Chinese Chemical Letters 33 (2022) 847–850

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Rhodium(III)-catalyzed benzo[*c*]azepine-1,3(2*H*)-dione synthesis *via* tandem C–H alkylation and intermolecular amination of *N*-methoxylbenzamide with 3-bromo-3,3-difluoropropene

Xu Xu[a,1], Guanyu Zhou[a,1], Guodong Ju[a], Dongjie Wang[a], Bao Li[b,*], Yingsheng Zhao[a,b,*]

[a] *Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical, Engineering and Materials Science, Soochow University, Suzhou 215123, China*
[b] *School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang 453000, China*

A R T I C L E I N F O

Article history:
Received 13 June 2021
Revised 26 July 2021
Accepted 30 July 2021
Available online 4 August 2021

Keywords:
Rhodium catalysis
Tandem reaction
Seven-membered nitrogen heterocycle

A B S T R A C T

Here, a rhodium(III)-catalyzed benzo[*c*]azepine-1,3(2*H*)-dione synthesis *via* tandem C–H alkylation and intramolecular amination of *N*-methoxylbenzamide with 3-bromo-3,3-difluoropropene as the alkylation agent is reported. The substituted benzamides and protected indoles are all tolerated, yielding the corresponding products in moderate to good yields. Further study revealed those bioactive compounds such as piperic acid and a key precursor of Roflumilast all perform well, highlighting the synthetic utility of this method.

Azaheterocyclic compounds exist widely in organic materials, natural products, and pharmaceuticals [1-6], causing researchers to search for efficient methods to construct these skeletons. Azepines and their derivatives are representatives of this category, which include tolazamide (**A**), azelastine (**B**), debromohymenialdisine (**C**) and galanthamine (**D**) (Fig. 1).

Transition-metal-catalyzed C–H bond functionalization is an attractive approach for constructing important synthetic units [7]. In previous reports, *N*-methoxylbenzamides were used as the precursor for the synthesis of cyclic compounds [8]. For example, various groups such as Rovis [9-11], Glorius [12-14], Ackermann [14-17] demonstrated they can directly react with alkenes [9,12,18-25], alkynes [10,13-17,26-28], and diazonium compounds [11,29-31] to form five or six-membered nitrogen heterocyclic compounds; however, the formation of seven-membered nitrogen heterocycles has rarely been reported due to ring strain. Few studies have reported the synthesis of seven-membered nitrogen heterocycles. For example, Glorius's group reported the route to prepare azepinones from benzamides and α,β-unsaturated aldehydes [32]. Cui's group disclosed a Rh(III)-catalyzed cycloaddition of benzamides and vinylcarbenoids to afford azepinones [33]. Shi and coworkers demonstrated that seven-membered nitrogen heterocycles could be obtained by using ArC(O)NH–OBoc as the substrate with a rhodium catalyst [34]. Herein, we report a novel approach for constructing seven-membered nitrogen heterocycles by rhodium-catalyzed direct C-H functionalization of benzamides with 3-bromo-3,3-difluoropropene through tandem C–H alkylation and intramolecular amination (Scheme 1c).

3-Bromo-3,3-difluoropropene is an interesting coupling partner in C–H functionalizations and can provide a 3,3-difluoroallylation product. In 2016, Liu and co-workers firstly reported a palladium-catalyzed 3,3-difluoroallylation reaction with 3-bromo-3,3-difluoropropene as the olefination reagent [35]. In 2017, the group of Zhang disclosed the 3,3-difluoroallylation of pyridones with manganese as the catalyst (Scheme 1a) [36]. Recently, Liu's group reported the alkylation of indole derivatives by using 3-bromo-3,3-difluoropropene [37], followed by the introduction of *N*-iodosuccinimide (NIS), leading to the indole-1(2*H*)-ketone derivatives.

Zeng and co-worker reported a ruthenium-catalyzed alkylation of tertiary phosphines with α,β-unsaturated esters as the alkylation reagents (Scheme 1b) [38]. They found that the alkylation product is realized through the reaction of key intermediate cyclometalated ruthenium complex with a protic acid. Inspired by this result, we speculated when *N*-methoxybenzamide coupled with 3-bromo-3,3-difluoropropene under acidic conditions with a transition-metal-catalyst, the alkylation product **I** would be generated, which then undergoes intramolecular amination, providing a seven-membered nitrogen heterocyclic product (Scheme 2).

---

* Corresponding authors.
E-mail addresses: libao@htu.edu.cn (B. Li), yszhao@suda.edu.cn (Y. Zhao).

[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.cclet.2021.07.070
1001-8417/

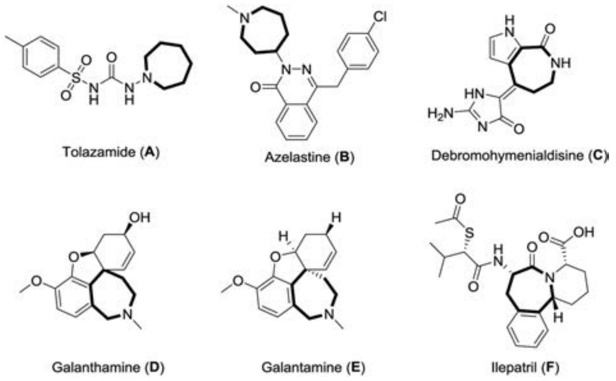
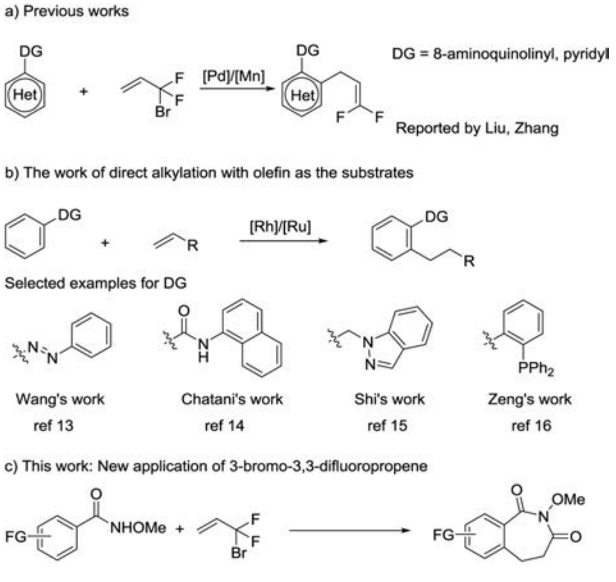
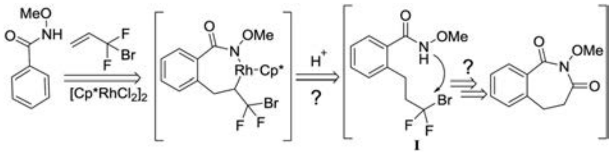


Fig. 1. Selected drugs containing azepine units.

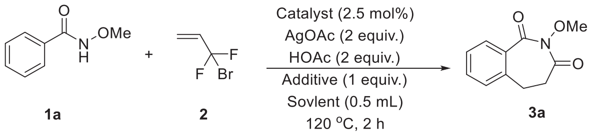


Scheme 1. Reactions of 3-bromo-3,3-difluoropropene.



Scheme 2. A new approach to seven-membered heterocycles.

Table 1
Optimization of conditions.[a]



Entry	Catalyst	Additive	Solvent	Yield (%)[b]
1	$[Cp^*RhCl_2]_2$	-	Hexane	34
2	$[Cp^*IrCl_2]_2$	-	Hexane	5
3	$[(Cymene)RuCl_2]_2$	-	Hexane	0
4	$[Cp^*Co(CO)I_2]$	-	Hexane	0
5	$Pd(OAc)_2$	-	Hexane	0
6	$[Cp^*RhCl_2]_2$	-	Methanol	0
7	$[Cp^*RhCl_2]_2$	-	*t*-AmOH	0
8	$[Cp^*RhCl_2]_2$	-	TFE	0
9	$[Cp^*RhCl_2]_2$	-	HFIP	52
10[c]	$[Cp^*RhCl_2]_2$	-	HFIP	37
11[d]	$[Cp^*RhCl_2]_2$	-	HFIP	20
12[e]	$[Cp^*RhCl_2]_2$	H_2O	HFIP	65
13	$[Cp^*RhCl_2]_2$	H_2O	HFIP	80 (77)[f]
14[g]	$[Cp^*RhCl_2]_2$	H_2O	HFIP	48
15[h]	$[Cp^*RhCl_2]_2$	H_2O	HFIP	0
16	-	H_2O	HFIP	0

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), **2** (0.3 mmol, 1.5 equiv.), catalyst (2.5 mol%), AgOAc (2 equiv.), HOAc (2.0 equiv.) and additive (1 equiv.) in anhydrous solvent (0.5 mL) for 2 h under Ar at 120 °C oil bath.

[b] GC yield with tridecane as the internal standard.

[c] HOAc (30 mol%).

[d] K_2CO_3 instead of HOAc.

[e] H_2O (0.5 equiv).

[f] Yield of isolated product.

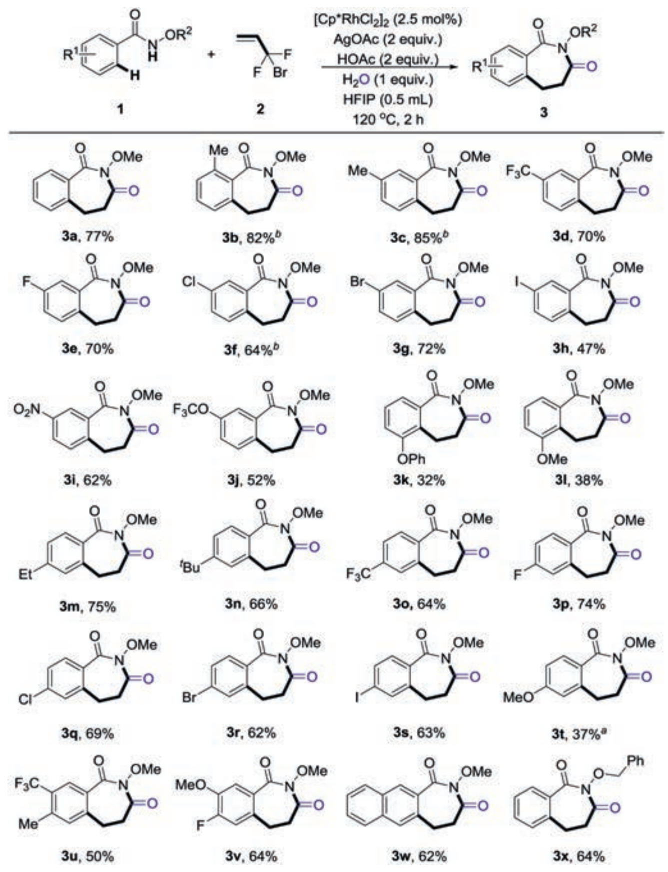
[g] H_2O (2.0 equiv.).

[h] Without AgOAc.

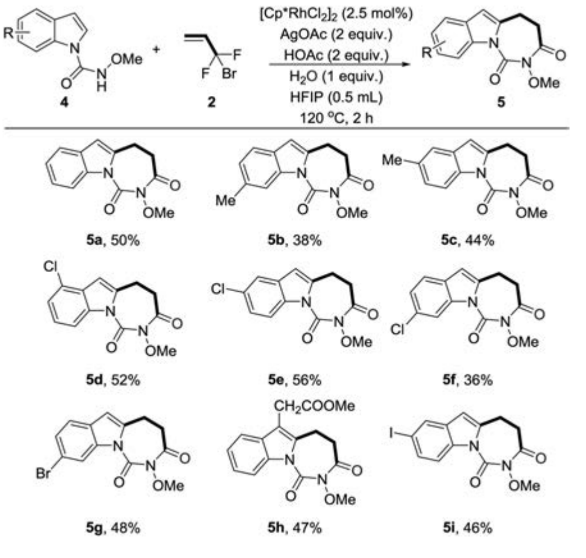
With these conditions in mind, *N*-methoxylbenzamide (**1a**) was treated with 3-bromo-3,3-difluoropropene (**2**) in the presence of $[Cp^*RhCl_2]_2$ (2.5 mol%), AgOAc (200 mol%), and HOAc (200 mol%) at 120 °C in hexane under an argon atmosphere. This reaction provided the desired seven-membered product **3a** in 34% yield in only 2 h (Table 1, entry 1). To explore the indispensable role of the rhodium catalyst in the cyclization reaction, we next screened several catalysts. When $[Cp^*IrCl_2]_2$ was used as the catalyst, we only obtained the desired product **3a** in a trace amount (Table 1, entry 2). Other catalysts such as $[(Cymene)RuCl_2]_2$, $[Cp^*Co(CO)I_2]$, and $Pd(OAc)_2$ also failed to produce the desired product (Table 1, entries 3–5). Several solvents that are commonly used to synthesize five- and six-membered nitrogen heterocyclic compounds using benzamide substrates with a rhodium catalyst (*e.g.*, methanol, *tert*-amyl alcohol, and trifluoroethanol) were not suitable for this system (Table 1, entries 6–8). When hexafluoroisopropanol (HFIP) was used as the solvent, the desired cyclized product **3a** was obtained in 52% yield (Table 1, entry 9). When only a catalytic amount of acetic acid was used, the yield of **3a** decreased to 37%, indicating the importance of a protic acid (Table 1, entry 10). As expected, the yield of **3a** decreased rapidly after K_2CO_3 was added to the reaction system (Table 1, entry 11). To our surprise, when H_2O was used as the additive, the yield of **3a** improved slightly (Table 1, entry 12), suggesting the participation of water in the reaction. The product **3a** was obtained in 80% yield when 1 equiv. water were used (Table 1, entry 13). Control experiments revealed that the rhodium catalyst and silver salt were crucial for this transformation (Table 1, entries 15 and 16).

Having established the optimal reaction conditions, various *N*-methoxy benzamides were evaluated (Scheme 3). First, substrates monosubstituted at the *meta* position with groups including Me, CF_3, F, Cl, Br, I and NO_2 were well-tolerated and provided the corresponding products in medium to good yields (**3c-3i**). Similarly, substrates with electron-withdrawing groups at the *para* position were also compatible in this transformation, leading to the corresponding products in good yields (**3m-3s**); however, The trifluoromethoxy, methoxy, or phenoxy substituted substrates only provide the corresponding products inmedium yields (**3j-3l**, **3t**), and the starting material was recovered. Interestingly, when the substrate was substituted with a methoxy or phenoxy group at *meta* position, the reaction selectively occurred on the side with greater steric hindrance (**3k**, **3l**). Double-substituted substrates performed well, affording the corresponding products in moderate to good yields **(3u-3v**). Substrates such as *N*-methoxy-2-naphthamide and *N*-benzyloxybenzamide were also compatible (**3w-3x**), generating the target products in good yields. Moreover, the single-crystal X-ray analysis of compound **3i** confirmed the presence of a seven-membered ring in its structure (see Supporting information for details).

Indoles are a class of important compounds that are ubiquitous in various bioactive natural compounds. Various *N*-methoxy-

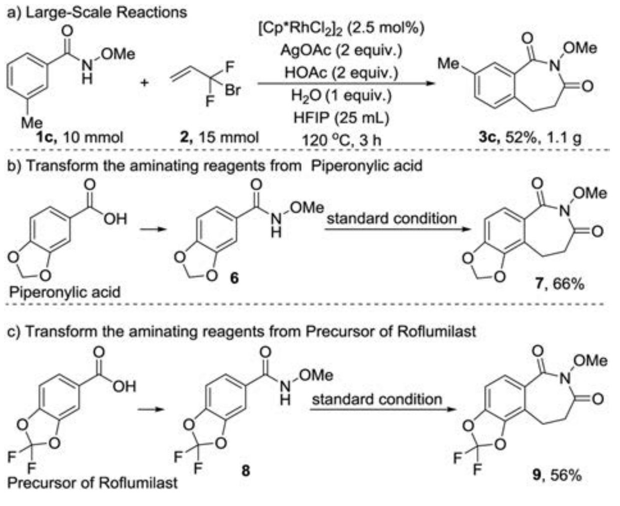


Scheme 3. The scope of benzamides. Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), AgOAc (2 equiv.), HOAc (2 equiv.), $[Cp^*RhCl_2]_2$ (2.5 mol%) and H_2O (1 equiv.) in anhydrous HFIP (0.5 mL) at 120 °C for 2 h under Ar in a sealed tube, isolated yields. [a]**2** (0.4 mmol).



Scheme 4. The sope of indole derivatives. Reaction conditions: **4** (0.2 mmol), **2** (0.3 mmol), AgOAc (2 equiv.), HOAc (2 equiv.), $[Cp^*RhCl_2]_2$ (2.5 mol%) and H_2O (1 equiv.) in anhydrous HFIP (0.5 mL) at 120 °C for 2 h under Ar in a sealed tube, isolated yields.

1*H*-indole-1-carboxamides were prepared and further subjected to standard reaction conditions. A wide variety of 2-methoxy-4,5-dihydro-1*H*-[1,3]diaza[1,7-*a*]indole-1,3(2*H*)-diones were obtained in moderate yield, highlighting the synthetic importance of this transformation (Scheme 4). However several by-products were also found, resulting in the poor yield of this transformation.



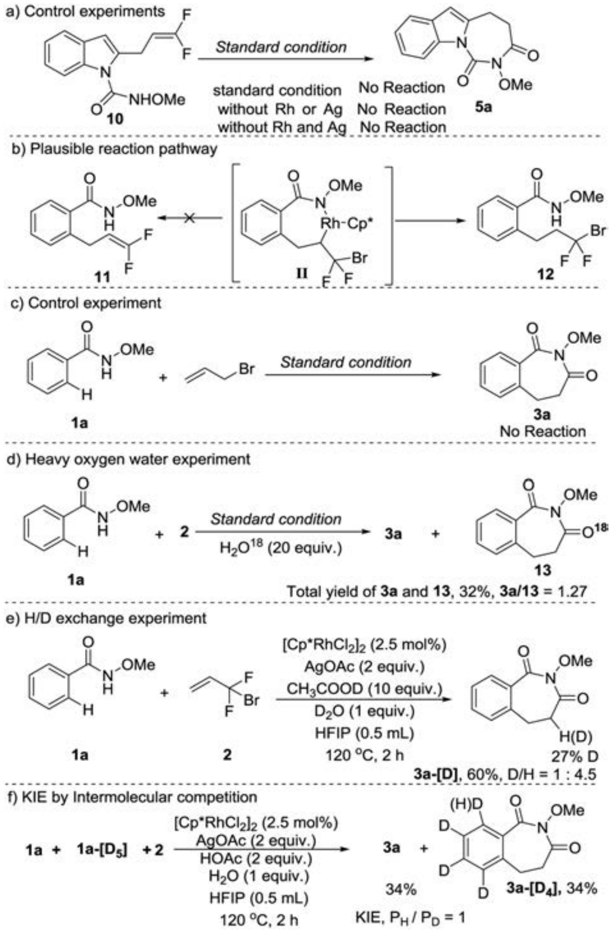
Scheme 5. Synthetic applications.

In addition, to the reaction can easily scaled up to gram-scale, leading to the product **3b** in 52% yield (1.1 g) (Scheme 5a). Piperic acid is an important intermediate of the antibacterial drug oxolinic acid, and can also be used to synthesize dyes and fragrances. It can be transformed into seven-membered nitrogen heterocyclic compound with this new method (Scheme 5b). A key precursor of Roflumilast could also be transformed into a seven-membered nitrogen heterocyclic compound (Scheme 5c).

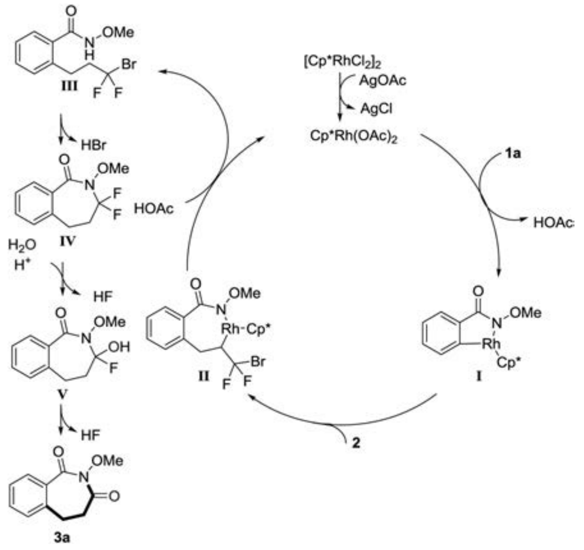
To explore the possible reaction pathways, several control experiments were performed. For example, substrate **10**, which can be prepared by Liu's method [37], was subjected to standard reaction conditions. Interestingly, the seven-membered cyclic compound **5a** was not detected, and the starting material was recovered (Scheme 6a). This may suggest compound **11** was not formed during the catalytic cycle, while product **12** might be generated as the key intermediate (Scheme 6b). To further support this result, heavy-oxygen (^{18}O) water was added into the standard reaction, and the oxygen-18-labeled product **13** was detected (Schemes 6b-d). In addition, when excess deuterated acetic acid was used instead of acetic acid, the deuterated product **3a-[D]** was obtained (Scheme 6e). These results indicate that the alkylation product (**12**) was the key intermediate in this transformation. Finally, a kinetic isotope effect of 1.0 suggests that C-H bond activation is not the rate-limiting step in this reaction (Scheme 6f).

Based on the above experiments and previous reports [39], a plausible reaction pathway is proposed (Scheme 7). The $Cp^*Rh(OAc)_2$ complex can be generated by anion-exchange between the rhodium catalyst and silver salt, which then undergoes *ortho* C-H activation with the benzamide substrate to form the cyclic rhodium intermediate **I**. Key intermediate **II** is further generated through olefin insertion, followed by protonation with acetic acid to release the alkylation product **III**. This provided intermediate **IV** *via* intramolecular amination. The final product **3a** was formed with the assistance of water and acetic acid.

Here, we developed a rhodium(III)-catalyzed tandem C–H alkylation and intramolecular amination of *N*-methoxylbenzamide with 3-bromo-3,3-difluoropropene to prepare the benzo[*c*]azepine-1,3(2*H*)-diones. Various substituted benzamides and protected indoles were well-tolerated, yielding the corresponding products in moderate to good yields. Further study revealed those bioactive compounds such as piperic acid and a key precursor of Roflumilast all performed well, highlighting the importance of this new synthetic method. Preliminary mechanistic studies indicate that the reaction proceeds through alkylation/intermolecular amination process.



Scheme 6. Preliminary mechanistic study.



Scheme 7. Proposed catalytic cycle.

Declaration of competing interest

The authors declare that they have no known competing financial interestsor personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by the Natural Science Foundation of China (No. 21772139), the Jiangsu Province Natural Science Found for Distinguished Young Scholars (No. BK20180041), and the PAPD Project. The project was also supported by the Open Research Fund of the School of Chemistry and Chemical Engineering, Henan Normal University.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2021.07.070.

References

[1] D. O'Hagan, Nat. Prod. Rep. 17 (2000) 435–446.
[2] S.D. Roughley, A.M. Jordan, J. Med. Chem. 54 (2011) 3451–3479.
[3] D. O'Hagan, Nat. Prod. Rep. 14 (1997) 637–651.
[4] T.S. Harrison, L.J. Scott, Drugs 65 (2005) 2309–2336.
[5] D. Zhang, H. Song, Y. Qin, Acc. Chem. Res. 44 (2011) 447–457.
[6] P.F. Salas, C. Herrmann, C. Orvig, Chem. Rev. 113 (2013) 3450–3492.
[7] M. Gulías, J.L. Mascareñas, Angew. Chem. Int. Ed. 55 (2016) 11000–11019.
[8] C. Zhu, R. Wang, J.R. Falck, Chem. Asian J. 7 (2012) 1502–1514.
[9] T.K. Hyster, D.M. Dalton, T. Rovis, Chem. Sci. 6 (2015) 254–258.
[10] T.K. Hyster, T. Rovis, J. Am. Chem. Soc. 132 (2010) 10565–10569.
[11] T.K. Hyster, K.E. Ruhl, T. Rovis, J. Am. Chem. Soc. 135 (2013) 5364–5367.
[12] F.W. Patureau, T. Besset, F. Glorius, Angew. Chem. Int. Ed. 50 (2011) 1064–1067.
[13] H. Wang, C. Grohmann, C. Nimphius, F. Glorius, J. Am. Chem. Soc. 134 (2012) 19592–19595.
[14] D.G. Yu, F. de Azambuja, T. Gensch, C.G. Daniliuc, F. Glorius, Angew. Chem. Int. Ed. 53 (2014) 9650–9654.
[15] L. Ackermann, A.V. Lygin, N. Hofmann, Angew. Chem. Int. Ed. 50 (2011) 6379–6382.
[16] (d) L. Ackermann, S. Fenner, Org. Lett. 13 (2011) 6548–6551.
[17] H. Huang, S. Nakanowatari, L. Ackermann, Org. Lett. 19 (2017) 4620–4623.
[18] F. Wang, G. Song, X. Li, Org. Lett. 12 (2010) 5430–5433.
[19] C. Zhu, J.R. Falck, Org. Lett. 13 (2011) 1214–1217.
[20] D.D. Li, T.T. Yuan, G.W. Wang, Chem. Commun. 47 (2011) 12789–12791.
[21] B. Li, J. Ma, N. Wang, et al., Org. Lett. 14 (2012) 736–739.
[22] Z.J. Jia, C. Merten, R. Gontla, et al., Angew. Chem. Int. Ed. 56 (2017) 2429–2434.
[23] J.Q. Wu, S.S. Zhang, H. Gao, et al., J. Am. Chem. Soc. 139 (2017) 3537–3545.
[24] K. Ghosh, Y. Nishii, M. Miura, ACS Catal. 9 (2019) 11455–11460.
[25] X. Li, T. Huang, Y. Song, et al., Org. Lett. 22 (2020) 5925–5930.
[26] N. Guimond, C. Gouliaras, K. Fagnou, J. Am. Chem. Soc. 132 (2010) 6908–6909.
[27] N.S. Upadhyay, V.H. Thorat, R. Sato, et al., Green Chem. 19 (2017) 3219–3224.
[28] R. Mei, N. Sauermann, J.C.A. Oliveira, L. Ackermann, J. Am. Chem. Soc. 140 (2018) 7913–7921.
[29] B. Ye, N. Cramer, Angew. Chem. Int. Ed. 53 (2014) 7896–7899.
[30] L. Shi, K. Yu, B. Wang, Chem. Commun. 51 (2015) 17277–17280.
[31] Y. Wu, P. Sun, K. Zhang, et al., J. Org. Chem. 81 (2016) 2166–2173.
[32] Z. Shi, C. Grohmann, F. Glorius, Angew. Chem. Int. Ed. 52 (2013) 5393–5397.
[33] S. Cui, Y. Zhang, D. Wang, Q. Wu, Chem. Sci. 4 (2013) 3912–3916.
[34] C. Ji, Q. Xu, M. Shi, Adv. Synth. Catal. 359 (2017) 974–983.
[35] C. Li, D. Zhang, W. Zhu, P. Wan, H. Liu, Org. Chem. Front. 3 (2016) 1080–1083.
[36] J. Ni, H. Zhao, A. Zhang, Org. Lett. 19 (2017) 3159–3162.
[37] S. Zhao, C. Li, B. Xu, H. Liu, Chin. J. Org. Chem. 40 (2020) 1549–1562.
[38] J.W. Li, L.N. Wang, M. Li, et al., Org. Lett. 22 (2020) 1331–1335.
[39] X. Jiang, G. Wang, Z. Zheng, et al., Org. Lett. 22 (2020) 9762–9766.