RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2022, **12**, 3783

Iron catalyzed C–C dehydrogenative coupling reaction: synthesis of arylquinones from quinones/hydroquinones†

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Received 4th December 2021
Accepted 24th January 2022

DOI: 10.1039/d1ra08828a

rsc.li/rsc-advances

An atom-economical approach for the synthesis of arylquinones was achieved successfully *via* direct oxidative C–C dehydrogenative coupling reaction of quinones/hydroquinones with electron-rich arenes using an inexpensive Fe–I_2–$(NH_4)_2S_2O_8$ system. The efficiency of this catalytic approach was established with a broad scope of substrates involving quinones and hydroquinones to give high yields (60–89%) of several arylated quinones. The present protocol is simple, practical, and shows good functional group tolerance.

Introduction

Quinone scaffolds are widely distributed in natural products and gained importance owing to their roles in biological systems,[1] and were utilized as intermediates in materials,[2] bioinspired synthetic products,[3] and biosynthesis.[4] They are also involved in many bioenergetic processes due to their electron transport properties.[5] Of particular importance, aryl substituted quinones possess unique electronic properties,[6] which have several applications in chemistry and many natural products. For example, *Belamcanda chinensis*, were used as a specific cyclooxygenase inhibitor, belamcandaquinones A and B isolated from the seed of a medicinal plant.[7] Furthermore, aryl-substituted quinones are very useful in the dye industry owing to their important coloring properties.[8] Thus, the synthesis of aryl substituted quinones has attracted significant attention and many methods have been developed.

Several approaches were described for the synthesis of arylated quinones involving different types of starting materials. Utilized of prefunctionalized quinones and arenes requires the presence of expensive transition metal reagents. Examples include the transition-metal-catalyzed coupling of a stannylquinone with an arylhalide,[9] haloquinone with a styrylstannane[10] and halogenated quinones with boronic acids.[11] Heck type arylation often comprises unfunctionalized quinones and pre-functionalized arenes. Commercially available, but costly arylboronic acids were used in such transformations, in the presence of metal reagents made of such as Ag, Rh, Ir, Pd, and Fe salts.[12] Furthermore, several metal free methods using diazonium salt-hydrazine catalysts, diazonium salts, diaryliodonium salts, and arylhydrazine salts have also been described.[13] On the other hand, oxidative C–H/C–H coupling assembling a diverse variety of complex aromatic systems was also employed in coupling of quinones and arenes. Such C–H/C–H coupling was carried out in the presence of metal salts such as $In(OTf)_3$, $Pd(OAc)_2$, Rh salts, $Pd(TFA)_2$, and $FeCl_3$.[14]

In general, the arylation of quinones compounds with carbon nucleophiles is achieved through Michael-type 1,4-conjugate addition reaction of electron-rich arenes[15] or through the transition-metal-catalyzed coupling reactions. However, arene–quinone coupling have certain limitations, such as organometallic reagents generated from prefunctionalized starting material, aryl radicals obtained from prefunctionalized arenes and expensive transition metals. Hence, a 1,4-conjugate addition reaction followed by oxidation is a preferred route for the arylation reactions of quinones and, based on this concept, a few metal-catalyzed reactions were reported. Despite these advances, efforts still need to be made in terms of mild reaction conditions, inexpensive reagents, and wide substrate scope.[16a]

We have already reported the coupling of indoles and quinones in the absence of any catalyst,[16c] but herein we add a catalyst to expand the scope and perform the coupling not only with indoles but also with other arenes. In consideration of these important points and continuing our research interest on functionalized of quinone derivatives, we wish to report a sequential one-pot approach to arylated quinones through direct oxidative C–C dehydrogenative coupling reaction of quinones/hydroquinones with electron-rich arenes using an inexpensive Fe–I_2–$(NH_4)_2S_2O_8$ system (Scheme 1).

Results and discussion

We selected the reaction of readily 1,4-naphthoquinone (**1a**) and *N*,*N*-dimethylaniline (**2a**) as the model reaction for optimizing

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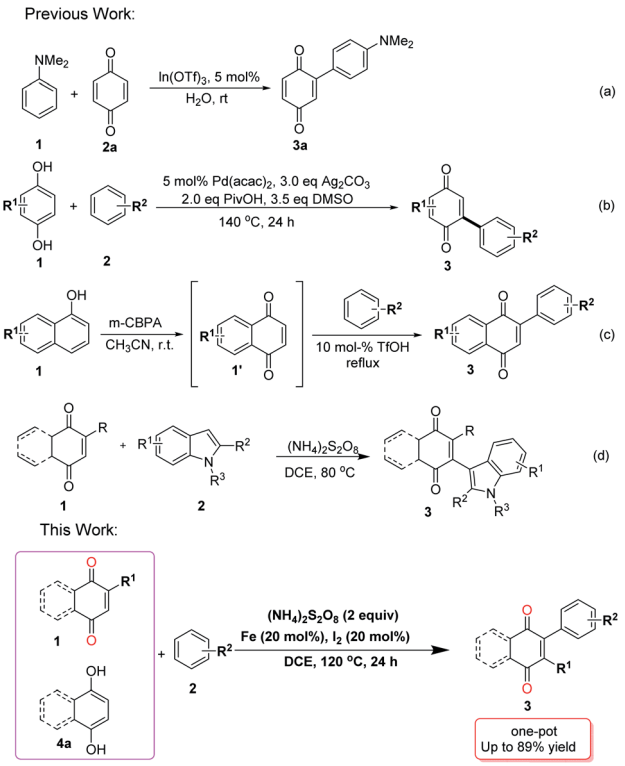
† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ra08828a

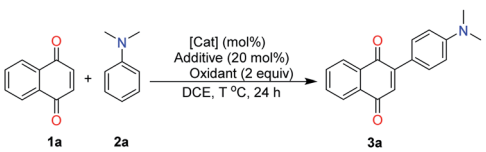


Scheme 1 Approaches to arylated quinones compounds.

the direct oxidative C–C dehydrogenative coupling reaction of quinones/hydroquinones with electron-rich arenes (see Table 1, as well as ESI†). Fortunately, under the reaction of Fe (10 mol%), oxidant $(NH_4)_2S_2O_8$ (2.0 equiv.) and DCE (2 mL), at 100 °C, for 24 h (Table 1, entry 1), the desired product **3a** was obtained in 58% isolated yield. Other metal salts did not provide better results including $FeSO_4 \cdot 7H_2O$, $FeCl_3$, Zn, and $Pd(OAc)_2$ also tested for the cross-coupling (entries 2–5, see ESI†). When the quantity of the catalyst (Fe) was increased to 20 mol% (entry 6), the yield of the product **3a** increased (65%). Among the various additives screened, I_2 was the most efficient (entries 8–10, see ESI†). Subsequently, the oxidant was screened. $(NH_4)_2S_2O_8$ was proved to be more efficient than others, such as $K_2S_2O_8$ and Oxone (entries 11–12, see ESI†). Furthermore, when the temperature was raised to 120 °C, the yield increased to 89% (entry 14). It should be noted that increasing or decreasing the reaction temperature gave slightly inferior results, indicating that the transformation was sensitive to temperature (see ESI†). Based on these results, the best yield of **3a** was obtained from the reaction of **2a** (2 equiv.) and Fe (20 mol%), additive I_2 (20 mol%), oxidant $(NH_4)_2S_2O_8$ (2 equiv.) in DCE at 120 °C under sealed tube.

With the optimized reaction conditions in hand, we next set out to explore the universality of this method (Table 2). Therefore, a series of electron-rich arenes with quinones, including anilines and indole derivatives, were subjected to this process. Subsequently, we evaluated the scope and the influence of the substituents on the electron-rich arenes moiety. A series of disubstituted anilines, such as dialkyl, dibenzyl, diallyl, and cycloalkylamine compounds, were examined and the desired arylated products obtained in high yields (**3a–3j**). The scale-up of the reaction was performed to reveal the applicability of this method. When 1,4-naphthoquinone **1a** was scaled up by 5 mmol, **3a** was isolated in 85% yield. When the benzyl group

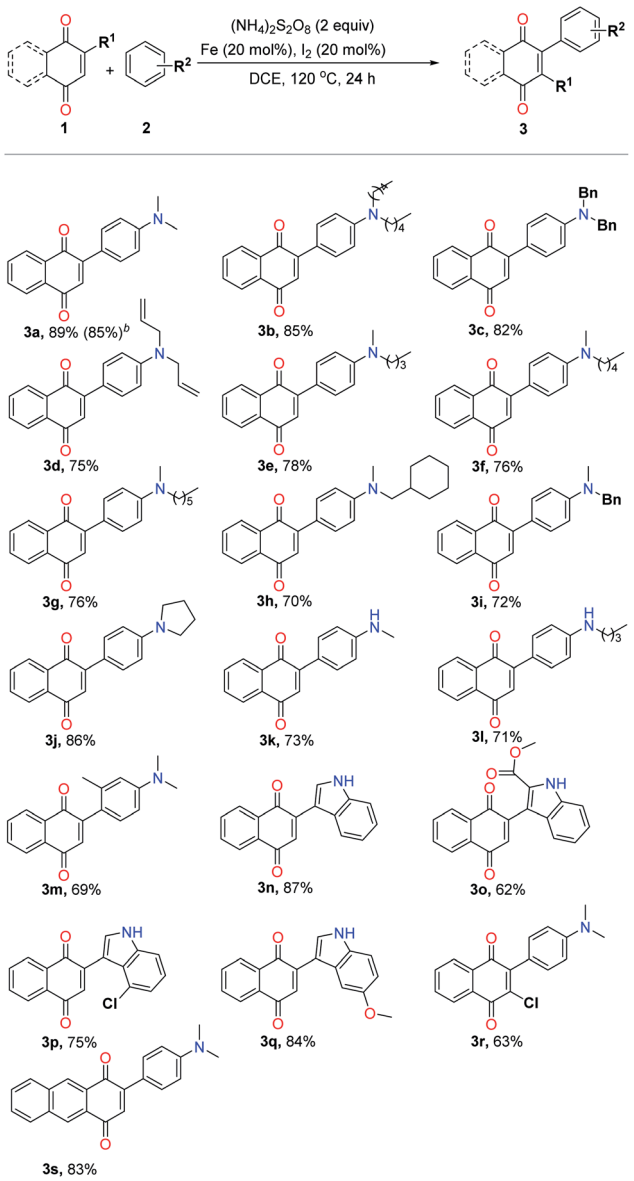
Table 1 Optimization of the reaction conditions[a]



Entry	[Cat] (mol%)	Additive (mol%)	Oxidants (2 equiv.)	T °C	Yield[b] (%)
1	Fe (10)	—	$(NH_4)_2S_2O_8$	100	58
2	$FeSO_4 \cdot 7H_2O$ (10)	—	$(NH_4)_2S_2O_8$	100	23
3	$FeCl_3$ (10)	—	$(NH_4)_2S_2O_8$	100	35
4	Zn (10)	—	$(NH_4)_2S_2O_8$	100	41
5	$Pd(OAc)_2$ (10)	—	$(NH_4)_2S_2O_8$	100	34
6	Fe (20)	—	$(NH_4)_2S_2O_8$	100	65
7	Fe (30)	—	$(NH_4)_2S_2O_8$	100	53
8	Fe (20)	CuBr	$(NH_4)_2S_2O_8$	100	24
9	Fe (20)	CuI	$(NH_4)_2S_2O_8$	100	31
10	Fe (20)	I_2	$(NH_4)_2S_2O_8$	100	76
11	Fe (20)	I_2	$K_2S_2O_8$	100	45
12	Fe (20)	I_2	Oxone	100	32
13	Fe (20)	I_2	$(NH_4)_2S_2O_8$	80	41
14	Fe (20)	I_2	$(NH_4)_2S_2O_8$	120	89
15	Fe (20)	I_2	$(NH_4)_2S_2O_8$	140	70

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol, 2 equiv.), [Cat] (mol%), additive (20 mol%), oxidant (0.6 mmol, 2 equiv.), DCE (2 mL), 80–140 °C, sealed tube for 24 h. DCE stands for 1,2-dichloroethane. [b] Isolated yield.

Table 2 Substrate scope for quinones with anilines[a]

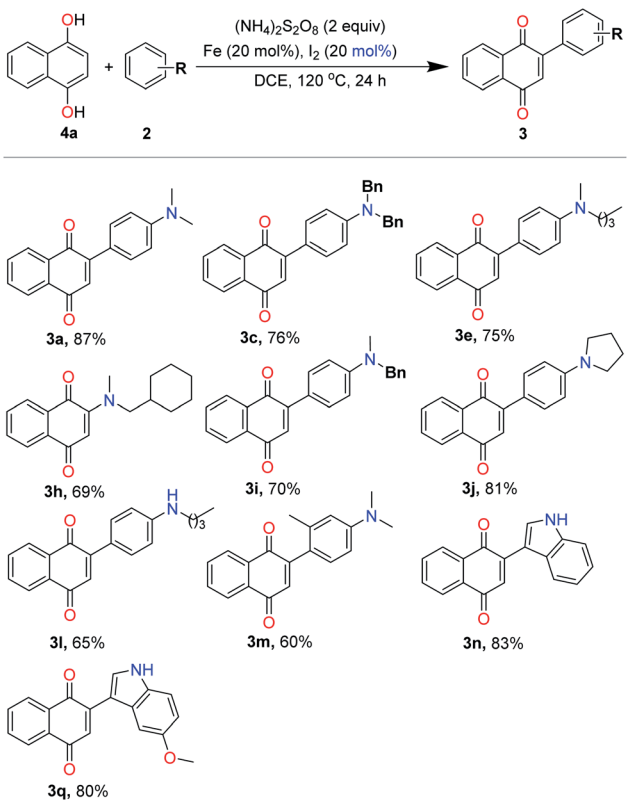


[a] Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), Fe (20 mol%), I_2 (20 mol%), $(NH_4)_2S_2O_8$ (2 equiv.), DCE (2 mL), 120 °C, sealed tube for 24 h. Isolated yield. Bn means benzyl. [b] In a 5 mmol scale.

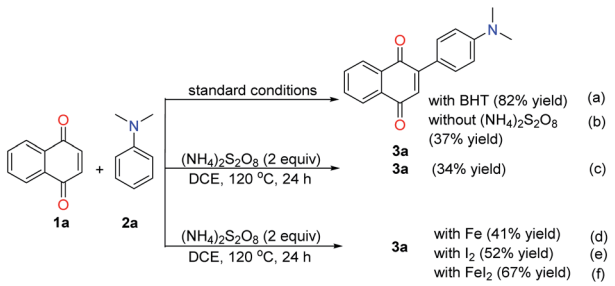
was attached to the *N* of the aniline, the product was obtained in excellent yield (**3c**). The exciting thing was that this protocol showed good compatibility with carbon–carbon double bonds (**3d**). Interestingly, the cyclic aniline compounds were capable of obtaining the corresponding products in good yields (**3j**). Monosubstituted aniline derivatives were converted into the respective products in moderate to good yields (**3k** and **3l**). Although there is a possibility of NH-attack on quinones, we exclusively observed the C–C products. When we carried out the reaction with a meta-meta-substituted *N*,*N*-dimethylaniline as a substrate, we were also able to obtain an arylated product, albeit at a moderate yield (**3m**), wherein the methyl group could hamper the coupling. It was possible that the steric hindrance effect of the meta positions and led to a decrease in yield. Heterocyclic compounds, such as indoles (C-3) were successfully arylated under the optimized conditions (**3n–3q**). It is noteworthy that electron withdrawing indoles (**2o**) with a substituent at the 2-position also proved to be suitable coupling partners to provide the corresponding products **3o** in 62% yield with a catalyst, but **3o** was obtained in traces in the absence of Fe/iodine system.[16c] At the beginning, Fe and I_2 gives FeI_2 under the conditions of heating. FeI_2 coordinates to the carbonyl oxygen of the 1,4-naphthoquinone, which increases the electrophilicity and assists 1,4-conjugative addition. Thus, Fe/iodine system can accelerate the reaction and increase the yield. We then proceeded to study the scope of quinone derivatives. We hypothesize that the sensitive chlorine at the β-position of naphthoquinone was compatible with the reaction conditions, which can easily be transformed further by cross-coupling reactions. Anthraquinone **1s** was also employed, affording the corresponding product **3s** in 83% yield.

Subsequently, the synthesis of arylated quinones for a broad substrate scope involved hydroquinone with various electron-rich arenes. As shown in Table 3, moderate to good yields of arylated quinones were obtained upon reacting 1,4 hydroquinone with various electron-rich arenes having disubstituted anilines, as in the case of dialkyl, dibenzyl and cycloalkylamine

Table 3 Substrate scope for hydroquinone with anilines[a]



[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.6 mmol), Fe (20 mol%), I_2 (20 mol%), $(NH_4)_2S_2O_8$ (2 equiv.), DCE (2 mL), 120 °C, sealed tube for 24 h. Isolated yield. Bn means benzyl.

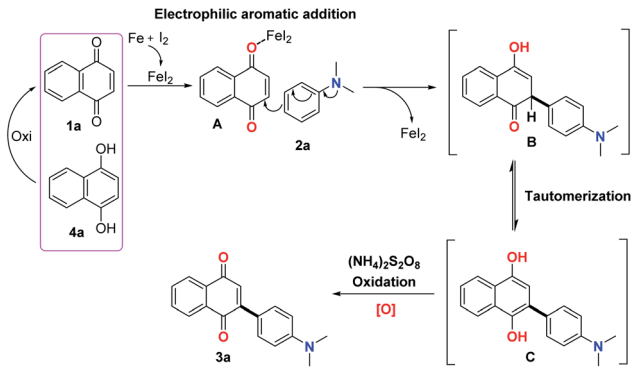


Scheme 2 Control experiments.

compounds. Monosubstituted aniline derivatives were converted into the respective products in moderate yields (**3l**). When we carried out the reaction with a meta-substituted *N*,*N*-dimethylaniline as a substrate, we were also able to obtain an arylated product, albeit at a moderate yield (**3m**). Heterocyclic compounds, such as indoles (C-3) were successfully arylated under the optimized conditions (**3n** and **3q**).

Next, to gain understanding about the mechanism, control experiments were carried out (Scheme 2). The studies revealed that the radical scavenger BHT (2,6-di-*tert*-butyl-4-methylphenol) did not inhibit the reaction under standard conditions, ruling out the radical mechanism (Scheme 2a). The reaction between compounds **1a** and **2a** generated the coupling product **3a** in a yield of 37% in the absence of $(NH_4)_2S_2O_8$ (Scheme 2b). The studies demonstrated the importance of $(NH_4)_2S_2O_8$. And the reaction of model compounds **1a** and **2a** generated the coupling product **3a** without Fe and I_2 in a yield of 34% (Scheme 2c). The corresponding product **3a** is formed in 41% and 52% yield respectively in the presence of $(NH_4)_2S_2O_8$ with Fe or I_2 (Scheme 2d and 2e), which showed that the Fe and I_2 played a pivotal role in obtaining the desired product. The corresponding product **3a** is formed in 67% yield in the presence of $(NH_4)_2S_2O_8$ with FeI_2 (Scheme 2f).

On the basis of this and previous reports,[16] a possible reaction mechanism was proposed (Scheme 3). At the beginning, we hypothesize that Fe and I_2 gives FeI_2 under the conditions of heating. The reaction starts with the *in situ* oxidation of hydroquinone (**4a**) to 1,4-naphthoquinone (**1a**) over a $(NH_4)_2S_2O_8$ oxidant. Then, FeI_2 coordinates to the carbonyl oxygen of the 1,4-naphthoquinone, which increases the electrophilicity and assists 1,4-conjugate addition. Due to nucleophilic nature of the electron-rich arenes **2a**, it would be attracted to the electrophilic C-2 positions of naphthoquinone, and subsequently, 1,4-addition of the **2a** to the 1,4-naphthoquinone afforded the intermediate **B** and aromatization by means of H abstraction. Finally, intermediate **C** undergoes $(NH_4)_2S_2O_8$ oxidation to give product **3a**.



Scheme 3 Plausible reaction mechanism.

Conclusions

In conclusion, we have successfully demonstrated iron-mediated oxidative C–H/C–H cross-coupling reaction between quinones/hydroquinones and various electron-rich arenes to accomplish the arylated quinones using an inexpensive Fe–I_2–$(NH_4)_2S_2O_8$ system. The significant aspects of our work allows modest functional group tolerance, including quinones and hydroquinones.

Experimental section

To a solution of DCE (2 mL) was added **1** or **4a** (0.3 mmol), **2** (0.8 mmol), Fe (0.06 mmol, 20 mol%), I_2 (0.06 mmol, 20 mol%), and $(NH4)_2S_2O_8$ (0.6 mmol, 2 equiv.). The reaction mixture was stirred at 120 °C for 24 h. After the completion of the reaction (monitored by TLC). The reaction was quenched with saturated salt water (2 mL) and the mixture was extracted with EtOAc (3 × 3 mL). The organic extracts were washed with brine, dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The crude product was purified by silica gel column chromatography to give **3**.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for the financial support from the project supported by National undergraduate training program for innovation and entrepreneurship (Grant No. 202114389016 and 202114389005), the Foundation of Chengdu Normal University Talent Introduction Research Funding (2021YJRC202020) and Chengdu Normal University Project (2021CS21ZCY02).

Notes and references

1 (*a*) S. J. Gould, *Chem. Rev.*, 1997, **97**, 2499–2510; (*b*) R. H. Thomson, *Naturally Occurring Quinones IV*, Blackie Academic & Professional, London, 1997; (*c*) B. Zhang, G. Salituro, D. Szalkowski, Z. Li, Y. Zhang, I. Royo, D. Vilella, M. T. Díez, F. Pelaez and C. Ruby, *Science*, 1999, **284**, 974–977; (*d*) J.-K. Liu, *Chem. Rev.*, 2006, **106**, 2209–2223.
2 E. J. Son, J. H. Kim, K. Kim and C. B. Park, *J. Mater. Chem. A*, 2016, **4**, 11179–11202.
3 (*a*) J. L. Bolton and T. Dunlap, *Chem. Res. Toxicol.*, 2017, **30**, 13–37; (*b*) N. El-Najjar, H. Gali-Muhtasib, R. A. Ketola,

P. Vuorela, A. Urtti and H. Vuorela, *Phytochem. Rev.*, 2011, **10**, 353–370; (*c*) G. G. Dias, A. King, F. De Moliner, M. Vendrell and E. N. da Silva Júnior, *Chem. Soc. Rev.*, 2018, **47**, 12–27.

4 (*a*) M. Sugumaran and V. Semensi, *J. Biol. Chem.*, 1991, **266**, 6073–6078; (*b*) J. P. Klinman and F. Bonnot, *Chem. Rev.*, 2014, **114**, 4343–4365.

5 B. Nowicka and J. Kruk, *Biochim. Biophys. Acta*, 2010, **1797**, 1587–1605.

6 (*a*) I. CFR Ferreira, J. A Vaz, M. H. Vasconcelos and A. Martins, *Anti-Cancer Agents Med. Chem.*, 2010, **10**, 424–436; (*b*) C. Asche, *Mini-Rev. Med. Chem.*, 2005, **5**, 449–467.

7 (*a*) Y. Fukuyama, J. Okino and M. Kodama, *Chem. Pharm. Bull.*, 1991, **39**, 1877–1879; (*b*) Y. Fukuyama, Y. Kiriyama, J. Okino and M. Kodama, *Tetrahedron Lett.*, 1993, **34**, 7633–7636.

8 (*a*) T. Bechtold, in *Handbook of Natural Colorants*, ed. T. Bechtold and R. Mussak, Wiley, New York, 2009, p. 151; (*b*) B. Nowicka and J. Kruk, *Biochim. Biophys. Acta*, 2010, **1797**, 1587–1605.

9 T. P. Adarsh Krishna, S. Pandaram and A. Ilangovan, *Org. Chem. Front.*, 2019, **6**, 3244–3251.

10 (*a*) N. Tamayo, A. M. Echavarren and M. C. Paredes, *J. Org. Chem.*, 1991, **56**, 6488–6491; (*b*) Ó. d. Frutos, C. Atienza and A. M. Echavarren, *Eur. J. Org. Chem.*, 2001, **2001**, 163–171.

11 (*a*) X. Gan, W. Jiang, W. Wang and L. Hu, *Org. Lett.*, 2009, **11**, 589–592; (*b*) M. K. Hadden, S. A. Hill, J. Davenport, R. L. Matts and B. S. Blagg, *Bioorg. Med. Chem.*, 2009, **17**, 634–640; (*c*) Z. Hassan, I. Ullah, I. Ali, R. A. Khera, I. Knepper, A. Ali, T. Patonay, A. Villinger and P. Langer, *Tetrahedron*, 2013, **69**, 460–469; (*d*) A. d. R. Louvis, N. A. Silva, F. S. Semaan, F. d. C. Da Silva, G. Saramago, L. C. de Souza, B. L. Ferreira, H. C. Castro, J. P. Salles and A. L. Souza, *New J. Chem.*, 2016, **40**, 7643–7656.

12 (*a*) Y. Fujiwara, V. Domingo, I. B. Seiple, R. Gianatassio, M. Del Bel and P. S. Baran, *J. Am. Chem. Soc.*, 2011, **133**, 3292–3295; (*b*) D. Wang, B. Ge, L. Du, H. Miao and Y. Ding, *Synlett*, 2014, **25**, 2895–2898; (*c*) D. Wang, B. Ge, A. Ju, Y. Zhou, C. Xu and Y. Ding, *J. Organomet. Chem.*, 2015, **780**, 30–33; (*d*) S. E. Walker, J. A. Jordan-Hore, D. G. Johnson, S. A. Macgregor and A. L. Lee, *Angew. Chem.*, 2014, **126**, 14096–14099; (*e*) A. Ortega, Á. Rincón, K. L. Jiménez-Aliaga, P. Bermejo-Bescós, S. Martín-Aragón, M. T. Molina and A. G. Csákÿ, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 2183–2187; (*f*) J. Wang, S. Wang, G. Wang, J. Zhang and X.-Q. Yu, *Chem. Commun.*, 2012, **48**, 11769–11771; (*g*) K. Komeyama, T. Kashihara and K. Takaki, *Tetrahedron Lett.*, 2013, **54**, 1084–1086; (*h*) A. Deb, S. Manna, A. Maji, U. Dutta and D. Maiti, *Eur. J. Org. Chem.*, 2013, **2013**, 5251–5256.

13 (*a*) S. Shaaban, A. Jolit, D. Petkova and N. Maulide, *Chem. Commun.*, 2015, **51**, 13902–13905; (*b*) J. F. Bagli and P. L'Écuyer, *Can. J. Chem.*, 1961, **39**, 1037–1048; (*c*) A. Honraedt, F. Le Callonnec, E. Le Grognec, V. Fernandez and F. o.-X. Felpin, *J. Org. Chem.*, 2013, **78**, 4604–4609; (*d*) D. Wang, B. Ge, L. Li, J. Shan and Y. Ding, *J. Org. Chem.*, 2014, **79**, 8607–8613; (*e*) P. Patil, A. Nimonkar and K. G. Akamanchi, *J. Org. Chem.*, 2014, **79**, 2331–2336.

14 (*a*) Y. Yang, J. Lan and J. You, *Chem. Rev.*, 2017, **117**, 8787–8863; (*b*) T. Itahara, *J. Org. Chem.*, 1985, **50**, 5546–5550; (*c*) S. Zhang, F. Song, D. Zhao and J. You, *Chem. Commun.*, 2013, **49**, 4558–4560; (*d*) Y. Moon, Y. Jeong, D. Kook and S. Hong, *Org. Biomol. Chem.*, 2015, **13**, 3918–3923; (*e*) Z. She, Y. Shi, Y. Huang, Y. Cheng, F. Song and J. You, *Chem. Commun.*, 2014, **50**, 13914–13916; (*f*) H. B. Zhang, L. Liu, Y. J. Chen, D. Wang and C. J. Li, *Adv. Synth. Catal.*, 2006, **348**, 229–235; (*g*) T. P. Adarsh Krishna, S. Pandaram and A. Ilangovan, *Org. Chem. Front.*, 2019, **6**, 3244–3251.

15 (*a*) K. B. Jensen, J. Thorhauge, R. G. Hazell and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2001, **40**, 160–163; (*b*) R. Rasappan, M. Hager, A. Gissibl and O. Reiser, *Org. Lett.*, 2006, **8**, 6099–6102; (*c*) B. Suchand, J. Krishna, K. Mritunjoy and G. Satyanarayana, *RSC Adv.*, 2014, **4**, 13941–13945.

16 (*a*) J. H. Jiang, S. S. K. Boominathan, W. P. Hu, C. Y. Chen, J. K. Vandavasi, Y. T. Lin and J. J. Wang, *Eur. J. Org. Chem.*, 2016, **2016**, 2284–2289; (*b*) M. C. Pirrung, K. Park and Z. Li, *Org. Lett.*, 2001, **3**, 365–367; (*c*) Y. Dong, J.-X. Ye, Q.-Q. Luo, T. Mei, A. Shen, P. Huang, J. Chen, X. Zhang, C. Xie and Z.-C. Shi, *Synlett*, 2021, **32**, 1772–1776.