ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: R. Lai, X. wu, S. Lv, C. Zhang, M. He, Y. Chen, Q. Wang, L. Hai and Y. Wu, *Chem. Commun.*, 2019, DOI: 10.1039/C9CC01146C.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/C9CC01146C

COMMUNICATION

Synthesis of Indoles and Quinazolines via additive-controlled selective C-H activation/annulation of *N*-arylamidines and sulfoxonium ylides

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

DOI: 10.1039/x0xx00000x

Ruizhi Lai, Xiaohua Wu, Songyang Lv, Chen Zhang, Maoyao He, Yuncan Chen, Qiantao Wang, Li Hai* and Yong Wu*

Selective synthesis of indole and quinazoline products was achieved through a precise control of the C-H activation/annulation by changing the additives from NaOAc to CuF_2/CsOAc. This strategy constructs indole and quinazoline scaffolds efficiently, hence are of great interests in pharmaceutical, agricultural and chemical industries.

Transition-metal-catalyzed C–H activation has been extensively explored as it usually avoids the multistep preactivation of the starting materials providing an atom- and step-economical strategy for organic synthesis.[1] For instance, C–H activation/annulation, which represents one of the hottest topics in recent years,[2] does not only specifically functionalize the inert C–H bonds, but also forms a variety of cyclic compounds by coupling and cyclization with the introduced functional groups.

Indoles and quinazolines are two well-known classes of nitrogen-containing heterocyclic compounds that pose a broad-spectrum of biological activities and have been widely used in pharmaceutical, agricultural and chemical industries (Figure 1).[3] Therefore, a more economical and environment-friendly synthetic strategy would be of great interest to the field. Among the published works, the formation of indoles was achieved mainly through the C–H activation of aniline derivatives with coupling reagents, such as alkene, alkyne and diazo (Scheme 1a).[4] On the other hand, quinazolines were mainly afforded via the C–H activation of benzimidates with amino reagents (dioxazolones and alkyl azides) or by the reactions of *N*-arylamidines with the "one-carbon coupling reagents" (C1 unit) like isonitrile and alkyne derivatives (Scheme 1b).[5]

Although the synthesis of indoles and quinazolines has been widely studied, most of the methods still have some drawbacks, such as the use of toxic and dangerous reagents (isonitrile, diazo, azide and etc) and the unsatisfactory yields. Recently, sulfoxonium ylides have been widely used as a convenient and safe carbene precursor reagent in transition-metal-catalyzed C–H activation/annulation.[6] Many groups independently reported C–H activation/annulation cascade reactions of different directing groups (DGs) with sulfoxonium ylides as the C2 unit to obtain lactones, lactams, isoquinolines,

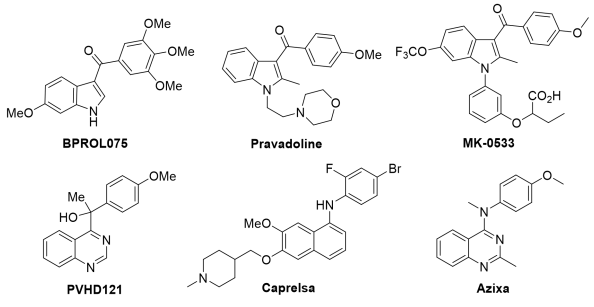
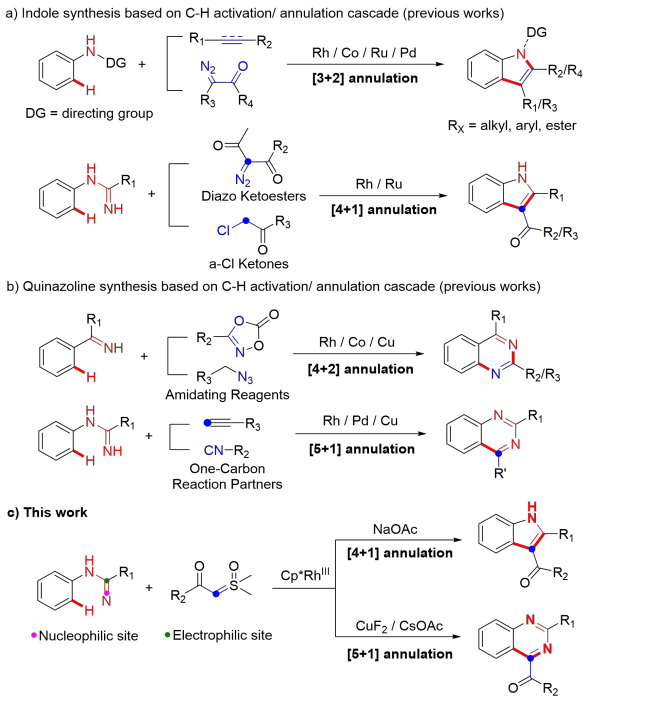


Figure 1. Selected examples of bioactive indoles and quinazolines.



Scheme 1. C-H activation/annulation for the synthesis of indoles and quinazolines.

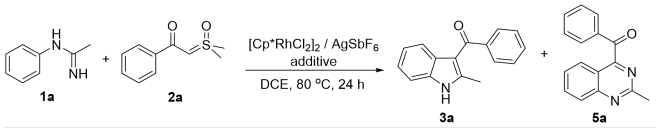
Key Laboratory of Drug-Targeting of Education Ministry and Department of Medicinal Chemistry, West China School of Pharmacy, Sichuan University, Chengdu 610041 (China).
Email: wyong@scu.edu.cn (Yong Wu); smile@scu.edu.cn (Li Hai).
Electronic Supplementary Information (ESI) available. See DOI: 10.1039/x0xx00000x

azolopyrimidines, naphthols and etc.[6a-i] In addition, Kim's group recently used azobenzene with sulfoxonium ylide as the C1 unit to synthesize indazoles.[6j] Collectively, these results revealed that sulfoxonium ylide had an important role in C–H activation/annulation. As our group has been interested in C–H activation in recent years,[7] we were wondering whether it is possible to use *N*-arylamidines and sulfoxonium ylides to synthesize *N*-heterocycles through C-H activation/annulation. Herein, to answer this question, we report our most recent work in additive-controlled selective synthesis of indoles and quinazolines by using *N*-arylamidines and sulfoxonium ylides as the starting material (Scheme 1c).

Initially, we selected *N*-phenylacetimidamide **1a** as a substrate to react with dimethyloxosulfonium benzoylmethylide **2a** using $[Cp^*RhCl_2]_2$ (5 mol%)/ $AgSbF_6$ (20 mol%) as the catalyst. To our delight, (2-methyl-*1*H-indol-3-yl)(phenyl)methanone **3a** and 2-methyl-4-benzoylquinazoline **5a** were obtained in 1:1 with a 62% total yield (Table 1, entry 1). Then, the relationship between additive and reaction results were explored (entries 2-11). It showed that NaOAc as a base was obviously favored to generate the indole product **3a** (entry 3), while Cu salt, expetially CuF_2, afforded quinazoline product **5a** mostly (entry 11). Effect of the solvent was also examined, and it turned out DCE was the best (see in ESI). Increasing the reaction temperature would cause serious side-reactions of ylide hence lowering the yield (see in ESI). Increasing the amount of **2a** only improved the yield of **3a** (entries 12 and 13), and the formation of **5a** was favored by the oxygen environment (entry 14). In addition, as we found CsOAc had a mild preference on **5a** (entry 5), we combined it with CuF_2 to see if it can further boost the yield. Fortunately, the 74% yield of **5a** was obtained (entry 15).

With the optimized reaction conditions in hand, the C-H activation of imidamides was examined. Firstly, the substrate generality of indole products was explored, and the results were showed in Table 2. Unsubstituted *N*-phenylacetimidamide afforded **3a** with a 78% isolated yield. The introduction of electron-donating, electron-withdrawing and halogen groups to different positions of the benzene ring were fully tolerated (**3b**-**3q**), giving good to excellent yields (60-85%) of the indole products. Notably, when isopropyl, isobutyl, methoxyethyl and benzyl groups were introduced to C-alkyl imidamides, the reaction also successfully afforded desired products (**3r-3u**). Given the above results, it was found that the electron-donating groups, such as Me and OMe, and halogens on the phenyl were more favorable for this transformation than the electron-withdrawing groups including CF_3, nitro, acetyl and ester (**3g**-**3j**). In addition, the different substituting positions of the benzene ring affected the yields as well. The para-substitution was slightly better than the meta-, and the meta- was better than the ortho-. It was also found that when the imidamide was meta-monosubstituted by Me, both **3k** and **3'k** were produced with a ratio of 5:1. However, when Me was changed to F or Cl, only one regioisomer could be obtained (**3l** and **3m**). The difference in regioisomers formation may be the result of a combination of the steric effects and the electrical effects. Then, the change of sulfoxonium ylides were also investigated. When Me, MeO and halogen groups were attached to the different positions on the benzene ring of sulfoxonium ylides, the reactions were

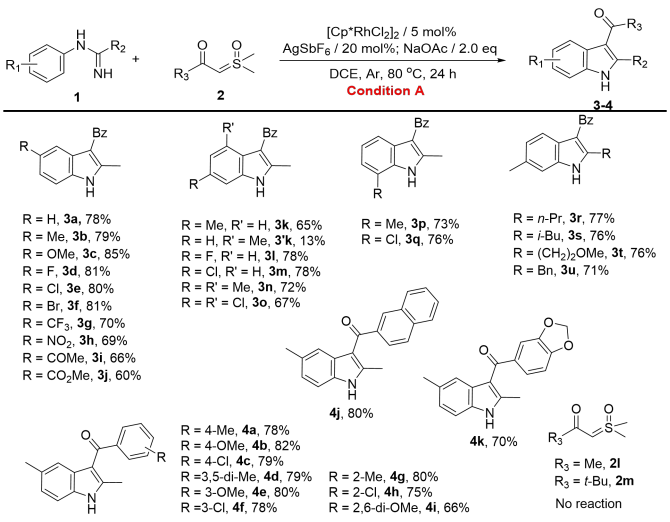
Table 1. Optimization of the reaction conditions[a]



Entry	Additive	Yield (%)[b] 3a	5a
1	/	33	29
2	HOAc	28	31
3	NaOAc	62	10
4	AgOAc	58	10
5	CsOAc	21	43
6	$CsCO_3$	27	35
7	$Cu(OAc)_2$	<5	51
8	$Cu(TFA)_2$	<5	42
9	$Cu(OTf)_2$	<5	45
10	$CuCl_2$	<5	31
11	CuF_2	<5	54
12[c]	**NaOAc**	**78**	**<5**
13[c]	CuF_2	<5	52
14[d]	CuF_2	<5	68
15[d,e]	**CuF_2/CsOAc**	**<5**	**74**

[a] Unless otherwise noted, all the reactions were carried out using *N*-phenylacetimidamide **1a** (0.20 mmol) and dimethyloxosulfonium benzoylmethylide **2a** (0.40 mmol) in the presence of $[Cp^*RhCl_2]_2$ (0.01 mmol) $AgSbF_6$ (0.04 mmol), additive (0.40 mmol) and DCE (1.0 mL) in a Schlenk tube, and stirred at 80 °C for 24 h under Ar. [b] Isolated yield by chromatography on silica gel. [c] Dimethyloxosulfonium benzoylmethylide **2a** = 0.60 mmol. [d] O_2 atmosphere. [e] CsOAc = 0.20 mmol.

Table 2. Synthesis of indoles[a]



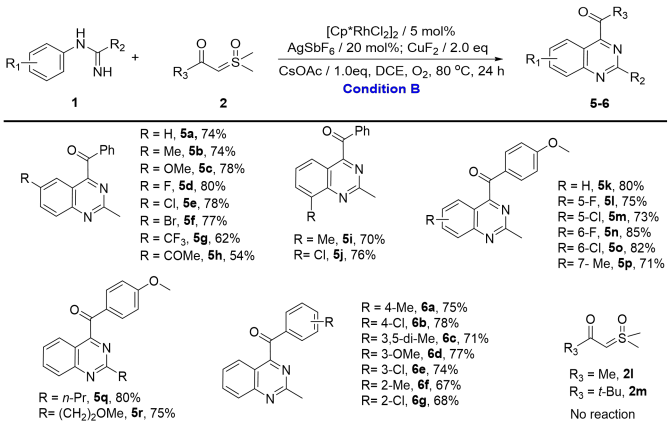
[a] Reaction conditions: *N*-arylethanimidamides **1** (0.20 mmol), dimethyloxosulfonium benzoylmethylide **2a** (0.60 mmol), $[Cp^*RhCl_2]_2$ (0.01 mmol), $AgSbF_6$ (0.04 mmol), NaOAc (0.40 mmol) and DCE (1.0 ml) to a Schlenk tube. The mixture was stirred at 80 °C for 24h under Ar. Then, without any post processing, the reaction mixture was purified by column chromatography on silica gel (eluent: PE/DCM = 1/1) to afford desired product.

fully tolerated (**4a**-**4i**), furnishing the desired products in good to excellent yields (66-82%). Notably, sulfoxonium ylides with MeO ortho-bisubstitution on the benzene ring had a yield of 66% only (**4i**). This may be due to the greatly increasing steric hindrance. When the benzene ring of ylide was changed to a naphthalene ring or a 1,3-benzodioxole ring, the reaction still proceeded smoothly and gave good yields (**4j** and **4k**). Once the benzene ring of the ylide was changed to Me (**2l**) or *t*-Bu (**2m**), no product was formed. It seemed that the aromaticity of the sulfoxonium ylide could be necessary in this reaction .

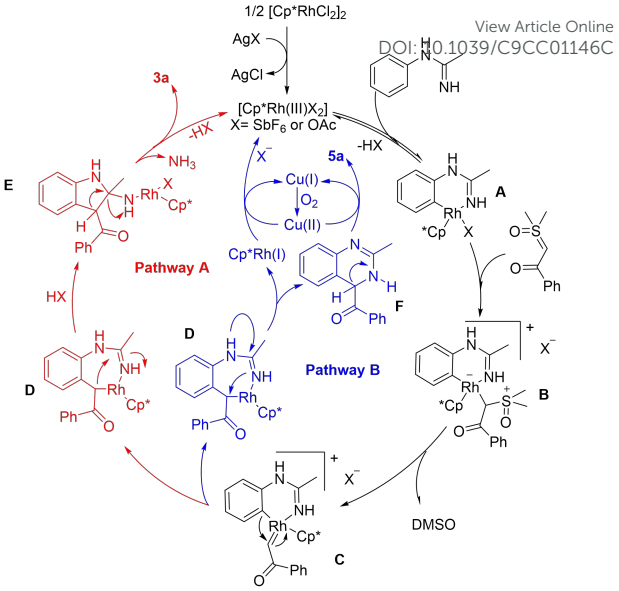
Then, we turned our attention to the synthesis of quinazolines (Table 3). Unsubstituted *N*-phenylacetimidamide gaved a 74% isolated yield of **5a**. The introduction of electron-donating, electron-withdrawing and halogen groups to different positions of the benzene ring were fully tolerated (**5a-5p**), and the extension of the terminal carbon chain seemed to have no effect on the reaction (**5q** and **5r**), giving moderate to excellent yields (54-85%). Notably, when the benzene ring was meta-monosubstituted with Me, C-H activation took place in C(6) site producing **5p**. However, when Me was changed to F or Cl, C-H activation took place in C(2) site producing **5l** or **5m**. The results above may be the interaction of the steric effects and the electrical effects. Then, sulfoxonium ylides were investigated to further explore the substrate generality of quinazoline products. When Me, MeO and halogen groups were attached to the different positions on the benzene ring of sulfoxonium ylides, the reactions were fully tolerated (**6a**-**6g**), furnishing the desired products in good yields (67-78%). Similarly, once the benzene ring of the ylide was changed to Me (**2l**) or *t*-Bu (**2m**), no product was found.

To gain mechanistic insight of the reaction, a series of experiments have been conducted (see in ESI).[8] Based on the above results and previous related studies,[6g,9] a possible mechanism for this protocol was showed in Scheme 2. Cyclometalation of *N*-phenylacetimidamide **1a** and the active

Table 3. Synthesis of quinazolines[a]



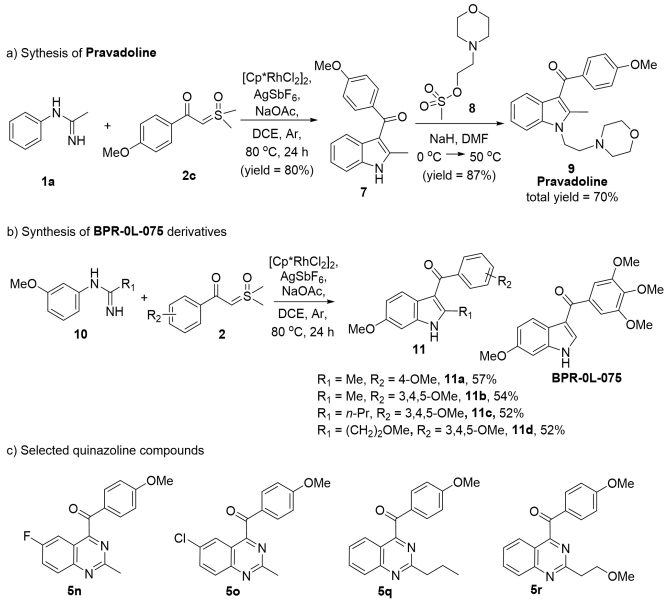
[a]Reaction conditions: *N*-arylethanimidamides **1** (0.20 mmol), dimethyloxosulfonium benzoylmethylide **2a** or **2c** (0.40 mmol), $[Cp^*RhCl_2]_2$ (0.01 mmol), $AgSbF_6$ (0.04 mmol), CuF_2 (0.40 mmol), CsOAc (0.20 mmol) and DCE (1.0 ml) to a Schlenk tube. The mixture was stirred at 80 °C for 24h under O_2. Then, without any post processing, the reaction mixture was purified by column chromatography on silica gel (eluent: PE/ acetone = 50/ 1) to afford desired product.



Scheme 2. Possible pathways of the C–H activation/cyclization.

Rh(III) catalyst gives a rhodacyclic intermediate **A**. Coordination of dimethyloxosulfonium benzoylmethylide **2a** generates a Rh(III) alkyl species **B**, and the subsequent α-elimination of DMSO from **B** affords a reactive rhodium α-oxo carbene species **C**. Following the formation of **C**, two pathways may be possible. In pathway A, **C** is proposed to undergo migratory insertion of the Rh-C bond to generate a seven-membered rhodacyclic intermediate **D**. Intermediate **E** is then formed from unstable intermediate **D** by Rh-C(alkyl) migratory insertion into the C-N bond. Eventually, the final product **3a** is released from **E** by elimination of the active Rh(III) catalyst and one molecule of ammonia from **E** upon protonolysis and intramolecular protonolysis. In pathway B, the seven-membered rhodacyclic intermediate **D** is still generated. Then, the reductive elimination from the intermediate **D** forms partially reduced quinazoline **F**. Subsequently, the oxidation of **F** affords the quinazoline product **5a**. On the other hand, the resulting Cp*Rh(I) can be reoxidized into the starting Rh(III) species by the action of Cu(II) and/or O_2 to complete the catalytic cycle.

It is noteworthy that this protocol really has many practical applications. For example, Pravadoline, a phase II drug, was recognized as a cannabinoid CB1 receptor agonist and has a strong analgesic effect (IC_{50} = 4.9 μM).[10] *N*-methylacetimidamide **1a** and dimethyloxosulfonium 4-methoxybenzoylmethylide **2c** was used to synthesize Pravadoline **9** in a shorter route yet a higher yield, i.e. a total yield of 70% in two steps (Scheme 3a). On the other hand, indole and quinazoline scaffolds have a broad-spectrum of biological activities. Based on the previous work,[11] we synthesized several indole compounds using our protocol (Scheme 3b), and we also choosed several quinazoline compounds we synthesized (Scheme 3c). The anti-tumor activity of these indole and quinazoline compounds were evaluated. 3-aroylindoles (**11a-11d**) all had excellent anti-tumor activity, while quinazolines products (**5n,5o,5q,5r**) put up a poor show. In comparison with **BPR-0L-075**, compounds **11b, 11c** and **11d** displayed similar or greater growth inhibitory



Scheme 3. The practical applications of this protocol.

activities (see in ESI). It is worthy to pinpoint that our highly efficient and scalable methodology for the synthesis of 3-aroylindoles and 4-aroylquinazolines will be extremely useful in discovering the novel anti-tumor compounds, and it may provide new ideas for drug design and synthesis.

In summary, we report the first example, to our best knowledge, of additive-controlled selective C-H activation/annulation reaction of *N*-arylamidines and sulfoxonium ylides to selectively synthesize indoles and quinazolines. In this process, the additives were shown to play a key role in selectively controlling the [4+1] and [5+1] annulation. With the additive of NaOAc, the reaction predominantly gave the indoles because of the [4+1] annulation. Changing the additives to CuF_2/CsOAc, the preference of the annulation was switched to [5+1], hence selectively afforded the quinazolines products. Furthermore, this simple, rapid and efficient strategy may provide a new toolbox for the synthesis of *N*-heterocycles, hence facilitating the chemical synthesis and the drug design.

Financial support from the National Natural Science Foundation of China (NSFC; grant number 81573286, 81773577 and 81602954) and the Fundamental Research Funds for the Central Universities (YJ201561) are gratefully acknowledged.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 Selected reviews for C-H activation: (a) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.,* 2010, **110,** 624; (b) N. Kuhl, N. Schröder, F. Glorius, *Adv. Synth. Catal.,* 2014, **356,** 1443; (c) X.-S. Zhang, K. Chen, Z.-J. Shi, *Chem. Sci.,* 2014, **5,** 2146; (d) P. L. Arnold, M. W. McMullon, J. Rieb, F. E. Kühn, *Angew. Chem., Int. Ed.,* 2015, **54,** 82; (e) F. Wang, S. Yu, X. Li, *Chem. Soc. Rev.,* 2016, **45,** 6462.

2 Selected reviews for C-H activation/annulation: (a) T. Satoh and M. Miura, *Chem. - Eur. J.,* 2010**, 16,** 11212; (b) G. Song, F. Wang and X. Li, *Chem. Soc. Rev.,* 2012, **41,** 3651.

3 (a) M. Somei, F. Yamada, *Nat. Prod. Rep.,* 2004, **21,** 278; (b) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.,* 2010, **110,** 4489; (c) G. Marzaro, A. Guiotto, A. Chilin, *Expert Opin. Ther. Pat.,* 2012, **22,** 223.

4 Selected examples: (a) J. Chen, G. Song, C. Pan, X. Li, *Org. Lett.,* 2010, **12,** 5426; (b) M. P. Huestis, L. R. Chan, D. R. Stuart, K. Fagnou, *Angew. Chem., Int. Ed.,* 2011, **50,** 1338; (c) C. Wang, H. Sun, Y. Fang, Y. Huang, *Angew. Chem., Int. Ed.,* 2013, **52,** 5795; (d) Y. Liang, K. Yu, B. Li, S. Xu, H. Song, B. Wang, *Chem. Commun.,* 2014, **50,** 6130; (e) D. Zhao, S. Vasquez-Cespedes, F. Glorius, *Angew. Chem., Int. Ed.,* 2015, **54,** 1657; (f) Z. Qi, S. Yu, X. Li, *Org. Lett.,* 2016, **18,** 700; (g) K. S. Halskov, H. S. Roth, J. A. Ellman, *Angew. Chem., Int. Ed.,* 2017, **56,** 9183; (h) F. Xu, W.-F. Kang, Y. Wang, C.-S. Liu, J.-Y. Tian, R.-R. Zhao, M. Du, *Org. Lett.,* 2018, **20,** 3245; (i) J. Zhou, J. Li, Y. Li, C. Wu, G. He, Q. Yang, Y. Zhou, H. Liu, *Org. Lett.,* 2018, **20,** 7645.

5 Selected examples: (a) Y. Wang, H. Wang, J. Peng, Q. Zhu, *Org. Lett.,* 2011, **13,** 4604; (b) H. Wang, M. M. Lorion, L. Ackermann, *Angew. Chem., Int. Ed.,* 2016, **55,** 10386; (c) F. Wang, H. Wang, Q. Wang, S. Yu, X. Li, *Org. Lett.,* 2016*,* **18,** 1306; (d) X. Wang, N. Jiao, *Org. Lett.,* 2016, **18,** 2150; (e) F. Xu, W.-F. Kang, Y. Wang, C.-S. Liu, J.-Y. Tian, R.-R. Zhao, M. Du, *Org. Lett.,* 2018, **20,** 3245.

6 (a) A. M. Phelps, V. S. Chan, J. G. Napolitano, S. W. Krabbe, J. M. Schomaker, S. Shekhar, *J. Org. Chem.,* 2016, **81,** 4158; (b) J. Vaitla, A. Bayer, K. H. Hopmann, *Angew. Chem., Int. Ed.,* 2017, **56,** 4277; (c) Y. Xu, G. Zheng, X. Yang, X. Li, *Chem. Commun.,* 2018, **54,** 670; (d) X. Wu, H. Xiong, S. Sun, J. Cheng, *Org. Lett.,* 2018, **20,** 1396; (e) K. S. Halskov, M. R.Witten, G. L. Hoang, B. Q. Mercado, J. A. Ellman, *Org. Lett.,* 2018, **20,** 2464; (f) G. L. Hoang, J. A. Ellman, *Tetrahedron,* 2018, **74,** 3318; (g) G. Zheng, M. Tian, Y. Xu, X. Chen, X. Li, *Org. Chem. Front.,* 2018, **5,** 998; (h) C. Zhou, F. Fang, Y. Cheng, Y. Li, H. Liu, Y. Zhou, *Adv. Synth. Catal.,* 2018, **360,** 2546; (i) C.-F. Liu, M. Liu, L. Dong, *J. Org. Chem.,* 2019, **84,** 409; (j) H. Oh, S. Han, A. K. Pandey, S. H. Han, N. K. Mishra, S. Kim, R. Chun, H. S. Kim, J. Park, I. S. Kim, *J. Org. Chem.,* 2018, **83,** 4070.

7 C. Zhang, X.-M. Chen, Y. Luo, J.-L. Li, M. Chen, L. Hai, Y. Wu, *ACS Sustainable Chem. Eng.,* 2018, **6,** 13473.

8 (a) E. M. Simmons, J. F. Hartwig, *Angew. Chem., Int. Ed.,* 2012, **51**, 3066; (b) M. Tian, B. Liu, J. Sun, X. Li, *Org. Lett.,* 2018, **20**, 4946.

9 (a) M. Brasse, J. Cámpora, J. A. Ellman, R. G. Bergman, *J. Am. Chem. Soc.,* 2013, **135,** 6427; (b) X. Zhou, Z. Qi, S. Yu, L. Kong, Y. Li, W. Tian, X. Li, *Adv. Synth. Catal.,* 2017, **359,** 1620; (c) Y. Xu, G. Zheng, X. Yang, X. Li, *Chem. Commun.,* 2018, **54,** 670; (d) B. Alcaide, P. Almendros, I. Fernández, T. M. D. Campo, T. Naranjo, *Adv. Synth. Catal.,* 2013, **355**, 2681; (e) J. Schießl, J. Schulmeister, A. Doppiu, E. Wörner, M. Rudolph, R. Karch, A. S. K. Hashmi, *Adv. Synth. Catal.,* 2018, **360**, 3949.

10 J. M. Frost, M. J. Dart, K. R. Tietje, T. R. Garrison, G. K. Grayson, A. V. Daza, O. F. El-Kouhen, B. B. Yao, G. C. Hsieh, M. Pai, C. Z. Zhu, P. Chandran, M. D. Meyer, *J. Med. Chem.,* 2010, **53,** 295.

11 (a) J.-P. Liou, Y.-L. Chang, F.-M. Kuo, C.-W. Chang, H.-Y. Tseng, C.-C. Wang, Y.-N. Yang, J.-Y. Chang, S.-J. Lee, H.-P. Hsieh, *J. Med. Chem.,* 2004, **47,** 4247; (b) M. A. Soussi, O. Provot, G. Bernadat, J. Bignon, D. Desravines, J. Dubois, J.-D. Brion, S. Messaoudi, M. Alami, *ChemMedChem.,* 2015, **10,** 1392; (c) K. Kuroiwa, H. Ishii, K. Matsuno, A. Asai, Y. Suzuki, *ACS Med. Chem. Lett.,* 2015, **6,** 287.