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Oxidative spirolactonisation for modular access of γ-spirolactones *via* a radical tandem annulation pathway

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ABSTRACT

An oxidative annulation of 2-arylidene-1,3-indanediones with Meldrum's acid has been developed for the divergent syntheses of spirolactones with a spirocenter located at the γ-position with respect to the carbonyl group. This heteroannulation protocol tolerates various functional groups and delivers moderate-to-good product yields. Interestingly, the reaction outcomes are exclusively controlled by the reaction oxidant/medium. This annulation strategy can also be executed in the flow system with decent product yields. Control experiments revealed that the reaction proceeds *via* a radical tandem annulation pathway.

γ-Spirolactones are essential and distinctive functional heterocyclic units embodied in many biologically active and natural products [1–5], clinical pharmaceuticals (such as spironolactones) and chemiluminescent materials [6–10]. Considerable research has been dedicated to investigating synthetic pathways for reaching these valuable compounds, for instance intramolecular oxidative dearomatisation [11–22], *N*-heterocyclic carbene (NHC)-catalysed heteroannulation [23–27], metal-catalysed cyclisation/spirolactonisation [28–32] and other reactions [33–36]. Despite these remarkable progresses, it is highly desirable to explore a versatile and efficient synthetic protocol aiming at the direct construction of γ-spirolactones.

In 2013, Krische and co-workers reported a Ru(0)-catalysed hydrohydroxyalkylation of acrylates with diols for accessing the γ-spirolactones (Scheme 1A-i) [37]. Later, Marchalín and Daïch showed the synthesis of the γ-spirolactones using a multi-step Pt(II)-catalysed carbocyclisation of benzaldehyde bearing alkynenitrile (Scheme 1A-ii) [38]. Recently, γ-spirolactones with contiguous sterocenters were made through a specially designed dinuclear zinc complex-catalysed asymmetric tandem reaction of α–hydroxy-1-indanone (Scheme 1A-iii) [39].

In fact, the synthesis of γ-spirolactones with tri-carbonyl group remains sporadically investigated. In 2000, Chatani and Murai unveiled prominent research on the ruthenium-catalysed intermolecular cyclocoupling between indane-1,2,3-trione, ethylene (3 atm) and carbon monoxide (5 atm), leading to the formation of the γ-spirolactone in 51% yield (Scheme 1B-i) [40]. Kim independently reported a similar transformation using an indium-mediated protocol (Scheme 1B-ii) [41]. Nevertheless, the reaction between allylic bromide and ninhydrin gave rise to mixtures of γ-hydroxyester derivatives and the target γ-spirolactones. After column separation and the treatment with pyridinium *p*-toluenesulfonate (PPTS), the γ-spirolactones was isolated in 64% yield. Despite these attempts to synthesize γ-spirolactones, the development of more concise synthetic route under milder reaction conditions remains challenging. In addition, the construction of α,β-disubstituted γ-spirolactones is still less explored (one example of 4-methylene-3-phenyl-3,4-dihydro-5*H*-spiro[furan-2,2′-indene]−1′,3′,5-trione (66%) was shown [41]. Hence the exploration of an operationally simple strategy for accessing these valuable γ-spirolactones remains a prominent goal in organic synthesis. In continuation of our former works on heterocycle construction [42–45] and annulation reaction [46–48], herein we present an oxidative annulation of 2-arylidene-1,3-indanediones for the divergent synthesis of γ-spirolactones (Scheme 1C).

Our initial attempt employed 2-benzylideneindane-1,3–dione (**1a**) and Meldrum's acid (**2**) as the prototypical substrates for opti-

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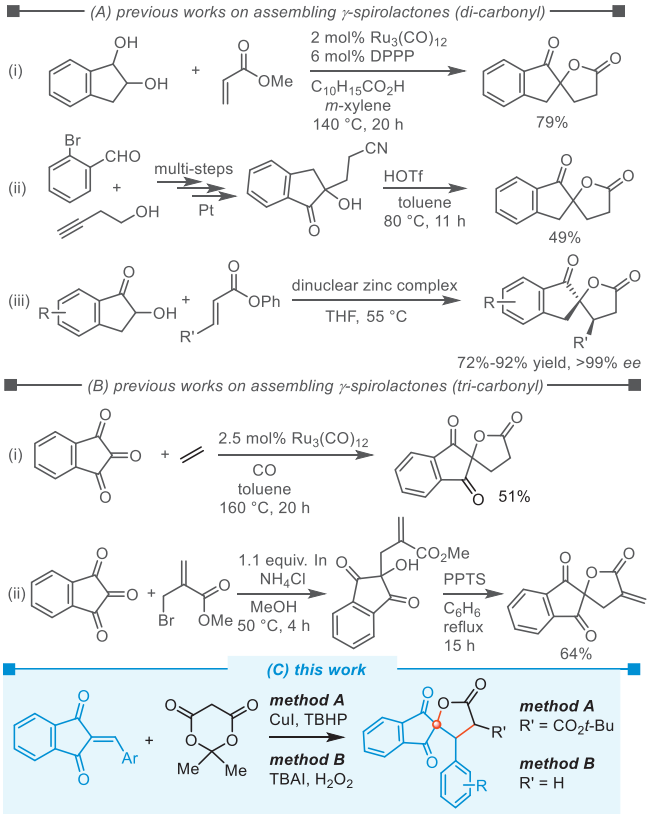


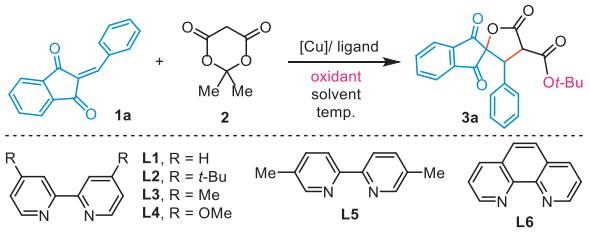
Scheme 1. Previous methods and our design for γ-spirolactones synthesis.

mizing the oxidative annulation reaction parameters (Table 1). The choice of catalyst and oxidant were critical to succeed this coupling reaction. TBHP and DTBP gave the desired product **3a** in 55% and 52% yield, respectively (entries 1 and 4), while TBPB was entirely ineffective in this reaction (entry 3). The spirolactonisation did not occur in the absence of ligand (entry 2). The addition of 4,4′-dimethyl-2,2′-dipyridyl (**L3**) was found to be superior in affording the product **3a** in 71% yield (entry 7). Other copper salts, such as CuBr, $Cu(OAc)_2$ and Cu_2O were also evaluated, yet their efficacy were less than CuI (entries 7 *vs.* 11–13). Increasing the copper catalyst loading to 20 mol% gave comparable result to that of 10 mol% (entries 7 *vs.* 14). A brief survey of solvents showed that DCE is the most appropriate solvent. Increasing the reaction temperature to 90 °C led to a slightly lower yield of **3a** (entry 19).

With the optimised reaction conditions, we next commenced to investigate the scope of 2-arylidene-1,3-indanediones **1** with Meldrum's acid (**2**) and the results are summarized in Scheme 2. Various 2-arylidene-1,3-indanediones were subjected in the spirolactonisation and the corresponding γ-spirolactones were successfully delivered. To further evaluate the practical utility of this methodology, a gram-scale experiment was conducted, producing **3a** in 65% yield. The structure of **3a** was unambiguously confirmed by single-crystal X-ray diffraction analysis (CCDC: 2175973). It is worth noting that this reaction protocol tolerated the chloro– (products **3b**, **3g**) and bromo–groups (products **3h**, **3i**), providing an excellent opportunity for further functionalisation *via* well-known cross-coupling processes. Despite the possible steric hindrance arising from the substitution at the *ortho*-position of the phenyl ring, **1i** was a feasible coupling partner that did not affect the reaction efficiency, yielding the desired product in 64% yield.

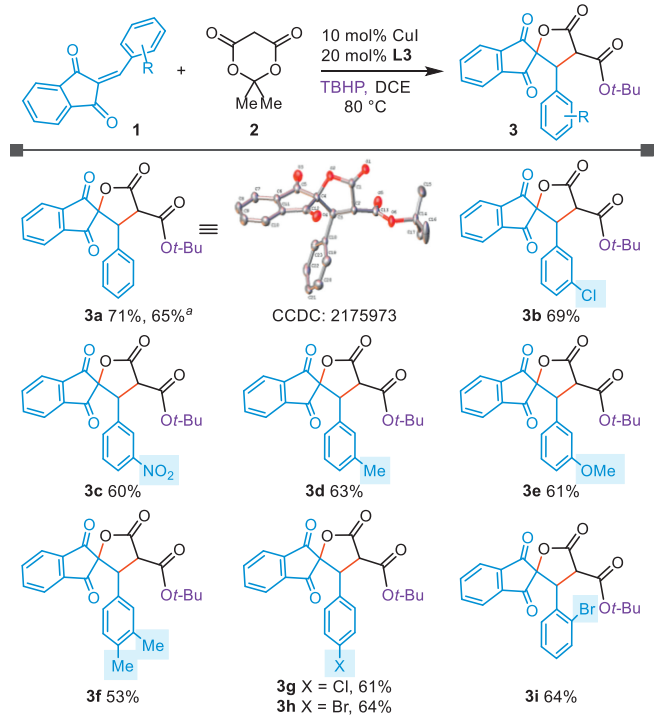
The outcome of a chemical transformation can often be divergent when the reaction conditions are modified. To our delight, under the reciprocal metal-free conditions, a new series of prod-

Table 1
Optimization of the reaction conditions.[a]

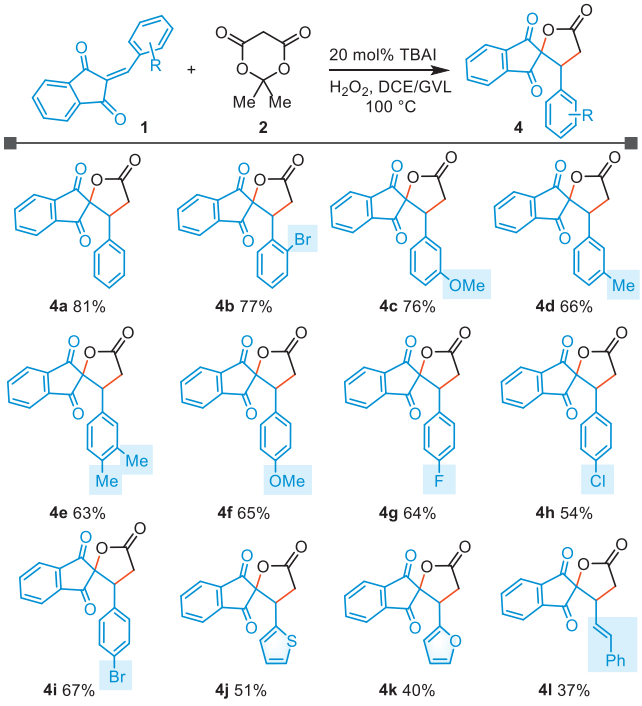


Entry	[Cu]	Ligand	Oxidant	Solvent	Yield (%)[b]
1	CuI	**L1**	TBHP	DCE	55
2	CuI	–	TBHP	DCE	trace
3	CuI	**L1**	TBPB	DCE	trace
4	CuI	**L1**	DTBP	DCE	52
5[c]	CuI	**L1**	TBHP	DCE	51
6	CuI	**L2**	TBHP	DCE	64
7	CuI	**L3**	TBHP	DCE	71
8	CuI	**L4**	TBHP	DCE	57
9	CuI	**L5**	TBHP	DCE	61
10	CuI	**L6**	TBHP	DCE	25
11	CuBr	**L3**	TBHP	DCE	49
12	$Cu(OAc)_2$	**L3**	TBHP	DCE	33
13	Cu_2O	**L3**	TBHP	DCE	36
14[d]	CuI	**L3**	TBHP	DCE	65
15	CuI	**L3**	TBHP	PhCl	40
16	CuI	**L3**	TBHP	MeCN	31
17	CuI	**L3**	TBHP	THF	trace
18	CuI	**L3**	TBHP	$CHCl_3$	trace
19[e]	CuI	**L3**	TBHP	DCE	66

[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.2 mmol), Cu salt (10 mol%), ligand (20 mol%), and TBHP (0.6 mmol, 70% aqueous solution) or oxidant (0.6 mmol) in solvent (1 mL) at 80 °C for 5 h.
[b] Isolated yield.
[c] TBHP (5.5 mol/L in decane) was used.
[d] 20 mol% of CuI was used.
[e] 90 °C was used.



Scheme 2. Copper-catalysed spirolactonisation of 2-benzylideneindane-1,3-diones. Reaction conditions: **1** (0.3 mmol), **2** (0.2 mmol), CuI (10 mol%), **L3** (4,4′-dimethyl-2,2′-dipyridyl) (20 mol%), and TBHP (0.6 mmol, 70% aqueous solution) in DCE (1 mL) at 80 °C for 5 h. Isolated yields were reported. [a] A gram-scale experiment was conducted.

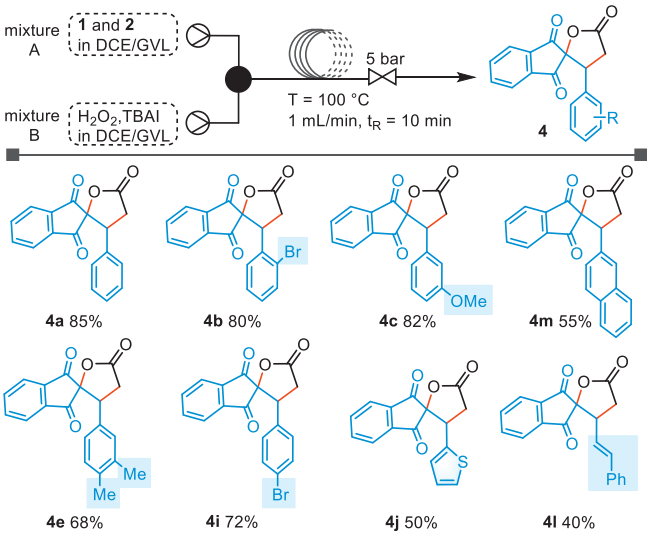


Scheme 3. TBAI-catalysed spirolactonisation of 2-benzylideneindane-1,3-diones. Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), TBAI (20 mol%), and H_2O_2 (0.6 mmol, 30% aqueous solution) in DCE/GVL (v/v = 1:1, 1 mL) at 100 °C for 5 h. Isolated yields were reported.

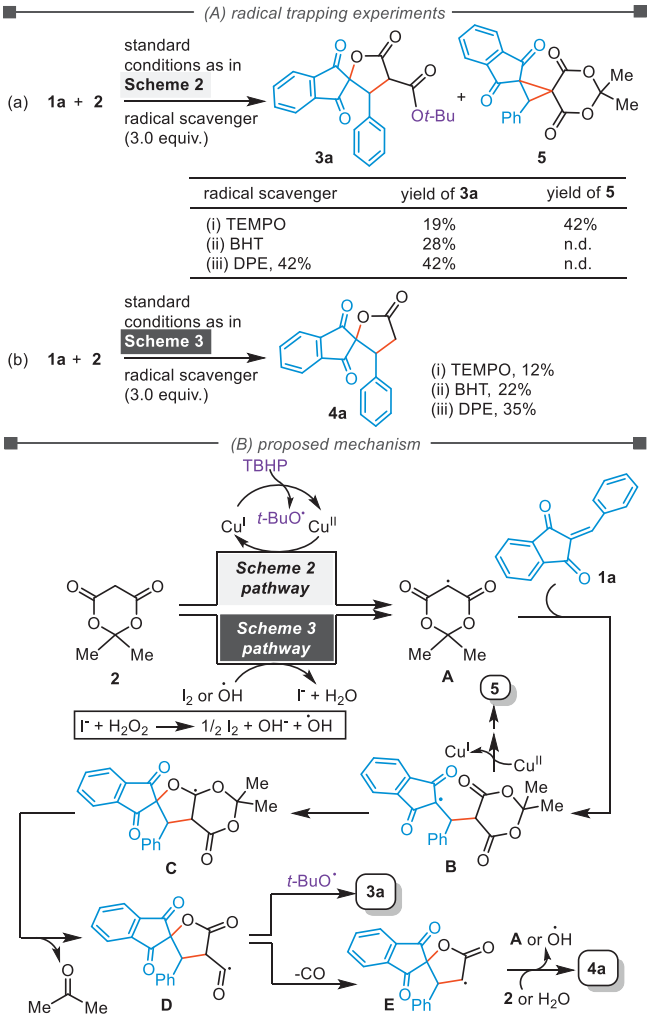
uct **4** was successfully attained (Scheme 3). This product framework thus even provides more manipulation opportunity for possible functionalization, such as diarylation at the α-position [49]. Attempt conducting the reaction with **1a** and **2** under TBAI (20 mol%) and 3 equiv. of H_2O_2 in the solvent mixture of DCE/GVL (γ-valerolactone) at 100 °C, the desired product **4a** was obtained in 81% yield (see Supporting information for optimization of reaction conditions). Encouraged by this fruitful result, representative substrates with substituents at the *ortho*-, *meta*-, and *para*-position of the phenyl ring were tested (products **4b**-**4f**). Substrates bearing halo substituent at *ortho*- and/or *para*-position were also well-tolerated with good product yields (products **4b**, **4g**, **4h** and **4i**). Particularly noteworthy is that this transformation was able to accommodate thienyl-, furyl-, and styryl-containing substrates, providing the corresponding products **4j**, **4k** and **4l**, respectively.

Flow chemistry has become a valuable tool in many organic syntheses [50–52] and often enriches the productivity by improving the reactivity through better heat and mass transfer. To demonstrate the synthetic utility of spirolactonisation, we examined the reaction in a continuous flow protocol using a Vapourtec flow reactor (Scheme 4). Under the flow conditions, the reaction proceeded efficiently to give the corresponding γ-spirolactones in improved yields with a significantly shorten reaction time (10 min *vs.* 5 h) when compared to previous studies.

To elucidate the reaction mechanism, radical-trapping experiments were performed (Scheme 5A). When 3.0 equiv. of radical scavengers, such as TEMPO, BHT, or 1,1-diphenylethylene (DPE) was added to the reaction, the product yields of **3a** and **4a** were decreased. The corresponding radical-quenched products were also detected using electrospray ionisation-time-of-flight-mass spectrometry (ESI-TOF-MS) (see Supporting information for details), suggesting that the reaction likely involves a radical mechanism. Furthermore, product **5** was isolated in the copper-catalysed spirolactonisation of 2-benzylideneindane-1,3-diones with the addition of TEMPO (Scheme 5A, a(i)). Based on the aforementioned mech-



Scheme 4. TBAI-catalysed spirolactonisation of 2-benzylideneindane-1,3–dione in flow conditions. Reaction conditions: Mixture A: 1 (5.0 mmol), **2** (7.5 mmol) in DCE:GVL = 1:1 (20 mL). Mixture B: 30 wt% H_2O_2 (15.0 mmol), TBAI (1.0 mmol) in DCE:GVL = 1:1 (20 mL). Mixture A and B were each pumped at 0.5 mL/min and the streams were combined in a T-mixer followed by a coiled reactor with the rate of 1 mL/min (vol = 10 mL; t_R = 10 min; T = 100 °C) equipped with a 5 bar back pressure valve. Isolated yields were reported.



Scheme 5. Radical-trapping experiments and proposed mechanism.

anistic studies [53] and experimental results, a postulated mechanism is illustrated in Scheme 5B. Initially, radical intermediate **A** is generated through the Cu(I)/TBHP oxidation system (Scheme 5B, for Scheme 2 pathway). Alternatively, the reaction is suggested to begin with the decomposition of H_2O_2 catalysed by TBAI to generate hydroxyl radical and I_2, which capture an α-hydrogen atom from Meldrum's acid **2** to form radical intermediate **A** (Scheme 5B, for Scheme 3 pathway). Species **A** then generates radical **B** *via* a C=C bond addition step. The resulting **B** reacts with copper(II) species, followed by reductive elimination to afford product **5** [54]. Subsequently, radical **B** undergoes a radical addition to the C=O bond to give the geometry-favored five-membered ring radical **C**. The radical **C** is likely thermally-unstable and can be easily converted to radical **D** with an expulsion of acetone. With the help of *t*-BuO·, the radical trapping reaction occurs with **D**, resulting in the formation of product **3a**. Otherwise, in the absence of trapping species *t*-BuO· (*i.e.*, Scheme 3 pathway), the intermediate **D** thus undergoes a decarbonylation pathway and subsequent proton abstraction to give product **4a**. It is of note that all the proposed intermediates **A**, **B**, **C**, **D** and **E** were successfully captured by radical scavengers, and the resulting intermediates were detected by ESI-TOF-MS (see Supporting information for details).

In summary, we have developed a divergent method for accessing β-arylspirolactones with a spirocenter at the γ-position to the lactone-moiety. Interestingly, the CuI/**L3**/TBHP catalyst system provided a range of γ-spirolactones **3** in good yields, while the metal-free system allowed for the synthesis of various γ-spirolactones **4** with complementary structures. The mild reaction conditions offered decent functional group compatibility, especially the remained intact –Br and –Cl groups which are advantages to the inherent shortcomings of existing metal-catalyzed protocols. Notably, the metal-free protocol was found applicable even in a flow system, resulting in significantly shorter reaction times. Mechanistic investigation revealed that this annulation process proceeds through a radical pathway, with specific intermediates being detected by ESI-TOF-MS.

Declaration of competing interest

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

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.109565.

References

[1] A. Bartoli, F. Rodier, L. Commeiras, J. Parrain, G. Chouraqui, Nat. Prod. Rep. 28 (2011) 763–782.
[2] A. Quintavalla, Curr. Med. Chem. 25 (2018) 917–962.
[3] P. Liu, S. Hong, S.M. Weinreb, J. Am. Chem. Soc. 130 (2008) 7562–7563.
[4] Y. Fan, H. Zhang, Y. Zhou, et al., J. Am. Chem. Soc. 137 (2015) 138–141.
[5] S.S. Thorat, M.N. Palange, R. Kontham, ACS Omega 3 (2018) 7036–7045.
[6] C.M. Marson, Chem. Soc. Rev. 40 (2011) 5514–5533.
[7] K. Hiesinger, D. Dar'in, E. Proschak, M. Krasavin, J. Med. Chem. 64 (2021) 150–183.
[8] B. Bister, D. Bischoff, M. Ströbele, et al., Angew. Chem. Int. Ed. 43 (2004) 2574–2576.
[9] A.M. Sherwood, R.S. Crowley, K.F. Paton, et al., J. Med. Chem. 60 (2017) 3866–3878.
[10] T.Z. Li, X.T. Yang, J.P. Wang, et al., Org. Lett. 23 (2021) 8380–8384.
[11] S. Rodriguez, P. Wipf, Synthesis 17 (2004) 2767–2783.
[12] W.T. Wu, L. Zhang, S.L. You, Chem. Soc. Rev. 45 (2016) 1570–1580.
[13] A. Yoshimura, V.V. Zhdankin, Chem. Rev. 116 (2016) 3328–3435.
[14] R. Kumar, F.V. Singh, N. Takenaga, T. Dohi, Chem. Asian J. 17 (2022) e202101115.
[15] M. Uyanik, T. Yasui, K. Ishihara, Angew. Chem. Int. Ed. 49 (2010) 2175–2177.
[16] M. Uyanik, T. Yasui, K. Ishihara, Angew. Chem. Int. Ed. 52 (2013) 9215–9218.
[17] T. Dohi, N. Takenaga, T. Nakae, et al., J. Am. Chem. Soc. 135 (2013) 4558–4566.
[18] C. Hempel, C. Maichle-Mössmer, M.A. Pericàsc, B.J. Nachtsheim, Adv. Synth. Catal. 359 (2017) 2931–2941.
[19] T. Dohi, H. Sasa, K. Miyazaki, et al., J. Org. Chem. 82 (2017) 11954–11960.
[20] H. Li, E. Subbotina, A. Bunrit, F. Wang, J.S.M. Samec, Chem. Sci. 10 (2019) 3681–3686.
[21] M. Uyanik, T. Kato, N. Sahara, O. Katade, K. Ishihara, ACS Catal. 9 (2019) 11619–11626.
[22] C. Zhang, F. Bu, C. Zeng, et al., CCS Chem. 4 (2022) 1199–1207.
[23] Y. Liu, X. Zhang, R. Zeng, et al., Molecules 22 (2017) 1882.
[24] J.L. Li, B. Sahoo, C.G. Daniliuc, F. Glorius, Angew. Chem. Int. Ed. 53 (2014) 10515–10519.
[25] Y. Gao, Y. Ma, C. Xu, et al., Adv. Synth. Catal. 360 (2018) 479–484.
[26] H. Zhang, Q. Ma, D. Liu, X. Hui, Chem. Commun. 55 (2019) 298–301.
[27] Y. Gao, D. Liu, Z. Fu, W. Huang, Org. Lett. 21 (2019) 926–930.
[28] Y. Mostinski, D. Lankri, D. Tsvelikhovsky, Synthesis 49 (2017) 2361–2373.
[29] Q. Deng, H. Wadepohl, L.H. Gade, J. Am. Chem. Soc. 134 (2012) 2946–2949.
[30] Y. Qiu, B. Yang, T. Jiang, C. Zhu, J.E. Bäckvall, Angew. Chem. Int. Ed. 56 (2017) 3221–3225.
[31] N.A. Weires, Y. Slutskyy, L.E. Overman, Angew. Chem. Int. Ed. 58 (2019) 8561–8565.
[32] B. Lin, T. Yang, D. Zhang, et al., Angew. Chem. Int. Ed. 61 (2022) e202201739.
[33] S. Sternativo, A. Calandriello, F. Costantino, et al., Angew. Chem. Int. Ed. 50 (2011) 9382–9385.
[34] B. Cui, J. Zuo, J. Zhao, et al., J. Org. Chem. 79 (2014) 5305–5314.
[35] J. Cao, S. Dong, D. Jiang, et al., J. Org. Chem. 82 (2017) 4186–4193.
[36] X. Sun, M. Zhou, J. Zhu, et al., Org. Chem. Front. 9 (2022) 2316–2321.
[37] E.L. McInturff, J. Mowat, A.R. Waldeck, M.J. Krische, J. Am. Chem. Soc. 135 (2013) 17230–17235.
[38] P. Šafář, Š. Marchalín, M. Šoral, J. Moncol, A. Daïch, Org. Lett. 19 (2017) 4742–4745.
[39] M.M. Liu, X.C. Yang, Y.Z. Hua, J.B. Chang, M.C. Wang, Org. Lett. 21 (2019) 7089–7093.
[40] M. Tobisu, N. Chatani, T. Asaumi, et al., J. Am. Chem. Soc. 122 (2000) 12663–12674.
[41] K.Y. Lee, D.Y. Park, J.N. Kim, Bull. Korean Chem. Soc. 27 (2006) 1489–1492.
[42] Q. Wu, L. Li, B. Xu, et al., Green Synth. Catal. 4 (2023) 150–153.
[43] G. Xu, C. Jia, X. Wang, et al., Org. Lett. 24 (2022) 1060–1065.
[44] J. Duan, G. Xu, B. Rong, et al., Green Synth. Catal. 2 (2021) 237–240.
[45] S. Zhang, G. Xu, H. Yan, et al., Chin. Chem. Lett. 33 (2022) 5128–5131.
[46] M. Li, F.Y. Kwong, Angew. Chem. Int. Ed. 57 (2018) 6512–6516.
[47] T. Liu, K.B. Gan, R.L. Zhong, X. He, F.Y. Kwong, Org. Lett. 24 (2022) 6805–6809.
[48] X. He, R. Li, P.Y. Choy, et al., Chem. Sci. 13 (2022) 13617–13622.
[49] P.Y. Yeung, K.H. Chung, F.Y. Kwong, Org. Lett. 13 (2011) 2912–2915.
[50] M.B. Plutschack, B. Pieber, K. Gilmore, P.H. Seeberger, Chem. Rev. 117 (2017) 11796–11893.
[51] C.A. Hone, C.O. Kappe, Chem. Methods 1 (2021) 454–467.
[52] W.C. Fu, P.M. MacQueen, T.F. Jamison, Chem. Soc. Rev. 50 (2021) 7378–7394.
[53] A.S. Ivanov, Chem. Soc. Rev. 37 (2008) 789–811.
[54] S. Manna, A.P. Antonchick, Angew. Chem. Int. Ed. 54 (2015) 14845–14848.