RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2020, **10**, 39708

Rhodium(III)-catalyzed C–H annulation of 2-acetyl-1-arylhydrazines with sulfoxonium ylides: synthesis of 2-arylindoles†

He Li,‡ Ye Lu,‡ Xinxin Jin, Shuang Sun, Limei Duan* and Jinghai Liu *

Received 8th September 2020
Accepted 23rd October 2020

DOI: 10.1039/d0ra07701a

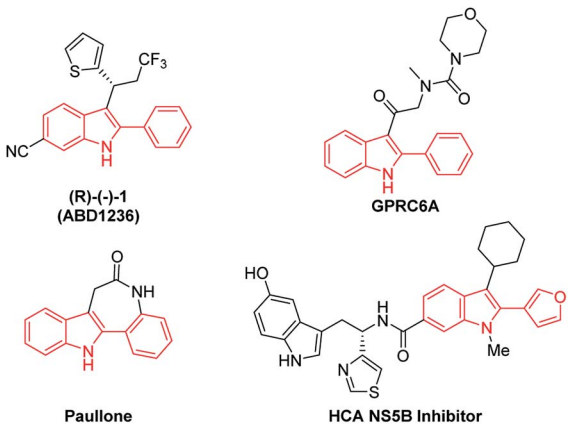
rsc.li/rsc-advances

An efficient Rh(III)-catalyzed synthesis of 2-arylindole derivatives *via* intermolecular C–H annulation of arylhydrazines with sulfoxonium ylides was accomplished. A variety of 2-acetyl-1-arylhydrazines with sulfoxonium ylides were converted into 2-arylindoles in satisfactory yields. Excellent selectivity and good functional group tolerance of this transformation were also observed.

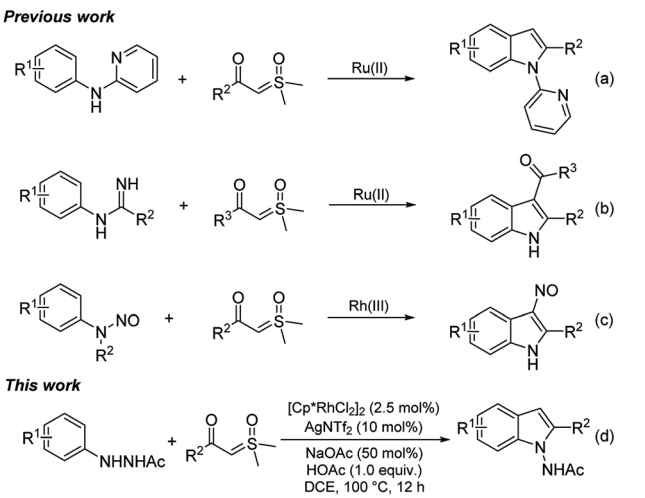
Introduction

Indoles represent one of the most abundant heterocycles in natural products, biologically active molecules, pharmacological compounds, and materials.[1] Particularly, 2-arylindole and its derivatives are core structural frameworks in numerous drug molecules (Scheme 1).[2] Traditional strategies to access 2-arylindoles include Fisher,[3] Larock,[4] Buchwald,[5] and Hegadus indole synthesis.[6] However, the above methods usually suffer from harsh reaction conditions, multistep synthesis, limited substrate scope, and undesirable toxic waste was inevitable in some transformations. Therefore, developing more convenient, efficient and sustainable methods to access 2-arylindole derivatives is highly desirable.

Over the past decades, transition-metal-catalyzed directed C–H activation has been developed as a powerful and straightforward synthetic approach to heterocycles.[7] Moreover, efficient synthesis of indole derivatives using this strategy has also been greatly employed.[8] In recent years, sulfoxonium ylides, featuring operational safety and synthetic convenience as popular carbene surrogates,[9] were used as important building blocks in transition-metal-catalyzed C–H annulation reactions with nucleophilic directing groups for synthesis of indole derivatives. In 2019, Huang and co-workers realized efficient synthesis of 2-arylindole *via* Ru(II)-catalyzed tandem annulation of *N*-aryl-2-aminopyridines and sulfoxonium ylides (Scheme 2a).[10] In the same year, Liu's group reported [Ru(*p*-cymene)Cl_2]$_2$ catalyzed imidamides C–H activation and coupling with sulfoxonium



Scheme 1 Important representative 2-arylindole derivatives.



Scheme 2 Ru/Rh-catalyzed C–H annulation of sulfur ylides to 2-arylindole.

Inner Mongolia Key Laboratory of Carbon Nanomaterials, Nano Innovation Institute (NII), College of Chemistry and Materials Science, Inner Mongolia University for Nationalities, Tongliao 028000, China. E-mail: jhliu2008@sinano.ac.cn; duanlmxie@126.com

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ra07701a

‡ These authors contributed equally to this work.

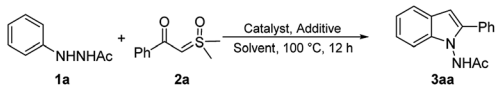
ylides to give 2-arylindole (Scheme 2b).[11] In 2020, Wu's and Cui's group developed a novel synthesis of 2-arylindole from *N*-nitrosoanilines and sulfoxonium ylides *via* Rh(III)-catalyzed acylmethylation (Scheme 2c).[12] Encouraged by these eminent studies, herein a simple Rh(III)-catalyzed synthesis of 2-arylindole was disclosed by easily available arylhydrazines with sulfoxonium ylides as substrates (Scheme 2d).

Results and discussion

The C–H annulation reaction of 2-acetyl-1-phenylhydrazine (**1a**) with α-benzoyl sulfoxonium ylide (**2a**) was used as a model to optimize the reaction conditions (Table 1). Catalyst systems were first screened in the presence of NaOAc, which was used as the additive, in 1,2-dichloroethane (DCE) at 100 °C under a nitrogen atmosphere. The desired product **3aa** was obtained with 35% yield by using $[Cp^*RhCl_2]_2/AgSbF_6$ as the catalyst system (entry 1). The transformation does not occur in the presence of other catalysts such as $[Cp^*Co(CO)I_2]_2$ and $[RuCl_2(p\text{-cymene})]_2$ (entry 2 and 3). The effect of silver salts was investigated (entry 1 *vs.* entry 4). $AgNTf_2$ gave the desired product **3aa** in 62% yield. The solvents were subsequently screened using $[Cp^*RhCl_2]_2/AgNTf_2$ as the catalyst system. Among the solvents examined [1,2-dichloroethane (DCE), 1,4-dioxane (dioxane), toluene, and methanol (MeOH)], DCE was the best solvent (entry 4 *vs.* entries 5–7). Among the various additives tested, NaOAc/HOAc showed the highest efficiency for the reaction (entries 8–11). Further enhancement of the yield (93%) of **3aa** was achieved by increasing the loading of HOAc (entry 12). No reaction was observed when the model reaction was conducted in the absence of $AgNTf_2$ (entry 13). Therefore, the optimal reaction conditions were identified as follows: 2.5 mol% of $[Cp^*RhCl_2]_2$ with $AgNTf_2$ (10 mol%) as the catalyst system, NaOAc (50 mol%) with HOAc (1.0 equiv.) as the additives in DCE at 100 °C under a nitrogen atmosphere for 12 h.

With the optimized reaction conditions in hand, the scope and limitation of various 2-acetyl-1-arylhydrazines **1a–1q** with α-benzoyl sulfoxonium ylide (**2a**) were further investigated, as

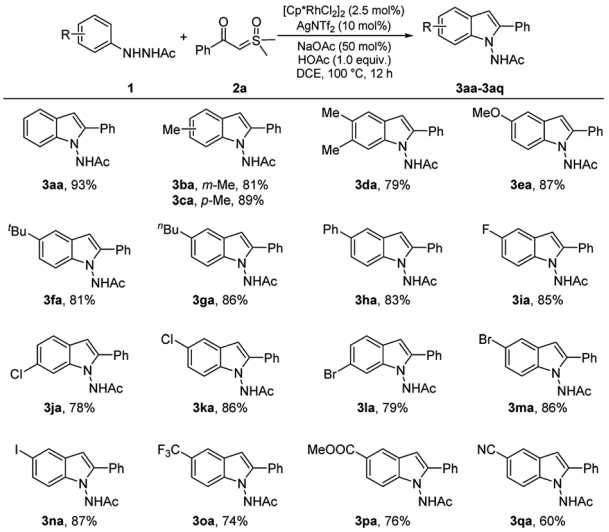
Table 1 Screening of the reaction conditions[a]



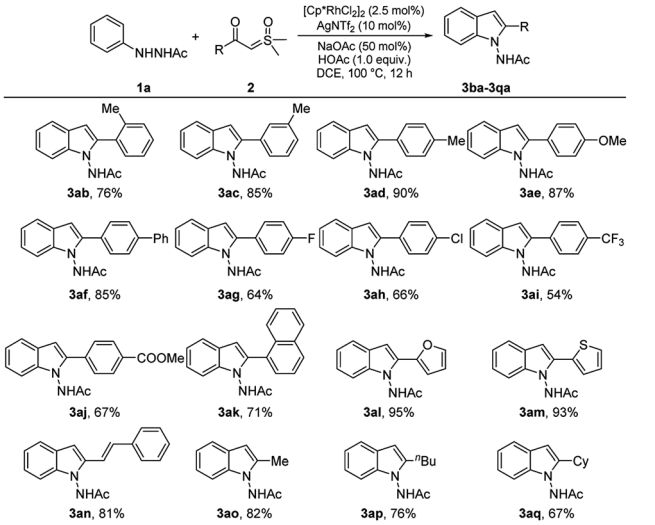
1a 2a 3aa

Entry	Catalyst system	Additive	Solvent	Yield[b] (%)
1	$[Cp^*RhCl_2]_2/AgSbF_6$	NaOAc	DCE	35
2	$[Cp^*Co(CO)I_2]_2/AgSbF_6$	NaOAc	DCE	0
3	$[RuCl_2(p\text{-cymene})]_2/AgSbF_6$	NaOAc	DCE	0
4	$[Cp^*RhCl_2]_2/AgNTf_2$	NaOAc	DCE	62
5	$[Cp^*RhCl_2]_2/AgNTf_2$	NaOAc	Dioxane	0
6	$[Cp^*RhCl_2]_2/AgNTf_2$	NaOAc	Toluene	0
7	$[Cp^*RhCl_2]_2/AgNTf_2$	NaOAc	MeOH	0
8	$[Cp^*RhCl_2]_2/AgNTf_2$	NaOAc	DCE	43
9	$[Cp^*RhCl_2]_2/AgNTf_2$	KOAc	DCE	35
10	$[Cp^*RhCl_2]_2/AgNTf_2$	CsOAc	DCE	0
11[c]	$[Cp^*RhCl_2]_2/AgNTf_2$	NaOAc	DCE	79
12[d]	$[Cp^*RhCl_2]_2/AgNTf_2$	NaOAc	DCE	93
13[d]	$[Cp^*RhCl_2]_2$	NaOAc	DCE	0

[a] Reaction conditions: 2-acetyl-1-phenylhydrazine (**1a**, 0.2 mmol, 30.0 mg), α-benzoyl sulfoxonium ylide (**2a**, 0.24 mmol, 47.1 mg), catalyst (2.5 mol%), $AgSbF_6$ or $AgNTf_2$ (10 mol%), and additive (50 mol%) in solvent (1.0 mL) at 100 °C under a nitrogen atmosphere for 12 h. [b] Isolated yield. [c] 1.0 equiv. of PivOH was used. [d] 1.0 equiv. of HOAc was used.



Scheme 3 Substrate scope of 2-acetyl-1-arylhydrazines. Reaction conditions: arylhydrazines (**1a–1q**, 0.2 mmol), α-benzoyl sulfoxonium ylide (**2a**, 0.24 mmol, 47.1 mg), $[Cp^*RhCl_2]_2$ (2.5 mol%, 3.1 mg), $AgNTf_2$ (10 mol%, 7.8 mg), NaOAc (50 mol%, 8.2 mg) and HOAc (1.0 equiv., 12.0 mg) in DCE (1.0 mL) at 100 °C under a nitrogen atmosphere for 12 h. Isolated yield.

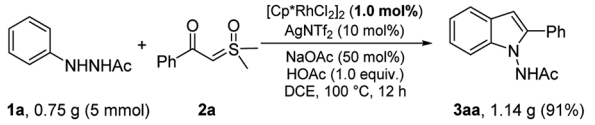


Scheme 4 Substrate scope of (hetero)aroyl sulfoxonium ylides. Reaction conditions: 2-acetyl-1-phenylhydrazine (**1a**, 0.2 mmol, 30.0 mg), (hetero)aroyl sulfoxonium ylides (**2a–2p**, 0.24 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%, 3.1 mg), $AgNTf_2$ (10 mol%, 7.8 mg), NaOAc (50 mol%, 8.2 mg) and HOAc (1.0 equiv., 12.0 mg) in DCE (1.0 mL) at 100 °C under a nitrogen atmosphere for 12 h. Isolated yield.

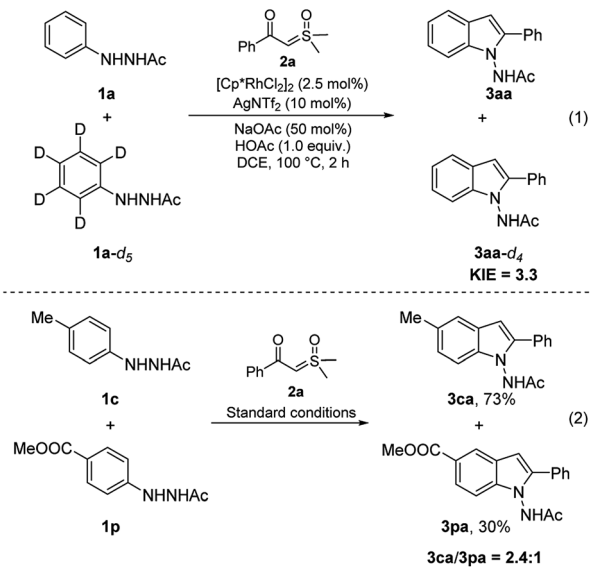
shown in Scheme 3. As expected, some functional groups, such as methyl (**3ba–3da**, 79–89%), methoxy (**3ea** 87%), butyl (**3fa**, 81%; **3ga**, 86%), and phenyl (**3ha**, 83%), were well compatible under the reaction conditions with good yields. Remarkably, halogen atoms (F, Cl, Br, and I) linked to the benzene rings of substrates **1i–1n** were maintained in the structures of products **3ia–3na** (78–87%), suggesting that further manipulation may produce additional useful compounds. Relatively low yields were observed in the reactions of substrates **1o**, **1p**, and **1q** bearing the strong electron-withdrawing groups CF_3, COOMe, and CN on their benzene rings (**3oa–3qa**, 60–76%).

Then, the scope of (hetero)aroyl sulfoxonium ylides were also examined (Scheme 4). Benzoyl-substituted sulfoxonium ylides bearing a variety of important functional groups, such as electron-donating groups (Me, OMe, phenyl), the halogens (F, Cl), and electron-withdrawing groups (CF_3, COOMe) at the *ortho*, *meta*, and *para* positions of the phenyl ring reacted smoothly with **1a** to afford the corresponding products (**3ab–3aj**) in moderate to high yields (54%–90%). The reactants could contain a naphthalene or furan/thiophene ring and the corresponding products (**3ak–3am**) were obtained in 71%, 95%, and 93% yields, respectively. Moreover, the sulfoxonium ylides were not limited to (hetero)aryl-substituted substrates, an alkenyl (**3an**, 81%) and several alkyl substrates (**3ao–3aq**, 67–82%) were also compatible.

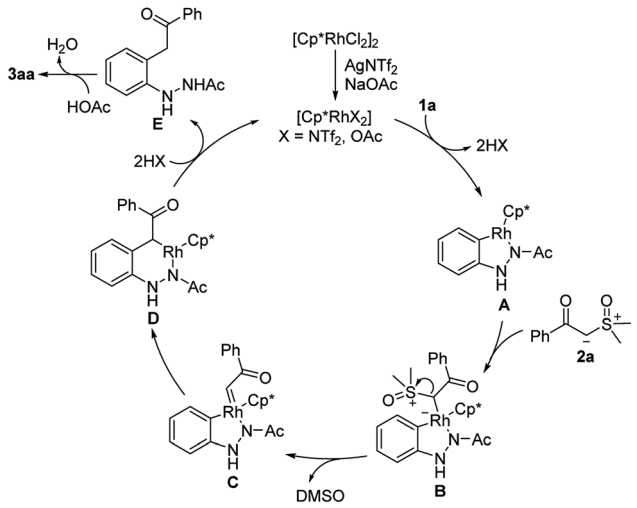
To further explore the practicability of our methodology, the Rh(III)-catalyzed annulation was scaled up to the gram scale



Scheme 5 Gram-scale synthesis.



Scheme 6 Mechanistic studies.



Scheme 7 Proposed mechanism.

(Scheme 5). The product **3aa** was also isolated in excellent yield (91%) even with a reduced catalyst loading.

For insight into the mechanism of this reaction, control experiments were performed (Scheme 6). The deuterium kinetic isotope effect was investigated by conducting an intermolecular competition reaction between **1a** and **1a**-d_5. The 3.3 : 1 ratio of **3aa** to **3aa**-d_4 demonstrated that the cleavage of the aromatic C–H bond is probably involved in the turnover-limiting step (eqn (1)). A 2.4 : 1 ratio of **3ca** to **3pa** was observed in the intermolecular competition reaction between **1c** and **1p** (eqn (2)), indicating that C–H activation probably occurs through an electrophilic aromatic substitution (S_EAr) process.

Based on previous reports[11–13] and our experimental outcomes, a plausible mechanism is shown in Scheme 7. First, the active cationic rhodium catalyst species [Cp*RhX_2] is formed through the reaction of the precatalyst [Cp*$RhCl_2$]$_2$ with $AgNTf_2$ or NaOAc. The coordination of **1a** to rhodium catalyst species and subsequent *ortho* C–H bond activation generates cationic five-membered rhodacyclic intermediate **A** with the release of HX (X = NTf_2 or OAc). Next, sulfoxonium ylide **2a** reacts with intermediate **A** to form Rh(III) intermediate **B**, which in turn gives the reactive carbene species **C** by α-elimination of DMSO. Subsequently, a migratory insertion of carbene group into the Rh–C bond to afford a six-membered rhodacycle intermediate **D**. Then, protonolysis of the intermediate **D** releases acylmethylated intermediate **E** with regenerating active [Cp*RhX_2]. Finally, the ketone carbonyl **E** could undergo keto–enol tautomerism and cyclization in the presence of HOAc to give the desired product **3aa**.

Conclusions

In summary, we have developed a Rh(III)-catalyzed synthesis of 2-arylindoles from easily available arylhydrazines and sulfoxonium ylides under mild conditions. The protocol is useful to prepare various 2-arylindoles because of its high atom economy, broad substrate scope, and simple procedure. The synthesis

could be easily scaled up to gram scale even with a reduced catalyst loading.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (21961024 and 21961025), Inner Mongolia Natural Science Foundation (2018JQ05, 2020BS02009, and 2020BS02014), Inner Mongolia Autonomous Region Science & Technology Planning Project for Applied Technology Research and Development (2019GG261), Inner Mongolia Autonomous Region Funding Project for Science & Technology Achievement Transformation (CGZH2018156) and IMUN Doctoral Research Startup Fund Project (BS481 and BS560).

Notes and references

1 (*a*) D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893–930; (*b*) M. Somei and F. Yamada, *Nat. Prod. Rep.*, 2005, **22**, 73–103; (*c*) T. Kawasaki and K. Higuchi, *Nat. Prod. Rep.*, 2005, **22**, 761–793; (*d*) A. J. Kochanowska-Karamyan and M. T. Hamann, *Chem. Rev.*, 2010, **110**, 4489–4497; (*e*) S. A. Patil, R. Patil and D. D. Miller, *Future Med. Chem.*, 2012, **4**, 2085–2115.

2 (*a*) D. R. Stuart, P. Alsabeh, M. Kuhn and K. Fagnou, *J. Am. Chem. Soc.*, 2010, **132**, 18326–18339; (*b*) H. Johansson, M. W. Boesgaard, L. Nørskov-Lauritsen, I. Larsen, S. Kuhne, D. E. Gloriam, H. Brauner-Osborne and D. S. Pedersen, *J. Med. Chem.*, 2015, **58**, 8938–8951; (*c*) P. Prasad, P. G. Shobhashana and M. P. Patel, *R. Soc. Open Sci.*, 2017, **4**, 170764; (*d*) C.-C. Tseng, G. Baillie, G. Donvito, M. A. Mustafa, S. E. Juola, C. Zanato, C. Massarenti, S. D. Angelo, W. T. A. Harrison, A. H. Lichtman, R. A. Ross, M. Zanda and I. R. Greig, *J. Med. Chem.*, 2019, **62**, 5049–5062.

3 (*a*) R. B. V. Order and H. G. Lindwall, *Chem. Rev.*, 1942, **30**, 69–96; (*b*) B. Robinson, *Chem. Rev.*, 1963, **63**, 373–401.

4 (*a*) R. C. Larock and E. K. Yum, *J. Am. Chem. Soc.*, 1991, **113**, 6689–6690; (*b*) R. C. Larock, E. K. Yum and M. D. Refvik, *J. Org. Chem.*, 1998, **63**, 7652–7662.

5 (*a*) S. Wagaw, B. H. Yang and S. L. Buchwald, *J. Am. Chem. Soc.*, 1998, **120**, 6621–6622; (*b*) J. L. Rutherford, M. P. Rainka and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 15168–15169.

6 L. S. Hegedus, *Angew. Chem., Int. Ed.*, 1988, **27**, 1113–1126.

7 (*a*) T. Satoh and M. Miura, *Chem. – Eur. J.*, 2010, **16**, 11212–11222; (*b*) D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2012, **45**, 814–825; (*c*) G. Song and X. Li, *Acc. Chem. Res.*, 2015, **48**, 1007–1020; (*d*) Y. Minami and T. Hiyama, *Acc. Chem. Res.*, 2016, **49**, 67–77; (*e*) T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, *Chem. Soc. Rev.*, 2016, **45**, 2900–2936; (*f*) J. R. Hummel, J. A. Boerth and J. A. Ellman, *Chem. Rev.*, 2017, **117**, 9163–9227; (*g*) Z. Nairoukh, M. Cormier and I. Marek, *Nat. Rev. Chem.*, 2017, **1**, 0035; (*h*) J. Chen, S. Lv and S. Tian, *ChemSusChem*, 2019, **12**, 115–132; (*i*) Z. Shen, C. Pi, X. Cui and Y. Wu, *Chin. Chem. Lett.*, 2019, **30**, 1374–1378; (*j*) L.-Y. Xie, T.-G. Fang, J.-X. Tan, B. Zhang, Z. Cao, L.-H. Yang and W.-M. He, *Green Chem.*, 2019, **21**, 3858–3863; (*k*) Q.-W. Gui, X. He, W. Wang, H. Zhou, Y. Dong, N. Wang, J.-X. Tang, Z. Cao and W.-M. He, *Green Chem.*, 2020, **22**, 118–122; (*l*) W.-B. He, L.-Q. Gao, X.-J. Chen, Z.-L. Wu, Y. Huang, Z. Cao, X.-H. Xu and W.-M. He, *Chin. Chem. Lett.*, 2020, **31**, 1895–1898.

8 (*a*) N. Yoshikai and Y. Wei, *Asian J. Org. Chem.*, 2013, **2**, 466–478; (*b*) L. Ackermann, *Acc. Chem. Res.*, 2014, **47**, 281–295; (*c*) S. Wang, S.-Y. Chen and X.-Q. Yu, *Chem. Commun.*, 2017, **53**, 3165–3180; (*d*) G. Duarah, P. P. Kaishap, T. Begum and S. Gogoi, *Adv. Synth. Catal.*, 2019, **361**, 654–672; (*e*) Y. Xiang, C. Wang, Q. Ding and Y. Peng, *Adv. Synth. Catal.*, 2019, **361**, 919–944.

9 (*a*) M. Gandelman, B. Rybtchinski, N. Ashkenazi, R. M. Gauvin and D. Milstein, *J. Am. Chem. Soc.*, 2001, **123**, 5372–5373; (*b*) I. K. Mangion, I. K. Nwamba, M. Shevlin and M. A. Huffman, *Org. Lett.*, 2009, **11**, 3566–3569; (*c*) R. M. P. Dias and A. C. B. Burtoloso, *Org. Lett.*, 2016, **18**, 3034–3037; (*d*) R. Oost, J. D. Neuhaus, J. Merad and N. Maulide, *Sulfur Ylides in Organic Synthesis and Transition Metal Catalysis*, ed. V. H. Gessner and R.-U. Bochum, Springer, Berlin, 2017; (*e*) J. Vaitla, A. Bayer and K. H. Hopmann, *Angew. Chem., Int. Ed.*, 2017, **56**, 4277–4281; (*f*) M. Barday, C. Janot, N. R. Halcovitch, J. Muir and C. Aïssa, *Angew. Chem., Int. Ed.*, 2017, **56**, 13117–13221; (*g*) X. Wu, S. Sun, J.-T. Yu and J. Cheng, *Synlett*, 2019, **30**, 21–29.

10 X.-F. Cui, Z.-H. Ban, W.-F. Tian, F.-P. Hu, X.-Q. Zhou, H.-J. Ma, Z.-Z. Zhan and G.-S. Huang, *Org. Biomol. Chem.*, 2019, **17**, 240–243.

11 C. Wu, J. Zhou, G. He, H. Li, Q. Yang, R. Wang, Y. Zhou and H. Liu, *Org. Chem. Front.*, 2019, **6**, 1183–1188.

12 Y. Wu, C. Pi, X. Cui and Y. Wu, *Org. Lett.*, 2020, **22**, 361–364.

13 (*a*) W. Xie, X. Chen, J. Shi, J. Li and R. Liu, *Org. Chem. Front.*, 2019, **6**, 2662–2666; (*b*) N. Lv, Z. Chen, Z. Liu and Y. Zhang, *J. Org. Chem.*, 2019, **84**, 13013–13021.