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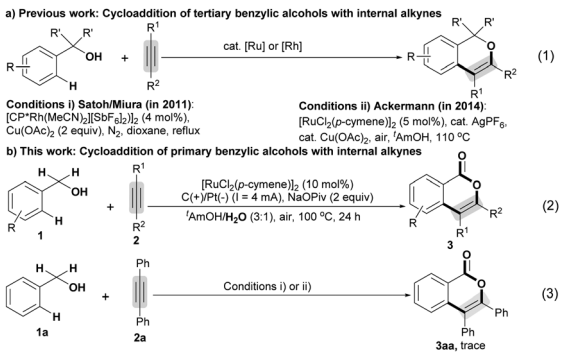
Ruthenium(II)-catalyzed electrooxidative [4+2] annulation of benzylic alcohols with internal alkynes: entry to isocoumarins†

Mu-Jia Luo,[a] Ming Hu,[b] Ren-Jie Song,*[b] De-Liang He*[a] and Jin-Heng Li *[abc]

A new ruthenium(II)-catalyzed electrooxidative [4+2] annulation of primary benzylic alcohols with internal alkynes is described, which enables benzylic alcohols as weakly directing group precursors to access isocoumarins *via* multiple C–H functionalization. The reaction works well with a broad substrate scope, tolerates a wide range of functional groups, and incorporates practically the isocoumarin unit into diverse bioactive molecules. Mechanistic studies indicate that activation of aryl C(sp^2)–H bonds is achieved through the generation of the active benzoyloxy–Ru(II) intermediates *via* oxidation of benzylic alcohols using an electrooxidative Ru(II) catalyst.

A transition-metal-catalyzed annulation reaction involving intermolecular C–H functionalization has become a powerful and atom-economic tool for building complex cyclic systems from readily available starting materials,[1,2] which avoids prefunctionalization of the C–H bonds through the generation of organometallic C-[M] species at the *ipso* position. However, the development of such a method is generally hindered by the requirement of strongly *ortho*-coordinating directing groups (often nitrogen-based groups), thereby limiting the cyclic structure choice partly because these directing group elements are generally integrated into the resulting cyclic frameworks.[1] Recently, strategies for annulation of substrates, especially acid derivatives[2–4] and alcohols,[5] containing a weakly *ortho*-coordinating directing group with 2π components using various transition-metal (*e.g.*, Pd, Rh, Ir, Co, Ru) catalysts have been successfully established, which enabled the formation of five-membered to six-membered cyclic systems. Attractive methods include transition-metal-catalyzed annulation with aryl-containing alcohols through C–H activation,[5] and offer a concise site-selective C–H activation to construct valuable *O*-heterocycles. However, such successful examples are rare and are all limited to tertiary alcohols presumably due to the challenge in the competitive oxidation of primary and secondary alcohols to carbonyl compounds and their relatively weaker coordination ability. Typically, the Satoh/Miura group[5d] and the Ackermann group[5e] have independently reported oxidative C–H activation and annulation of tertiary benzylic and allyl alcohols with alkynes using the Rh or Ru catalysts, which is driven by the use of the weakly coordinating aliphatic hydroxyl groups. We envisioned that by using the transition-metal oxidative catalysis, benzylic alcohols would be transformed *in situ* into higher reactive intermediates containing an effective weakly coordinating directing group, thereby offering a conceptually novel approach for C–H functionalization and annulation.

Herein, we report a new ruthenium(II)-catalyzed electrooxidative[3w,4f,6] [4+2] annulation of primary benzylic alcohols with internal alkynes that access isocoumarins *via* the formation of multiple chemical bonds (*e.g.*, C(sp^2)–C(sp^2) bond, and C(sp^2)–O bonds) (Scheme 1b). Mechanistic studies show that benzylic alcohols are converted into effective benzoyloxy–Ru(II) intermediates, not aryl acids, for achieving C–H functionalization. Notably, isocoumarins are frequently found in natural products and pharmaceuticals with strong bioactivities.[7]



Scheme 1 Ru-catalyzed [4+2] annulation of benzylic alcohols.

[a] State Key Laboratory of Chemo/Biosensing and Chemometrics, Hunan University, Changsha 410082, China. E-mail: delianghe@hnu.edu.cn, jhli@hnu.edu.cn
[b] Key Laboratory of Jiangxi Province for Persistent Pollutants Control and Resources Recycle, Nanchang Hangkong University, Nanchang 330063, China. E-mail: srj0731@hnu.edu.cn
[c] State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

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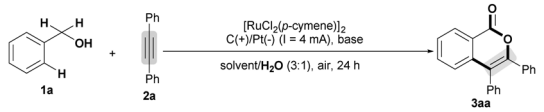
Initial experiments began with annulation of benzyl alcohol **1a** with 1,2-diphenylethyne **2a** under the reported reaction conditions[5d,e] (eqn (3); Scheme 1). The annulation reaction could not proceed when using the reported Rh[5d] or Ru[5e] catalyst combined with the conventional oxidants, such as $AgSbF_6/Cu(OAc)_2$/air, $Cu(OAc)_2$ and O_2 (eqn (3)). As shown in Table 1, the reaction could occur to enable access to the desired isocoumarin **3aa** in 64% yield under the electrocatalysis conditions ($[RuCl_2(p\text{-cymene})]_2$, NaOPiv, a graphite rod anode and a platinum plate cathode at 4 mA constant current in ^{t}AmOH/H_2O at 100 °C) (entry 1). Raising the reaction temperature to 110 °C caused no further improvement of the yield (entry 2), but lowering the temperature to 80 °C dramatically decreased the yield (entry 3). A higher (8 mA) and a lower (2 mA) constant current both had a negative effect (entries 4 and 5). In the absence of electric current (entry 6), the reaction could not form **3aa** in the presence of 10 mol% $[RuCl_2(p\text{-cymene})]_2$, but it afforded 51% yield of **3aa** at 100 mol% $[RuCl_2(p\text{-cymene})]_2$ (entry 7). Brief screening of bases indicated that 2 equiv. NaOPiv was optimal (entries 1 and 8–12), as other bases, including NaOAc, KOAc, Na_2CO_3 and K_2CO_3, were less effective. Using a graphite rod cathode instead of a platinum plate cathode exhibited lower efficiency (entry 13). Other solvents, such as ^{t}BuOH, HFIP and MeCN, were less reactive (entries 14–16). The reaction is specific to the Ru catalyst, as two Ru catalysts, $[RuCl_2(COD)]$ and $[Ru(bpy)_3]Cl_2$, showed no catalytic activity (entry 17) and the reaction could not proceed without Ru catalysts (entry 18). Reducing the loading of $[RuCl_2(p\text{-cymene})]_2$ to 5 mol% led to diminishing yield (entry 19), and raising the loading to 15 mol% gave the similar results to that obtained at 10 mol% (entry 20). However, the yield of **3aa** decreased in either argon (entry 21) or O_2 (entry 22) replaced by air, and O_2 showed the lowest efficiency. Use of a 1 : 2 alcohol **1a**/alkyne **2a** ratio decreased the yield (entry 23).

With the optimal reaction conditions in hand, the substrate scope of the Ru(II)-catalyzed electrooxidative [4+2] annulation protocol was explored (Table 2 and Scheme 2). This reaction worked well with a wide range of internal alkynes **2b–m** and **2p–t** (**3ab–am** and **3ap–at**), but was unsuitable for terminal alkynes **2n–o** (**3an–ao**). For diaryl alkynes, several substituents, such as Me, *t*-Bu, MeO, Cl and F, on the aryl ring were tolerated well, and the substitution electron effect had an obvious influence on the yield (**3ab–ag**). While alkynes **2b–d** and **2g** possessing an electron-donating substituent (*e.g.* Me, *t*-Bu, and MeO) formed **3ab–ad** and **3ag**, respectively, in high yields, alkyne **2f** having a F group delivered **3af** with diminishing yield (48%). 1,2-Di(thiophen-2-yl)ethyne **2h** was also suitable for accessing **3ah**. In the case of

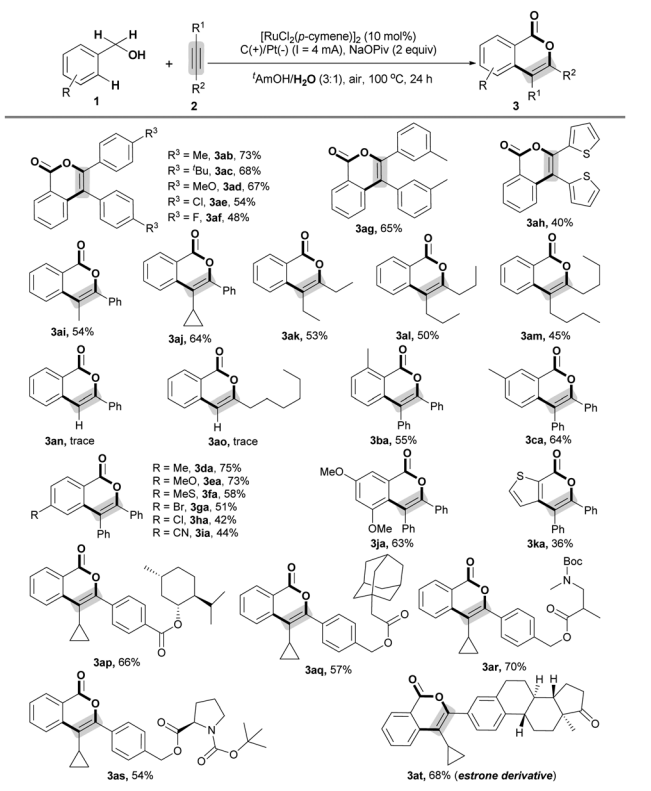
Table 1 Screening of optimal reaction conditions[a]



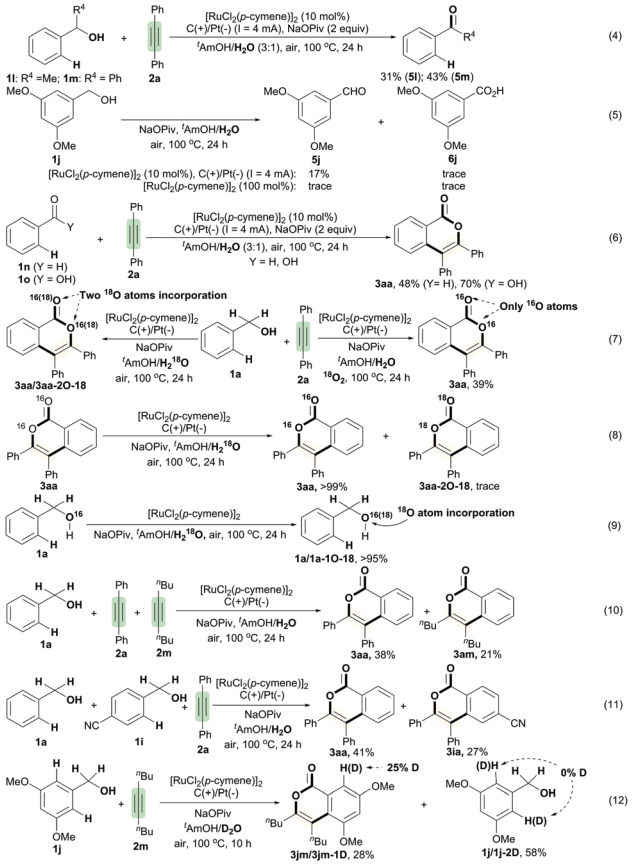
Entry	[Ru] (mol%)	*I* (mA)	Base (equiv.)	Solvent	*T* (°C)	Yield[b] (%)
1	10	4	NaOPiv (2)	^{t}AmOH	100	64
2	10	4	NaOPiv (2)	^{t}AmOH	110	60
3	10	4	NaOPiv (2)	^{t}AmOH	80	9
4[c]	10	8	NaOPiv (2)	^{t}AmOH	100	47
5	10	2	NaOPiv (2)	^{t}AmOH	100	38
6	10	0	NaOPiv (2)	^{t}AmOH	100	0
7	100	0	NaOPiv (2)	^{t}AmOH	100	51
8	10	4	NaOPiv (1)	^{t}AmOH	100	53
9	10	4	NaOAc (2)	^{t}AmOH	100	51
10	10	4	KOAc (2)	^{t}AmOH	100	54
11	10	4	Na_2CO_3 (2)	^{t}AmOH	100	52
12	10	4	K_2CO_3 (2)	^{t}AmOH	100	53
13[d]	10	4	NaOPiv (2)	^{t}AmOH	100	5
14	10	4	NaOPiv (2)	^{t}BuOH	100	44
15	10	4	NaOPiv (2)	HFIP	100	38
16	10	4	NaOPiv (2)	MeCN	100	28
17[e]	10	4	NaOPiv (2)	^{t}AmOH	100	Trace
18	0	4	NaOPiv (2)	^{t}AmOH	100	0
19	5	4	NaOPiv (2)	^{t}AmOH	100	35
20	15	4	NaOPiv (2)	^{t}AmOH	100	63
21[f]	10	4	NaOPiv (2)	^{t}AmOH	100	56
22[g]	10	4	NaOPiv (2)	^{t}AmOH	100	31
23[h]	10	4	NaOPiv (2)	^{t}AmOH	100	52

[a] Reaction conditions: undivided cell, graphite rod anode, platinum plate cathode, constant current = 4 mA, **1a** (0.6 mmol), **2a** (0.3 mmol), $[RuCl_2(p\text{-cymene})]_2$, base, solvent/$H_2O$ (3 : 1; 6 mL), and 24 h. Some by-products, including benzil (**4a**), benzaldehyde (**5a**) and benzoic acid (**6a**), were observed as determined by GC-MS analysis. [b] Isolated yield. [c] Benzil (**4a**) was isolated in 41% yield that relied on the amount of **2a**. [d] Graphite rod cathode instead of a Pt cathode. [e] Using $[RuCl_2(COD)]$ or $[Ru(bpy)_3]Cl_2$ instead of $[RuCl_2(p\text{-cymene})]_2$. [f] Using argon balloon. [g] Using O_2 balloon. [h] **1a** (0.3 mmol) and **2a** (0.6 mmol).

Table 2 Variation of benzylic alcohols (**1**) and alkynes (**2**)[a]



[a] Reaction conditions: undivided cell, graphite rod anode, platinum plate cathode, constant current = 4 mA, **1** (0.6 mmol), **2** (0.3 mmol), $[RuCl_2(p\text{-cymene})]_2$ (10 mol%), NaOPiv (2 equiv.), ^{t}AmOH/H_2O (3 : 1; 6 mL), 100 °C, and 24 h.



Scheme 2 Control experiments.

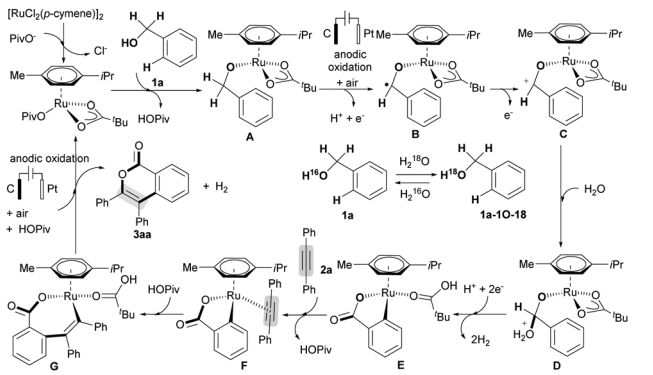
unsymmetrical alkyl aryl alkynes **2i–j** the reaction proceeded selectively (**3ai–aj**).[8] Dialkyl alkynes **2k–m** also succeeded in assembling **3ak–am**.

This electrooxidative [4+2] annulation was applicable to an array of primary benzylic alcohols **1b–k**. Tolerated on the aryl ring moiety were a number of substituents, including Me, MeO, MeS, Br and Cl, which make the corresponding benzylic alcohols **1b–h** highly effective four-atom annulation units (**3ba–ha**), albeit affecting the yields by their electronic properties and positions. For Me-substituted benzylic alcohols, the reactivity order increased from *ortho* (**3ba**) to *meta* (**3ca**) to *para* substitution (**3da**) in terms of yields. Importantly, halogen atoms, including Br and Cl, were tolerated, leaving ample room for further modification. Using diMeO-substituted benzylic alcohol **1j** enabled the formation of **3ja** in 63% yield. The reaction could be competent to furnish valuable thieno[2,3-*c*]pyran-7-one **3ka**. Synthetic utility of this electrooxidative [4+2] annulation reaction in modified bioactive molecule derivatives (**3ap–at**) was also assessed.[9] Alkynes **2p–s** built on the backbones of useful species[9a,b] and amino esters[9c,d] were converted efficiently to the desired complex 1*H*-isochromen-1-ones **3ap–3as** in 54–70% yields. The estrone unit[9e] was also readily incorporated into the resulting 1*H*-isochromen-1-one **3at** by annulation of estrone-containing alkyne **2t** with benzyl alcohol **1a**.

As shown in Scheme 2, two secondary benzylic alcohols **1l–m** were converted into ketones **5l–m**, not the expected annulation products **3** (eqn (4)). To understand the mechanism, control experiments with alcohol **1j** alone were performed under the optimal conditions, affording only 17% yield of aldehyde **5j** and a trace amount of acid **6j** (eqn (5)). However, no electric current led to a trace amount of aldehyde **5j** and acid **6j** even in the presence of 100 mol% Ru catalyst (eqn (5)). Transformation of benzaldehyde **1n** under the optimal conditions afforded only 48% yield of **3aa**, whereas benzoic acid **1o** was efficiently converted into **3aa** in 70% yield (eqn (6)). These results suggest that the annulation reaction proceeds not *via* the direct formation of aldehyde or acid intermediates, and electricity is needed (entry 6; Table 1). Surprisingly, two oxygen atoms in **3aa** are main the ^{18}O isotope when using $H_2{}^{18}O$ (eqn (7)), but no ^{18}O isotope exchange of $H_2{}^{18}O$ with product **3aa** occurs (eqn (8)). We found that ^{18}O isotope exchange of $H_2{}^{18}O$ with benzyl alcohol **1a** also took place (eqn (9)). Experiments using $^{18}O_2$ further support that two oxygen atoms are from H_2O, and not from air (eqn (7)). The results of intermolecular competition experiments show that the reaction of electron-rich arenes **1** or arylalkynes **2** is preferential (eqn (10) and (11)). The reactions with isotopically labelled D_2O suggest a reversible C–H cleavage *via* organometallic C–Ru formation, but the alcohol group is not enough to activate the *ortho*-C–H bond with the active Ru^{II} species (eqn (12)). These results support the fact that coordination of a benzylic alcohol with the active Ru^{II} species first occurs to form an alcohol–Ru(II) intermediate, which sequentially undergoes oxidation to afford an effective benzoyloxy–Ru(II) intermediate (not the acid monomer) and then generates the organometallic C–Ru(II) species *via* C–H activation.

The electrochemical activation of the Ru catalyst and the C–H bond by means of cyclovoltammetric analysis was examined (Fig. S1; ESI†). The oxidation potential peak of $[RuCl_2(p\text{-cymene})]_2$ left shifts from 0.142 $V_{Ag/AgCl}$ to −0.021 $V_{Ag/AgCl}$ in the presence of NaOPiv, suggesting the coordination of $[RuCl_2(p\text{-cymene})]_2$ with the $PivO^-$ group. A combination of $[RuCl_2(p\text{-cymene})]_2$ and alcohol **1a** gives an oxidation peak at 0.237 $V_{Ag/AgCl}$, verifying the formation of alcohol–Ru(II) species.

The possible mechanism for this electrooxidative [4+2] annulation protocol is proposed in Scheme 3.[2–6] Initially, the alcohol–Ru(II) species **A** is formed *via* complexation of alcohol **1a** with the active PivO-based Ru(II) species that is generated *in situ* from $[RuCl_2(p\text{-cymene})]_2$ coordinated with the $PivO^-$ group.[3p–w,5d,e] Anodic single electron oxidation of the O–Ru



Scheme 3 Possible mechanism.

intermediate **A** with the aid of air affords the cation intermediate **C**, which sequentially undergoes a nucleophilic reaction with H_2O, oxidation and C–H activation cascades to afford the organometallic C–Ru(II) intermediate **E**. Coordination of intermediate **E** with alkyne **2a** gives intermediate **F**, which rapidly executes migratory alkyne insertion to form the seven-membered ruthena(II)cycle **G**.[3p–w,5d,e] The electronic properties of the aryl groups might be more efficiently stabilized by the vinyl–Ru intermediate **G**, thus resulting in a high regioselectivity in the case of unsymmetrical alkynes. Finally, reductive elimination of intermediate **G** delivers the desired product **3aa** and the Ru(0) complex, followed by reoxidation through anodic oxidation of the Ru(0) complex to regenerate the active PivO-based Ru(II) species.

In summary, we have developed the first Ru(II)-catalyzed electrooxidative [4+2] annulation of benzylic alcohols with internal alkynes, where benzylic alcohols act as weakly directing group precursors to enable the formation of isocoumarins through multiple C–H functionalization. The reaction is distinguished by its success achieved through the use of a Ru(II)-catalyzed electrooxidative strategy with exquisite regio- and site-selectivity, as the conventional terminal oxidants, including Cu(II) salts, Ag(I) salts and O_2, had no effect on this event. Importantly, the reaction features facile incorporation of an isocoumarin unit into bioactive structural systems.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 For selective reviews on the annulation reactions *via* C–H functionalization: (*a*) P. Thansandote and M. Lautens, *Chem. – Eur. J.*, 2009, **15**, 5874; (*b*) D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2012, **45**, 814; (*c*) G. Song, F. Wang and X. Li, *Chem. Soc. Rev.*, 2012, **41**, 3651; (*d*) L. Ackermann, *Acc. Chem. Res.*, 2014, **47**, 281; (*e*) S. De Sarkar, W. Liu, S. I. Kozhushkov and L. Ackermann, *Adv. Synth. Catal.*, 2014, **356**, 1461; (*f*) M. Guías and J. L. Mascareñs, *Angew. Chem., Int. Ed.*, 2016, **55**, 11000; (*g*) Z. Wang, P. Xie and Y. Xia, *Chin. Chem. Lett.*, 2018, **29**, 47; (*h*) E. N. da Silva Júnior, G. A. M. Jardim, R. S. Gomes, Y.-F. Liang and L. Ackermann, *Chem. Commun.*, 2018, **54**, 7398.

2 For a review on isocoumarin synthesis *via* C–H functionalization, see: P. Saikiaa and S. Gogoi, *Adv. Synth. Catal.*, 2018, **360**, 2063.

3 For papers on annulation with acid derivatives with internal alkynes using the Pd(II) catalysis: (*a*) K. Ueura, T. Satoh and M. Miura, *Org. Lett.*, 2007, **9**, 1407; (*b*) Y. Yu, L. Huang, W. Wu and H. Jiang, *Org. Lett.*, 2014, **16**, 2146; (*c*) G. Jiang, J. Li, C. Zhu, W. Wu and H. Jiang, *Org. Lett.*, 2017, **19**, 4440. The Rh(III)catalysis: (*d*) K. Ueura, T. Satoh and M. Miura, *J. Org. Chem.*, 2007, **72**, 5362; (*e*) M. Shimizu, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2009, **74**, 3478; (*f*) S. Mochida, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2009, **74**, 6295; (*g*) M. Itoh, M. Shimizu, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2013, **78**, 1427; (*h*) Y. Unoh, K. Hirano, T. Satoh and M. Miura, *Tetrahedron*, 2013, **69**, 4454; (*i*) J. Mo, L. Wang and X. Cui, *Org. Lett.*, 2015, **17**, 4960; (*j*) E. Kudo, Y. Shibata, M. Yamazaki, K. Masutomi, Y. Miyauchi, M. Fukui, H. Sugiyama, H. Uekusa, T. Satoh, M. Miura and K. Tanaka, *Chem. – Eur. J.*, 2016, **22**, 14190; (*k*) L. Song, J. Xiao, W. Dong, Z. Peng and D. An, *Eur. J. Org. Chem.*, 2017, 341; (*l*) Y.-T. Li, Y. Zhu, G.-L. Tu, J.-Y. Zhang and Y.-S. Zhao, *Chem. – Asian J.*, 2018, **13**, 3281; the Ir(III)catalysis: (*m*) D. A. Frasco, C. P. Lilly, P. D. Boyle and E. A. Ison, *ACS Catal.*, 2013, **3**, 2421; the Co(III)catalysis: (*n*) R. Mandal and B. Sundararaju, *Org. Lett.*, 2017, **19**, 2544; (*o*) T. T. Nguyen, L. Grigorjeva and O. Daugulis, *Angew. Chem., Int. Ed.*, 2018, **57**, 1688; the Ru(II)catalysis: (*p*) L. Ackermann, J. Pospech, K. Graczyk and K. Rauch, *Org. Lett.*, 2012, **14**, 930; (*q*) R. K. Chinnagolla and M. Jeganmohan, *Chem. Commun.*, 2012, **48**, 2030; (*r*) M. Deponti, S. I. Kozhushkov, D. S. Yufit and L. Ackermann, *Org. Biomol. Chem.*, 2013, **11**, 142; (*s*) K. S. Singh, S. G. Sawant and P. H. Dixneuf, *ChemCatChem*, 2016, **8**, 1046; (*t*) R. Prakash, K. Shekarrao and S. Gogoi, *Org. Lett.*, 2015, **17**, 5264; (*u*) S. Warratz, C. Kornhass, A. Cajaraville, B. Niepoetter, D. Stalke and L. Ackermann, *Angew. Chem., Int. Ed.*, 2015, **54**, 5513; (*v*) J.-L. Yu, S.-Q. Zhang and X. Hong, *J. Am. Chem. Soc.*, 2017, **139**, 7224; (*w*) Y. Qiu, C. Tian, L. Massignan, T. Rogge and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, **57**, 5818.

4 For selected papers on oxidative [4+2] annulation of benzoic acids with other 2π components, see: (*a*) D. Nandi, D. Ghosh, S.-J. Chen, B.-C. Kuo, N. M. Wang and H. M. Lee, *J. Org. Chem.*, 2013, **78**, 3445; (*b*) M. Zhang, H.-J. Zhang, T. Han, W. Ruan and T.-B. Wen, *J. Org. Chem.*, 2015, **80**, 620; (*c*) C. Yang, X. He, L. Zhang, G. Han, Y. Zuo and Y. Shang, *J. Org. Chem.*, 2017, **82**, 2081; (*d*) W.-J. Han, F. Pu, J. Fan, Z.-W. Liu and X.-Y. Shi, *Adv. Synth. Catal.*, 2017, **359**, 3520; (*e*) A. Bechtoldt, M. E. Baumert, L. Vaccaro and L. Ackermann, *Green Chem.*, 2018, **20**, 398; (*f*) Y. Qiu, M. Stangier, T. H. Meyer, J. C. A. Oliveira and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, **57**, 14179.

5 (*a*) Y. Lu, D.-H. Wang, K. M. Engle and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 5916; (*b*) X. Wang, Y. Lu, H.-X. Dai and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 12203; (*c*) Y. Lu, D. Leow, X. Wang, K. M. Engle and J.-Q. Yu, *Chem. Sci.*, 2011, **2**, 967; (*d*) K. Morimoto, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2011, **76**, 9548; (*e*) S. Nakanowatari and L. Ackermann, *Chem. – Eur. J.*, 2014, **20**, 5409.

6 For selected reviews and representative papers on the electrooxidative transition-metal catalysis, see: (*a*) M. Yan, Y. Kawamata and P. S. Baran, *Chem. Rev.*, 2017, **117**, 13230; (*b*) Y. Jiang, K. Xu and C. Zeng, *Chem. Rev.*, 2018, **118**, 4485; (*c*) K. Liu, C. Song and A. Lei, *Org. Biomol. Chem.*, 2018, **16**, 2375; (*d*) N. Sauermann, T. H. Meyer, Y. Qiu and L. Ackermann, *ACS Catal.*, 2018, **8**, 7086; (*e*) N. Sauermann, T. H. Meyer and L. Ackermann, *Chem. – Eur. J.*, 2018, **24**, 16209; (*f*) N. Sauermann, T. H. Meyer, C. Tian and L. Ackermann, *J. Am. Chem. Soc.*, 2017, **139**, 18452; (*g*) R. Mei, N. Sauermann, J. C. A. Oliveira and L. Ackermann, *J. Am. Chem. Soc.*, 2018, **140**, 7913; (*h*) X. Gao, P. Wang, L. Zeng, S. Tang and A. Lei, *J. Am. Chem. Soc.*, 2018, **140**, 4195; (*i*) S. Tang, D. Wang, Y. Liu, L. Zeng and A. Lei, *Nat. Commun.*, 2018, **9**, 798; (*j*) N. Sauermann, R. Mei and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, **57**, 5090; (*k*) C. Tian, L. Massignan, T. H. Meyer and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, **57**, 2383; (*l*) F. Xu, Y.-J. Li, C. Huang and H.-C. Xu, *ACS Catal.*, 2018, **8**, 3820; (*m*) T. H. Meyer, J. C. A. Oliveira, S. C. Sau, N. W. J. Ang and L. Ackermann, *ACS Catal.*, 2018, **8**, 9140.

7 (*a*) T. Furuta, Y. Fukuyama and Y. Asakawa, *Phytochemistry*, 1986, **25**, 517; (*b*) H. Matsuda, M. Shimoda and M. Yoshikawa, *Bioorg. Med. Chem.*, 1999, **7**, 1445; (*c*) D. L. Yu, M. Suzuki, L. Xie, S. L. Morris-Natschke and K. H. Lee, *Med. Res. Rev.*, 2003, **23**, 322; (*d*) C. A. Kontogiorgis, K. Savvoglou and D. J. Hadjipavlou-Litina, *J. Enzyme Inhib. Med. Chem.*, 2006, **21**, 21; (*e*) R. Cai, Y. Wu, S. Chen, H. Cui, Z. Liu, C. Li and Z. She, *J. Nat. Prod.*, 2018, **81**, 1376.

8 CCDC 1874275 (**3aj**) contains the supplementary crystallographic data for this paper†.

9 (*a*) M. Miyazawa, S. Kumagae and H. Kameoka, *J. Agric. Food Chem.*, 1999, **47**, 3938; (*b*) X. Teng, S. Maksimuk, S. Frommer and H. Yang, *Chem. Mater.*, 2007, **19**, 36; (*c*) C. W. Smith, M. F. Ferger and W. Y. Chan, *J. Med. Chem.*, 1975, **18**, 822; (*d*) F. N. Shirota, H. T. Nagasawa and J. A. Elberling, *J. Med. Chem.*, 1977, **20**, 1176; (*e*) H. Elayadi and H. B. Lazrek, *Nucleosides, Nucleotides Nucleic Acids*, 2015, **34**, 433.

