ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2019, **55**, 12551

Received 20th August 2019,
Accepted 24th September 2019

DOI: 10.1039/c9cc06460e

rsc.li/chemcomm

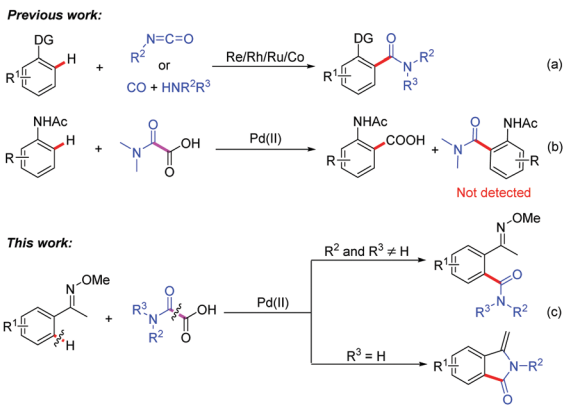
Palladium-catalyzed decarboxylative *ortho*-amidation of *O*-methyl ketoximes with oxamic acids†

Kun Jing, Peng-Cheng Cui and Guan-Wu Wang *

The first palladium-catalyzed *ortho*-amidation of ketoximes has been developed with readily available, easy to handle and environment-friendly *N*,*N*-disubstituted oxamic acids as the amidation sources. When *N*-monosubstituted oxamic acids are used as the substrates, the formed *ortho*-amidated ketoximes undergo further intramolecular cyclization to provide 3-methyleneisoindolinones.

Arylamides, one of the most important organic compounds, not only represent key structure motifs in many pharmaceuticals and bioactive compounds such as proteins, vitamins and hormones, but also have wide applications as crucial precursors for the synthesis of various valuable products.[1] Traditionally, arylamides are synthesized from amines and preactivated carboxylic acid derivatives such as acyl chlorides and anhydrides, or *in situ* activated carboxylic acids with coupling reagents such as carbodiimides.[2] Nevertheless, these methods always lack atom economy in terms of the demand of pre-functionalization of the substrates and conversion of carboxylic acids into more active acyl chlorides or the requirement of other coupling reagents. Therefore, it is of significant importance to the development of more atom- and step-economic methodologies for the synthesis of arylamides.

In the past decade, the transition-metal-catalyzed functional group-directed C–H bond functionalization has attracted substantial attention in construction of amide motifs attributable to its atom- and step-economy as well as high regioselectivity. The rhenium-,[3] rhodium-,[4] ruthenium-[5] and cobalt-catalyzed[6] *ortho*-amidations *via* C–H activation with isocyanates as the amidation sources have been developed over the years, while CO and amines were also employed as the amidation sources in multicomponent carbonylation reactions[7] (Scheme 1a). However, despite these considerable advances, the hypertoxicity and troublesome handling procedure of isocyanates and CO limit the application of these approaches. Consequently, it is necessary to find environmentally friendly, cheap and easily available compounds to serve as the amidation sources. In 2015, the Li group employed lower toxic formylamines as the amidation sources for these purposes, but the substrates were only limited to isoquinoline *N*-oxides.[8] Pioneering works utilizing oxamic acids to construct arylamides *via* decarboxylative cross-coupling have been explored.[9] Compared with isocyanates and CO, oxamic acids demonstrate advantages of being cheapness, hypotoxicity and easy handling. However, these reactions are somewhat restricted due to the requirement of pre-functionalization of the substrates into potassium aryltrifluoroborates, aryl halides or basic heterocycles. Consequently, it is more tempting to realize the direct C–H amidation of arenes with oxamic acids. When the palladium-catalyzed *ortho*-amidation of acetanilides with oxamic acids was attempted, *N*-acyl anthranilic acids were surprisingly obtained as the carboxylated products (Scheme 1b).[10] Within our ongoing interest in C–H activation reactions,[11] herein we report the first palladium-catalyzed *ortho*-amidation of *O*-methyl ketoximes with *N*,*N*-disubstituted oxamic acids, where the oxime directing group



Scheme 1 Transition-metal-catalyzed *ortho*-amidation.

CAS Key Laboratory of Soft Matter Chemistry, Hefei National Laboratory for Physical Sciences at Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, P. R. China.
E-mail: gwang@ustc.edu.cn; Tel: +86 551 63607864

† Electronic supplementary information (ESI) available: Detailed experimental procedures, characterization data, NMR spectra of **3**, **5**, **6–9**, **11**, and a mixture of **3aa** and [D_4]-**3aa**, as well as NOESY spectra of **5na** and **5na′**. See DOI: 10.1039/c9cc06460e

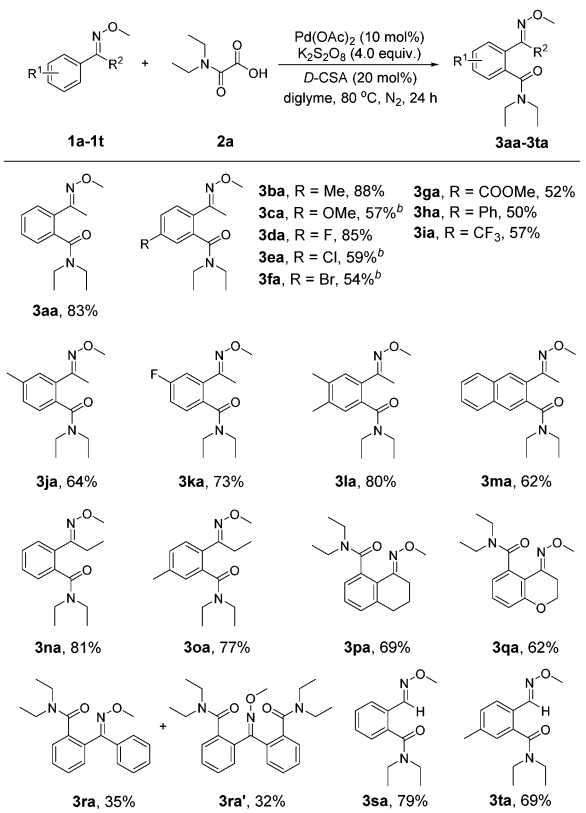
can be easily removed to provide synthetically valuable 2-acylbenzamide derivatives. Notably, when *N*-monosubstituted oxamic acids are utilized as the substrates, the formed *ortho*-amidated ketoximes can undergo further intramolecular cyclization to afford 3-methyleneisoindolinones (Scheme 1c).

At the outset of our studies, we tried to find the optimal reaction conditions for the representative *ortho*-amidation of acetophenone *O*-methyl oxime (**1a**) with *N*,*N*-diethyloxamic acid (**2a**). After extensive screenings (see Table S1 in the ESI† for details), the optimal conditions were established as follows: with 10 mol% $Pd(OAc)_2$ as the catalyst, 4.0 equiv. of $K_2S_2O_8$ as the oxidant, 20 mol% D-camphorsulfonic acid (D-CSA) as the additive and diglyme as the solvent, the reaction of **1a** and **2a** (2.0 equiv.) performed best at 80 °C for 24 h under a nitrogen atmosphere to give **3aa** in 83% yield.

With the optimized reaction conditions in hand, we then investigated the scope and functional group tolerance of this reaction with a range of ketoximes **1a–1t** (Table 1). In general, both electron-donating and -withdrawing groups were well tolerated under our reaction conditions, affording the corresponding *ortho*-amidated products in moderate to excellent yields. Ketoxime **1b** with a methyl group substituted at the *para* position proceeded smoothly and gave the desired product **3ba** in 88% yield. The substrate **1c** bearing the strong electron-donating methoxy group provided the corresponding product **3ca** in 57% yield. Halogen-substituted ketoximes **1d–1f** worked well and afforded products **3da–3fa** in 54–85% yields, and provided synthetic handles for further functionalization of the products *via* cross-coupling reactions. When an ester group was substituted at the *para* position of the oxime, the amidation occurred at the *ortho*-position of the oxime with high regioselectivity to afford **3ga** in 52% yield, demonstrating that the directing ability of the oxime group was stronger than the ester group. This reaction was also compatible with phenyl and trifluoromethyl groups, furnishing products **3ha** and **3ia** in 50% and 57% yields, respectively. However, the substrates with very strong electron-withdrawing nitro group failed to provide the *ortho*-amidated products owing to the increased electron deficiency of the aryl ring. As for the *meta*-substituted substrates **1j** and **1k**, the cleavage of C–H bonds occurred regioselectively at the less hindered sites to give the corresponding products **3ja** and **3ka** in 64% and 73% yields, respectively. Nevertheless, the substrates with *ortho*-substituents were not compatible with our standard conditions, probably due to the large steric hindrance, which may prevent the formation of palladacycle. Disubstituted ketoxime **1l** showed excellent reactivity and regioselectivity under our conditions and the corresponding product **3la** was isolated in 80% yield. When ketoxime **1m** was employed as the substrate, the amidation occurred preferentially at the less hindered C3 position instead of the more reactive C1 position, providing product **3ma** in 62% yield. The above results indicated that the steric hindrance exhibited an obvious influence on this reaction. Other ketoximes **1n–1q** also proved feasible for this procedure and afforded the corresponding products **3na–3qa** in good yields of 62–81%. The benzophenone oxime **1r** gave a mixture of monosubstituted and disubstituted products in similar yields of 35% and 32% under our optimal reaction conditions. In addition, aldoximes **1s** and **1t** were also found to be compatible with our conditions to yield the desired products **3sa** and **3ta** in 79% and 69% yields, respectively.

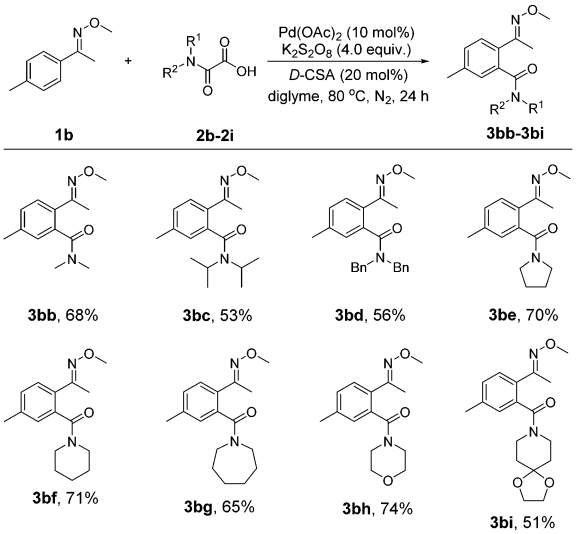
To further explore the scope and limitation of the substrates, we investigated the reactions of various *N*,*N*-disubstituted oxamic acids **2b–2i** with representative ketoxime **1b** (Table 2). *N*,*N*-Dimethyloxamic acid **2b** and *N*,*N*-diisopropyloxamic acid **2c** proceeded smoothly under the standard conditions and afforded the corresponding products **3bb** and **3bc** in 68% and 53% yields respectively. When *N*,*N*-dibenzyloxamic acid **2d** was employed, the desired product **3bd** was obtained in 56% yield. To our great delight, this reaction could also be extended to cyclic oxamic acids **2e–2i** to deliver the cyclic benzamides **3be–3bi** in 51–74% yields, and these cyclic benzamides usually play important roles in a large number of natural products and pharmaceuticals as crucial structure motifs.[12] Next, we attempted to extend the substrates from *N*,*N*-disubstituted oxamic acids to *N*-monosubstituted oxamic acids, while the reaction of ketoxime **1a** with *N*-ethyloxamic acid **4a** failed to provide the desired product under our standard conditions. Then great efforts had been made to seek out the appropriate conditions for the amidation with secondary oxamic acids. Fortunately, when 0.5 equiv. of AgOAc was added and 1,2-dimethoxyethane (DME) was used as the solvent, **1a** could react with **4a** to give 3-methyleneisoindolinone **5aa** in 51% yield, which should be *in situ* generated by the intramolecular cyclization of the formed *ortho*-amidated ketoxime. Likewise, other

Table 1 Scope of substituted ketoximes[a]



[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (10 mol%), $K_2S_2O_8$ (4.0 equiv.), D-CSA (20 mol%), diglyme (1.5 mL), 80 °C, N_2, 24 h. Isolated yields based on **1**. [b] 48 h.

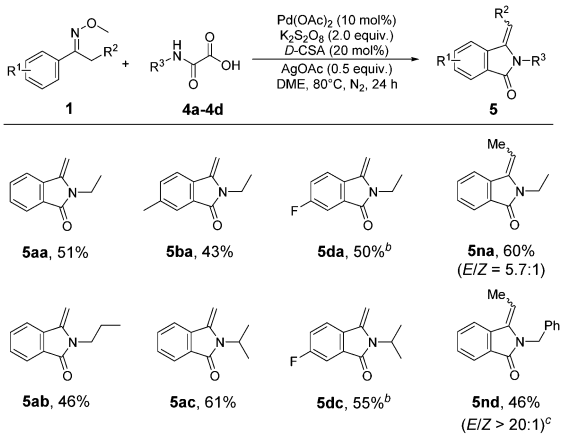
Table 2 Scope of *N*,*N*-disubstituted oxamic acids[a]



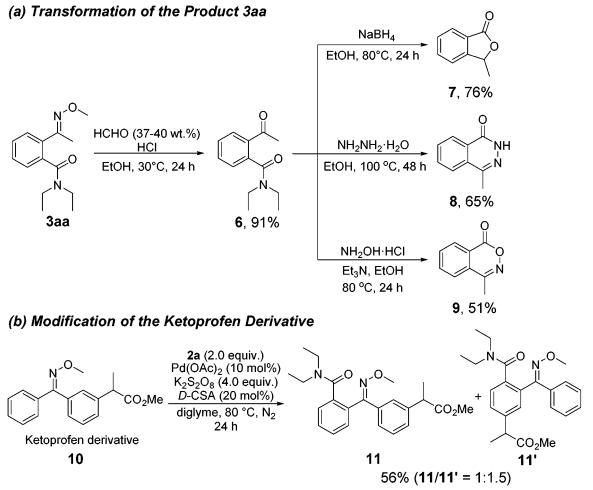
[a] Reaction conditions: **1b** (0.3 mmol), **2** (0.6 mmol), $Pd(OAc)_2$ (10 mol%), $K_2S_2O_8$ (4.0 equiv.), D-CSA (20 mol%), diglyme (1.5 mL), 80 °C, N_2, 24 h. Isolated yields based on **1b**.

representative ketoximes **1b** and **1d** could also react well with **4a** to afford the desired 3-methyleneisoindolinones **5ba** and **5da** in 43% and 50% yields, respectively. It should be noted that propiophenone oxime **1n** gave a mixture of *E* and *Z* isomers in a ratio of 5.7 : 1 (their configurations were determined by the NOESY measurement, for details see Fig. S93 and S94 in the ESI†). Other *N*-monosubstituted oxamic acids (**4b–4d**) were also explored, and the corresponding products **5ab**, **5ac**, **5dc** and **5nd** were obtained in 46–61% yields. Particularly, the reaction of **1n** with *N*-benzyloxamic acid **4d** gave *E* isomer as the major product with high stereoselectivity ($E/Z > 20:1$) because of the large steric hindrance of benzyl group (Table 3). 3-Methyleneisoindolinones display versatile biological activities and

Table 3 Scope of *N*-monosubstituted oxamic acids[a]



[a] Reaction conditions: **1** (0.3 mmol), **4** (0.9 mmol), $Pd(OAc)_2$ (10 mol%), $K_2S_2O_8$ (2.0 equiv.), AgOAc (0.5 equiv.), D-CSA (20 mol%), DME (3 mL), 80 °C, N_2, 24 h. Isolated yields based on **1**. [b] 90 °C. [c] The ratio was determined by ^1H NMR of the mixture of *E* and *Z* isomers.



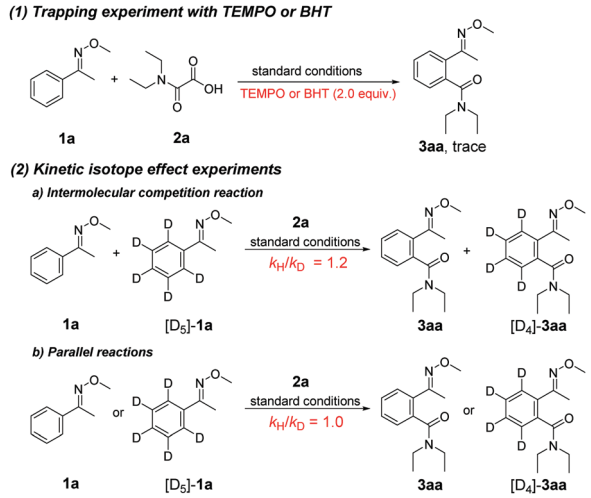
Scheme 2 Synthetic applications of the present method.

represent the core units of many promising drugs such as antihypertensive drugs fumaridine, magallanesine and so on.[13]

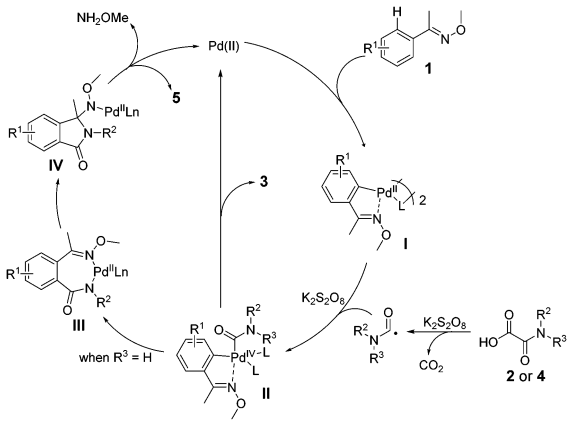
In order to illustrate the synthetic utility of the present method, we chose **3aa** as the representative example to conduct further transformations. The oxime directing group could be removed by adding formaldehyde and concentrated hydrochloric acid to provide 2-acetyl-*N*,*N*-diethylbenzamide **6** in 91% yield. Then, the synthetically valuable lactone **7** was generated in 76% yield by reduction of **6** with $NaBH_4$ and further intramolecular cyclization. In addition, **6** could also react with hydrazine and hydroxylamine to give phthalazinone **8** and benzoxazinone **9** in 65% and 51% yields, respectively (Scheme 2a). Moreover, the synthetic importance of this reaction could be demonstrated by the modification of ketoprofen derivative **10**, which is one of the bestselling anti-inflammatory drugs in the world. Gratifyingly, the *ortho*-amidation took place at two different phenyl rings, affording a mixture of amidated products **11** and **11′** in a total yield of 56% (**11**/**11′** = 1 : 1.5) (Scheme 2b).

It was proposed that oxamic acids could generate aminoacyl radicals in the presence of a persulfate.[14] Thus, we performed some control experiments to verify whether this reaction involved a free radical process. When radical scavengers 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or butylated hydroxytoluene (BHT) was added to the reaction of **1a** with **2a**, it was found that the formation of **3aa** was suppressed, suggesting that a radical intermediate was likely involved in this procedure. Then, the intermolecular competition kinetic isotope effect (KIE) experiment was studied, and the KIE was determined as 1.2 by analysis of the ^1H NMR of the product. Finally, independent parallel reactions using **1a** and [D_5]-**1a** were conducted, and the value of k_H/k_D was unraveled as 1.0. These results hinted that the C–H bond cleavage might not be the rate-determining step (Scheme 3).

On the basis of the above observations and previous literature,[11c,14] a plausible reaction pathway is proposed (Scheme 4). This transformation is believed to start with the formation of a five-membered palladacycle **I** by the *ortho*-palladation of **1** with a Pd(II) species.[11c] Then, **I** reacts with the aminoacyl radical produced by decarboxylation of *N*,*N*-disubstituted oxamic acid **2** with the aid of $K_2S_2O_8$, furnishing the Pd(IV) intermediate **II**.[14] It should be noted that



Scheme 3 Preliminary mechanistic studies.



Scheme 4 Plausible reaction mechanism.

the alternative Pd(III) species for **II** cannot be excluded. Subsequently, product **3** is generated by reductive elimination of the intermediate **II**. Meanwhile, the Pd(II) species is reproduced to complete the catalytic cycle. When *N*-monosubstituted oxamic acid **4** is employed as the substrate, the formed *ortho*-amidated product undergoes further coordination with the Pd(II) atom to give intermediate **III**, which is then transformed into intermediate **IV** *via* an intramolecular insertion of the oxime group into the N–Pd bond. Finally, β-H elimination with the removal of one molecule of methoxyamine affords 3-methyleneisoindolinone **5** and regenerates the Pd(II) catalyst. A similar cyclization process for the formation of 3-methyleneisoindolinones was proposed for the Rh-catalyzed amidation of *O*-methyl ketoximes with isocyanates.[4b] Unfortunately, the simplest oxamic acid H_2NCOCO_2H was also attempted for the *ortho*-amidation, yet no desired product could be obtained, probably due to that the primary aminoacyl radical was difficult to generate under our conditions.

In conclusion, we have developed the first palladium-catalyzed decarboxylative *ortho*-amidation of *O*-methyl ketoximes by using readily available, easy to handle and environment-friendly *N*,*N*-disubstituted oxamic acids as the amidation sources. This procedure features good functional group tolerance and broad substrate scope. In addition, the directing group can be easily deprotected to generate 1,2-dicarbonylated arenes, which provides the possibility for further transformation into synthetically valuable compounds like lactones. Intriguingly, when *N*-monosubstituted oxamic acids are employed as the substrates, the formed *ortho*-amidated ketoximes can undergo further intramolecular cyclization to produce biologically active 3-methyleneisoindolinones.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 For selected examples, see: (*a*) J. M. Humphrey and A. R. Chamberlin, *Chem. Rev.*, 1997, **97**, 2243; (*b*) J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem.*, 2006, **4**, 2337; (*c*) S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451.
2 (*a*) E. Valeur and M. Bradley, *Chem. Soc. Rev.*, 2009, **38**, 606; (*b*) V. R. Pattabiraman and J. W. Bode, *Nature*, 2011, **480**, 471.
3 (*a*) Y. Kuninobu, Y. Tokunaga, A. Kawata and K. Takai, *J. Am. Chem. Soc.*, 2006, **128**, 202; (*b*) S. Sueki, Y. Guo, M. Kanai and Y. Kuninobu, *Angew. Chem., Int. Ed.*, 2013, **52**, 11879; (*c*) X. Geng and C. Wang, *Org. Biomol. Chem.*, 2015, **13**, 7619.
4 (*a*) K. D. Hesp, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2011, **133**, 11430; (*b*) B. Zhou, W. Hou, Y. Yang and Y. Li, *Chem. – Eur. J.*, 2013, **19**, 4701; (*c*) X.-Y. Shi, A. Renzetti, S. Kundu and C.-J. Li, *Adv. Synth. Catal.*, 2014, **356**, 723; (*d*) S. Han, N. K. Mishra, S. Sharma, J. Park, M. Choi, S.-Y. Lee, J. S. Oh, Y. H. Jung and I. S. Kim, *J. Org. Chem.*, 2015, **80**, 8026.
5 (*a*) K. Muralirajan, K. Parthasarathy and C.-H. Cheng, *Org. Lett.*, 2012, **14**, 4262; (*b*) S. De Sarkar and L. Ackermann, *Chem. – Eur. J.*, 2014, **20**, 13932; (*c*) S. M. A. Shakoor, S. Kumari, S. Khullar, S. K. Mandal, A. Kumar and R. Sakhuja, *J. Org. Chem.*, 2016, **81**, 12340.
6 (*a*) J. R. Hummel and J. A. Ellman, *Org. Lett.*, 2015, **17**, 2400; (*b*) J. Li and L. Ackermann, *Angew. Chem., Int. Ed.*, 2015, **54**, 8551.
7 For selected reviews, see: (*a*) Q. Liu, H. Zhang and A. Lei, *Angew. Chem., Int. Ed.*, 2011, **50**, 10788; (*b*) X.-F. Wu, H. Neumann and M. Beller, *Chem. Rev.*, 2013, **113**, 1.
8 B. Yao, C.-L. Deng, Y. Liu, R.-Y. Tang, X.-G. Zhang and J.-H. Li, *Chem. Commun.*, 2015, **51**, 4097.
9 (*a*) M. Li, C. Wang, P. Fang and H. Ge, *Chem. Commun.*, 2011, **47**, 6587; (*b*) W.-M. Cheng, R. Shang, H.-Z. Yu and Y. Fu, *Chem. – Eur. J.*, 2015, **21**, 13191; (*c*) M. T. Westwood, C. J. C. Lamb, D. R. Sutherland and A.-L. Lee, *Org. Lett.*, 2019, **21**, 7119.
10 Y. Wu, C. Jiang, D. Wu, Q. Gu, Z.-Y. Luo and H.-B. Luo, *Chem. Commun.*, 2016, **52**, 1286.
11 For a review, see: (*a*) G.-W. Wang, *Top. Organomet. Chem.*, 2016, **55**, 119. For selected examples, see: (*b*) G.-W. Wang, T.-T. Yuan and D.-D. Li, *Angew. Chem., Int. Ed.*, 2011, **50**, 1380; (*c*) Z.-Y. Li and G.-W. Wang, *Org. Lett.*, 2015, **17**, 4866; (*d*) Z.-Y. Li, L. Li, Q.-L. Li, K. Jing, H. Xu and G.-W. Wang, *Chem. – Eur. J.*, 2017, **23**, 3285; (*e*) K. Jing, J.-P. Yao, Z.-Y. Li, Q.-L. Li, H.-S. Lin and G.-W. Wang, *J. Org. Chem.*, 2017, **82**, 12715; (*f*) K. Jing, Z.-Y. Li and G.-W. Wang, *ACS Catal.*, 2018, **8**, 11875; (*g*) K. Jing, X.-N. Wang and G.-W. Wang, *J. Org. Chem.*, 2019, **84**, 161.
12 (*a*) K. Seno, T. Okuno, K. Nishi, Y. Murakami, K. Yamada, S. Nakamoto and T. Ono, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 587; (*b*) L. I. James, V. K. Korboukh, L. Krichevsky, B. M. Baughman, J. M. Herold, J. L. Norris, J. Jin, D. B. Kireev, W. P. Janzen, C. H. Arrowsmith and S. V. Frye, *J. Med. Chem.*, 2013, **56**, 7358.
13 (*a*) G. Blaskó, D. J. Gula and M. Shamma, *J. Nat. Prod.*, 1982, **45**, 105; (*b*) E. Valencia, V. Fajardo, A. J. Freyer and M. Shamma, *Tetrahedron Lett.*, 1985, **26**, 993.
14 (*a*) J. Miao, P. Fang, S. Jagdeep and H. Ge, *Org. Chem. Front.*, 2016, **3**, 243; (*b*) Q.-L. Li, Z.-Y. Li and G.-W. Wang, *ACS Omega*, 2018, **3**, 4187; (*c*) S. Mandal, T. Bera, G. Dubey, J. Saha and J. K. Laha, *ACS Catal.*, 2018, **8**, 5085.

