause serious side-reactions of ylides, and decreasing the temperature also reduced starting material conversion.

With the optimized reaction conditions in hand, the substrate scope of 2-phenylpyridines was examined (Table 2).[10] Unsubstituted 2-phenylpyridine gave a 86% isolated yield of **3a**. Introduction of electron-donating and -withdrawing as well as halogen groups into different positions of the benzene ring was fully tolerated (**3b**-**3h**). When the phenyl moiety was replaced with β-naphthyl, thienyl, indole ring and 1,3-benzodioxole groups, the desired products **3i**-**3l** still owned moderate to excellent yields. Notably, **3k** was obtained as an reverse-steric effect regioisomeric product, and it may because the reaction was dominated by the electrical effect. Pyrimidine, pyrazole and isoquinoline were also seemed to be good directing groups affording **3m**-**3o**. In addition to aromatic sulfonium ylides, aliphatic sulfonium ylides also exhibited good reactivity, and expanded the application of the reaction (**3p** and **3q**).

To better define the scope of this strategy, the coupling of NH-sulfoximine with sulfoxonium ylides was also examined (Table 3).[11] The sulfoxonium ylide was not limited to aryl substitution, and the yields were comparably high when iso-propyl and tert-butyl substituted sulfoxonium ylides were used (**5a**-**5c**). To further demonstrate the substrates scope, methyl,

Table 1 Optimization of the reaction conditions[a]

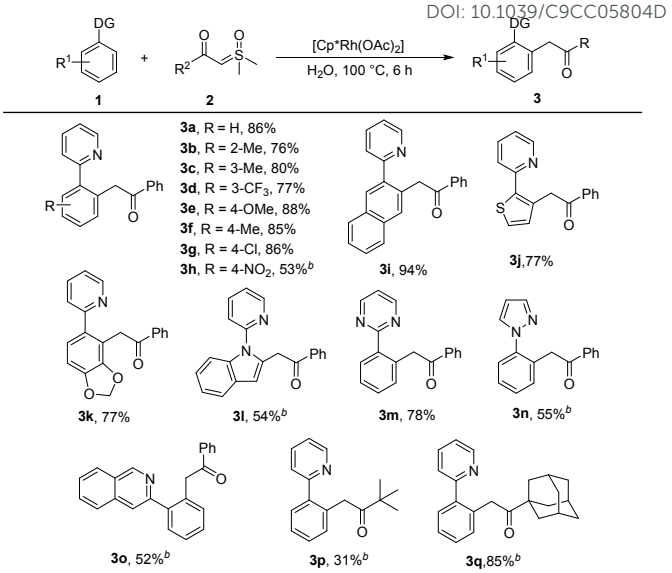


1a 2a 3a

Entry	Catalyst	Solvent	Yield[b]
1	$[Cp^*RhCl_2]_2/AgSbF_6$	H_2O	82%
2	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	H_2O	78%
3	$[Rh(COD)Cl]_2$	H_2O	trace
4	**$[Cp^*Rh(OAc)_2]$**	**H_2O**	**86%**
5	$[Cp^*RhCl_2]_2/AgOAc$	H_2O	85%

[a]Unless otherwise noted, all the reactions were carried out using: 2-phenylpyridine **1a** (0.2 mmol), dimethyloxosulfonium benzoylmethylide **2a** (0.4 mmol), Rh cat. (5 mol%), $AgSbF_6$ (20 mol%), solvent(1.5 ml), under air. [b]Isolated yields.

Table 2 Scope of arenes and sulfonium ylides[a]

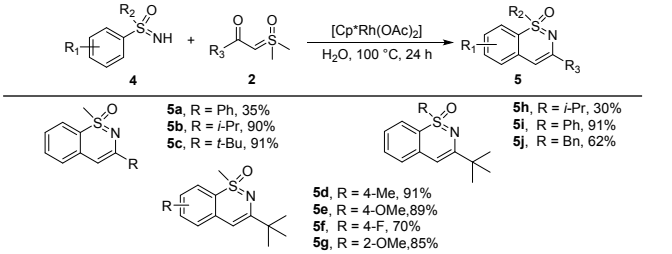


[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $[Cp^*Rh(OAc)_2]$ (5 mol%), H_2O (1.5 ml), under air. Desired product **3** was isolated by column chromatography on silica gel (eluent: PE/EA = 50/1). [b]Reaction time 24 hours.

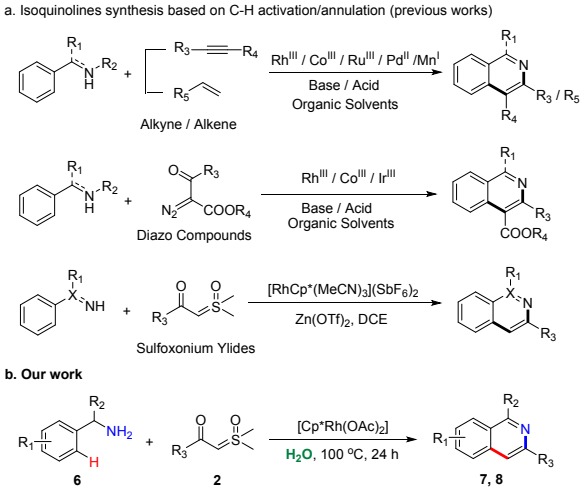
methoxy and halogen substituted S-aryl-S-methylsulfoximines coupled with dimethyloxosulfonium pivaloylmethylide respectively to give the corresponding products **5d**-**5g** with 70-91% yields. In addition, S-aryl-S-isopropylsulfoximine, S-diarylsulfoximine and even S-phenyl-S-benzylsulfoximine all coupled smoothly to give 1,2-benzothiazines **5h**-**5j** with 66-89% yields.

Encouraged by these initial experimental results, we sought to further explore this water-mediated C-H activation in order to increase the scope of this strategy to a greater extent. Isoquinolines and its related derivatives are the well-known nitrogen-containing heterocyclic compounds that pose broad-spectrum biological activities, and have been widely used in pharmaceutical, agricultural and chemical industries.[12] More efficient and environment-friendly synthesis of isoquinoline compounds is of great interest for the general chemistry field. Obviously, the emergence of C-H activation/annulation coincide with this requirement (Scheme 2a).[13] However, the previous works have not detached from the organic solvent system yet, and have limitations in practical application due to the substrate complexity. Therefore, we hope to achieve the synthesis of 3-

Table 3 Synthesis of 1,2-benzothiazines[a]



[a]Reaction conditions: **4** (0.2 mmol), **2** (0.4 mmol), $[Cp^*Rh(OAc)_2]$ (5 mol%), H_2O (1.5 ml), under air. Desired product **5** was isolated by column chromatography on silica gel (eluent: PE/EA = 50/1).

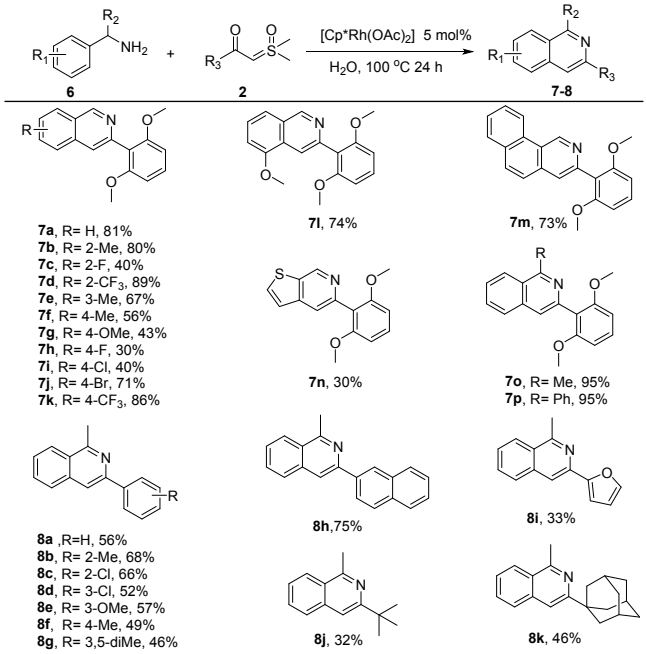


Scheme 2 Synthesis of isoquinoline *via* C-H activation

phenylisoquinolines by the water-mediated C-H activation strategy (Scheme 2b).

To our delight, the coupling of benzylamine **6a** and dimethyloxosulfonium 2,6-dimethoxyl-1-benzoylmethylide **2b** afforded the desired product **7a** with a 81% yield. Various benzylamine derivatives and analogues were tested following this method, and the results were summarized in Table 4. Both electron-donating groups (methyl, methoxy and dimethoxy) and electron-withdrawing groups (fluoro, chloro, bromo, and trifluoromethyl) were well tolerated, giving the corresponding isoquinolines in moderate to good yields (**7b**-**7l**). It was noteworthy that **7l** was obtained as a reverse steric effect regioisomeric product, possibly because of the dominance of the electrical effect. Naphthylamine afforded **7m** with a good yield, but 2-thiophenemethylamine afforded **7n** with a lower yield. This contrast may be caused by the different conjugation of the substrates. α-Substituted benzylamines gave the 1-substituted isoquinolines **7o** and **7p** both in 95% yield. Next, the scope of sulfoxonium ylides was studied. Both the electron-donating and-withdrawing groups of the phenyl ring were adapted well, affording **8a**-**8g** in moderate to good yields. When the phenyl ring was replaced by a naphthalene ring, **8h** was obtained with a good yield. However, when the phenyl ring was replaced by a furan ring or aliphatic chain, **8i**-**8k** was obtained with lower yields. The different results may be due to the conjugation change.

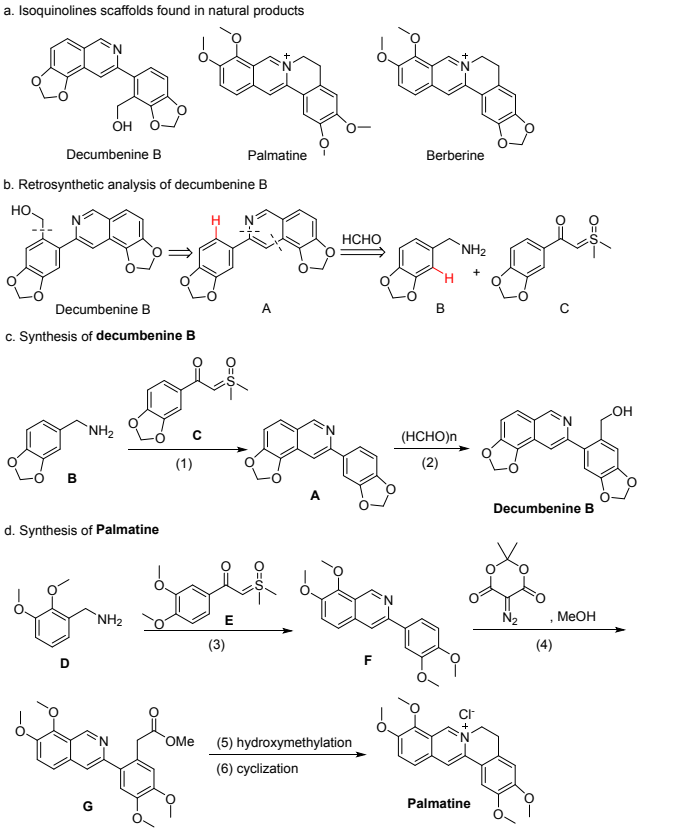
Table 4 Synthesis of isoquinoline derivatives[a]



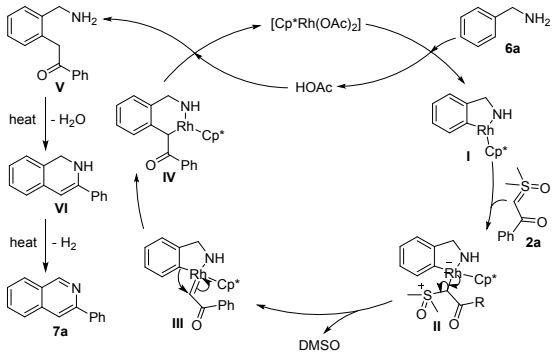
[a]Reaction conditions: **6** (0.2 mmol), **2** (0.4 mmol), [Cp*Rh(OAc)$_2$] (5 mol%), H_2O (1.5 ml), under air. Desired product **7** or **8** was isolated by column chromatography on silica gel (eluent: PE/EA = 20/1).

yield. This contrast may be caused by the different conjugation of the substrates. α-Substituted benzylamines gave the 1-substituted isoquinolines **7o** and **7p** both in 95% yield. Next, the scope of sulfoxonium ylides was studied. Both the electron-donating and-withdrawing groups of the phenyl ring were adapted well, affording **8a**-**8g** in moderate to good yields. When the phenyl ring was replaced by a naphthalene ring, **8h** was obtained with a good yield. However, when the phenyl ring was replaced by a furan ring or aliphatic chain, **8i**-**8k** was obtained with lower yields. The different results may be due to the conjugation change.

Isoquinolines are ubiquitous scaffolds found in numerous natural products (Scheme 3a).[14] Based on our recent work on the synthesis of natural products such as berberine,[15] B-homo Palmatine[16] and decumbenine B,[17] we noted that the easily available primary amines and sulfoxonium ylides could be the most suitable combination to form natural products and the related derivatives. For example, conjectured from the retrosynthetic analysis, decumbenine B can be easily obtained through two steps of C-H activation from 1,3-benzodioxol-5-methanamine and dimethyloxosulfonium 1,3-benzodioxol-5-formylmethylide (Scheme 3b). As the biologically active isoquinolines were successfully obtained, we tried to use this methodology for the total synthesis of natural products. Decumbenine B and Palmatine are both isoquinoline alkaloids existing in nature. Applying our methodology, intermediate **A** was easily obtained, and can easily transformed to decumbenine B through our established protocol (Scheme 3c,



Scheme 3 Synthesis of natural products.



Scheme 4 Possible mechanism

see ESI for details).[17] Similarly, intermediate **F** was also obtained, and then transformed to Palmatine following previous works (Scheme 3d, see ESI for details).[18] Thus, a more simple, green and efficient synthesis strategy of isoquinolines natural products was developed.

Benzylamines as C-H activation substrates had two possible paths according to previous related studies.[13b-c,19] In order to gain the insight into the reaction mechanism, a series of experiments was conducted (for details, see ESI). Based on the results, a possible mechanism for this protocol was shown in Scheme 4. Initially, cyclometalation of benzylamine **6a** gives a rhodacyclic intermediate **I**. Coordination of dimethyloxosulfonium benzoylmethylide **2a** generates a Rh(III) alkyl species **II**, and the subsequent α-elimination of DMSO from species **II** affords a reactive rhodium α-oxo carbene species **III**. Subsequently, intermediate **III** underwent migratory insertion of the Rh-C bond to generate a six-membered rhodacyclic intermediate **IV**. After that, protonation of **IV** delivered the alkylated imine **V** and released the active catalyst. Then, under heating, the alkylated imine **V** takes part in the intra-molecular annulation of amino and carbonyl to furnish ring closure leading to 1,2-dihydroisoquinoline **VI**. Eventually, the aromatization of 1,2-dihydroisoquinoline **VI** provides the final product isoquinoline **7a** by the extrusion of H_2.

In summary, we report the example of water-mediated C-H activation of arenes with sulfoxonium ylides. This work develops a green and sustainable approach to construct C-C bond without any organic solvents or additives. Furthermore, this methodology has been used to synthesis natural products successfully, indicating its great potential in developing green chemistry in chemical synthesis and drug design.

Financial support from NSFC (grant number 81373259, 81573286 and 81602954) are gratefully acknowledged.

There are no conflicts to declare.

Notes and references

1 (a) B. Li and P. H. Dixneuf, *Chem. Soc. Rev.*, 2013, **42**, 5744; (b) T. Kitanosono, K. Masuda, P. Xu, S. Kobayashi, *Chem. Rev.*, 2018, **118**, 679.

2 (a) A. Chanda and V. V. Fokin, *Chem. Rev.*, 2009, **109**, 725; (b) Y. J. Zuo and J. Qu, *J. Org. Chem.*, 2014, **79**, 6832; (c) K. Karhan, R. Z. Khaliullin, T. D. Kühne, *J. Chem. Phys.*, 2014, **141**, 22D528.

3 (a) B. H. Lipshutz, F. Gallou, S. Handa, *ACS Sustainable Chem. Eng.*, 2016, **4**, 5838; (b) R. A. Sheldon, *Green Chem.*, 2005, **7**, 267.

4 (a) C.-J. Li, *Acc. Chem. Res.* 2009, **42**, 335; (b) P. L. Arnold, M. W. McMullon, J. Rieb, F. E. Kühn, *Angew. Chem., Int. Ed.*, 2015, **54**, 82; (c) F. Wang, S. Yu, X. Li, *Chem. Soc. Rev.*, 2016, **45**, 6462; (d) Y. Hu, B. Zhou, C. Wang, *Acc. Chem. Res.* 2018, **51**, 816.

5 G. Song, F. Wang, X. Li, *Chem. Soc. Rev.*, 2012, **41**, 3651.

6 (a) Y. Liang, K. Yu, B. Li, S. Xu, H. Song, B. Wang, *Chem. Commun.*, 2014, **50**, 6130; (b) R. P. Wurz and A. B. Charette, *Org. Lett.*, 2002, **4**, 4531; (c) M. Álvarez, R. Gava, M. R. Rodríguez, S. G. Rull, P. J. Pérez, *ACS Catal.*, 2017, **7**, 3707.

7 (a) I. K. Mangion, I. K. Nwamba, M. Shevlin, M. A. Huffman, *Org. Lett.*, 2009, **11**, 3566; (b) I. K. Mangion, R. T. Ruck, N. Nivera, M. A. Huffmanm, M. A. Shevlin, *Org. Lett.*, 2011, **13**, 5480; (c) C. Molinaro, P. G. Bulger, E. E. Lee, B. Kosjek, S. Lau, D. Gauvreau, M. E. Howard, D. J. Wallace, P. D. O'Shea, *J. Org. Chem.*, 2012, **77**, 2299.

8 (a) J. Vaitla, A. Bayer, K. H. Hopmann, *Angew. Chem., Int. Ed.*, 2017, **56**, 4277; (b) Y. Xu, G. Zheng, X. Yang, X. Li, *Chem. Commun.*, 2018, **54**, 670; (c) X. Wu, H. Xiong, S. Sun, J. Cheng, *Org. Lett.*, 2018, **20**, 1396; (d) R. Lai, X. Wu, S. Lv, C. Zhang, M. He, Y. Chen, Q. Wang, L. Hai, Y. Wu, *Chem. Commun.*, 2019, **55**, 4039.

9 (a) H. Zhang, Z. Yang, Q. Ma, J. Liu, Y. Zheng, M. Guan, Y. Wu, *Green Chem.*, 2018, **20**, 3140; (b) S. Lv, Y. Li, T. Yao, X. Yu, C. Zhang, L. Hai, Y. Wu, *Org. Lett.*, 2018, **20**, 4994; (c) Q. Ma, X. Yu, R. Lai, S. Lv, W. Dai, C. Zhang, X. Wang, Q. Wang, Y. Wu, *ChemSusChem* 2018, **11**, 3672.

10 (a) Y. Xu, X. Zhou, G. Zheng, X. Li, *Org. Lett.*, 2017, **19**, 5256; (b) M. Barday, C. Janot, N. R. Halcovitch, J. Muir, C. Aïssa, *Angew. Chem., Int. Ed.*, 2017, **56**, 13117; (c) S. Ji, K. Yan, B. Li, B. Wang, *Org. Lett.*, 2018, **20**, 5981.

11 H. Xie, J. Lan, J. Gui, F. Chen, H. Jiang, W. Zeng, *Adv. Synth. Catal.* 2018, **360**, 3534.

12 (a) A. Tsuboyama, H. Iwawaki, M. Furugori, T. Mukaide, J. Kamatani, S. Igawa, T. Moriyama, S. Miura, T. Takiguchi, S. Okada, M. Hoshino, K. Ueno, *J. Am. Chem. Soc.*, 2003, **125**, 12971; (b) J. D. Scott and R. M. Williams, *Chem. Rev.*, 2002, **102**, 1669; (c) N. L. Subasinghe, J. Lanter, T. Markotan, E. Opas, S. McKenney, C. Crysler, C. Hou, J. O'Neill, D. Johnson, Z. A. Sui, *Bioorg. Med. Chem. Lett.*, 2013, **23**,1063.

13 (a) R. Chen, J. Qi, Z. Mao, S. Cui, *Org. Biomol. Chem.*, 2016, **14**, 6201; (b) Q. Wang and X. Li, *Org. Chem. Front.*, 2016, **3**, 1159; (c) X. Lin, R. Chauvin, Y. Yu, L. Wang, L. Xu, X. Cui, *ChemistrySelect* 2017, **2**, 2383; (d) G. Zheng, M. Tian, Y. Xu, X. Chen, X. Li, *Org. Chem. Front.*, 2018, **5**, 998; (e) R. He, Z.-T. Huang, Q.-Y. Zheng, C. Wang, *Tetrahedron Lett.* 2014, **55**, 5705; (f) R. He, Z.-T. Huang, Q.-Y. Zheng, C. Wang, *Angew. Chem., Int. Ed.* 2014, **53**, 4950.

14 (a) K. Bhadra and G. S. Kumar, *Med. Res. Rev.*, 2011, **31**, 821; (b) A. Y. Khan, G. S. Kumar, *Biophys. Rev.*, 2015, **7**, 407.

15 R. Li, J. Wu, Y. He, L. Hai, Y. Wu, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 1762.

16 Z. Yang, Y. Zhang, X. Chen, W. Li, G.-B. Li, Y. Wu, *Eur. J. Org. Chem.*, 2018, 1041.

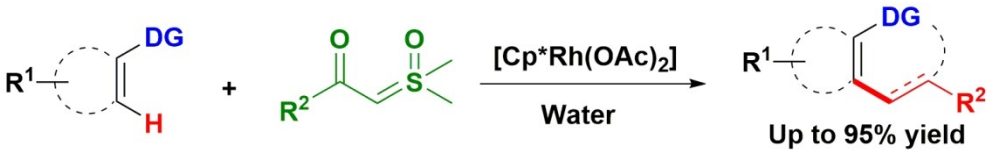
17 Y. Zhang, Z. Yang, L. Guo, W. Li, X. Cheng, X. Wang, Q. Wang, L. Hai, Y. Wu, *Org. Chem. Front.*, 2018, **5**, 1604.

18 (a) H. Lv, W. Xu, K. Lin, J. Shi, W. Yi, *Eur. J. Org. Chem.*, 2016, 5637; (b) A. L. Mclver and A. Deiters, *Org. Lett.*, 2010, **12**, 1288; (c) A. E. Gatland, B. S. Pilgrim, P. A. Procopiou, T. J. Donohoe, *Angew. Chem., Int. Ed.*, 2014, **53**, 14555.

19 (a) P. Villuendas and E. P. Urriolabeitia, *J. Org. Chem.*, 2013, **78**, 5254; (b) H. Chu, P. Xue, J.-T. Yu, J. Cheng, *J. Org. Chem.*, 2016, **81**, 8009. (c) S. Ruiz, P. Villuendas, M. A. Ortuño, A. Lledós, E. P. Urriolabeitia, *Chem. Eur. J.* 2015, **21**, 8626; (d) K. Morimoto, K. Hirano, T. Satoh, M. Miura, *Chem. Lett.* 2011, **40**, 600.

View Article Online
DOI: 10.1039/C9CC05804D

Water-mediated C-H activation



- Green and safe carbene
- Water as solent
- Broad scope
- External additive-free
- Natural products synthesis

131x41mm (300 x 300 DPI)