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dll publication charges for this article have been paid for by the Royal Society of Chemistry remote C-H functionalization of naphthalenes: modular and concise synthesis of multifunctional naphthalenes†

Ruthenium-catalyzed three-component tandem

The prevalence of naphthalene compounds in biologically active natural products, organic ligands and approved drugs has motivated investigators to develop efficient strategies for their selective synthesis. C–H functionalization of naphthalene has been frequently deployed, but mainly involves two-component reactions, while multiple-component C–H functionalization for the synthesis of naphthalene compounds has thus far proven elusive. Herein, we disclose a versatile three-component protocol for the modular synthesis of multifunctional naphthalenes from readily available simple naphthalenes, olefins and alkyl bromides *via* P(III)-assisted ruthenium-catalyzed remote C–H functionalization. This protocol not only tolerates various functional groups, but can be applied to many natural product and drug derivatives, and can involve a three-component reaction with two different bioactive molecules. Mechanism studies indicated that the utilization of tertiary phosphines as auxiliary groups is the key to achieving the three-component free-radical reaction.

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Naphthalene and its derivatives frequently occur in natural products and functional materials.1 They also play prominent roles in ligands (BINAP) as well as pharmaceuticals such as the commercial drug Naproxen (Fig. 1A).2 Traditional preparation of substituted naphthalene derivatives is achieved through intermolecular or intramolecular annulation reaction from complex multiple-step synthesized substrates.3 In contrast, the C-H activation technique has in recent years emerged as an increasingly viable alternative for late-stage functionalization, avoiding the use of complicated starting materials.4 In this context, C-H functionalization of naphthalenes has seen remarkable development (Fig. 1B).5 Chemists have in recent years successfully achieved selective C-H functionalization of naphthalene rings from adjacent C2 and C8 positions, as well as remote C4, C5, C6 and C7 positions with different strategies.6 Despite these advances, the present methods are limited to twocomponent coupling reactions that yield structurally uncomplicated naphthalenes. Conceptually, the direct functionalization of naphthalene molecules through multi-component reactions (MCRs) would be more attractive because it could efficiently synthesize valuable complicated naphthalene derivatives from multiple inexpensive and abundant starting materials, in particular those difficult to prepare using traditional methods (Fig. 1C).

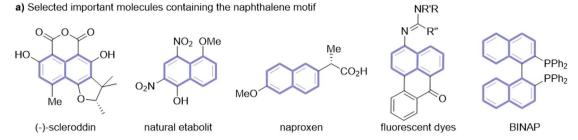
MCRs of olefins constitute one of the most important organic reactions for constructing complex molecules from simple raw materials. Remarkable advances have been made in metal-, light- and electricity-initiated MCRs of alkenes with different coupling reagents. In these reactions, the other two components usually need to be prefunctionalized to enable the success of reactions and control the selectivity. Deployment of MCRs involving the coupling of olefins with non-prefunctionalized substrates *via* C–H activation is a more attractive strategy for efficiently synthesizing complicated molecules. Although a few elegant works have been reported using nonprefunctionalized aromatic compounds, it remains a significant challenge to develop MCRs of substituted naphthalenes with more subtle C–H bonds (up to 7), especially for those C–H bonds at remote positions.

Very recently, we reported the first remote C5-functionalization of naphthalenes 6o via ruthenium-catalyzed δ -activation. 10 We found, while carrying out mechanism studies, that owing to the strong electron-donating effect of tertiary phosphine, the P(III)-coordinated cyclicoruthenium

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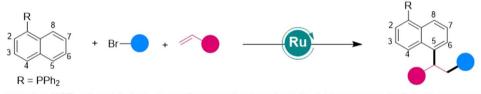


b) Previous achievements: C-H functionalization of naphthalene

c) Multiple-component reactions (MCRs) in C-H functionalization of naphthalene and its challenges

Challenge: control multiple site-selectivity and multiple chemical selectivity

d) This work: Three-component C5-H tandem functionalization of naphthalene with ruthenium catalysis



□ the first MCRs of naphthalene □ excellent remote site-selectivity □ high chemoselectivity □ complex and valuable products

Fig. 1 Important naphthalene-containing molecules and their synthesis via C-H functionalization of naphthalene.

intermediate could react with bromoalkanes to trigger formation of alkyl radicals under mild conditions and finally produce two-component C5-functionalized products. Inspired by this study, we assumed that the three-component radical reaction of alkenes with naphthalenes and alkyl bromides may be achieved using a strategy involving phosphine-assisted11 rutheniumcatalyzed δ-activation. Yet, achieving an MCR C-H functionalization of naphthalene is a great challenge, as it does not only require controlling the chemical selectivity of two-component coupling reactions, but also controlling the sequence selectivity and site selectivity of multi-component reactions, such as by (1) inhibiting C8-hydrogenarylation of alkenes with naphthalenes as previously reported, 6q (2) overcoming twocomponent C5-functionalization of naphthalenes with alkyl bromides, ⁶⁰ and (3) avoiding radical polymerization of olefins. Thus, whether the three-component remote C-H tandem reaction of naphthalenes with simple olefins and alkyl bromides could be realized is still not determined.

In the current work, we tested the above speculation by developing a three-component reaction of naphthalenes with olefins and alkyl bromides, with this reaction involving P(III)-assisted Ru-catalyzed remote C5–H activation (Fig. 1D). The reaction features excellent chemoselectivity and high remote C5-site selectivity. This achievement provides a concise and modular protocol for the synthesis of complicated and valuable 1,5-disubstituted naphthalenes from simple and inexpensive materials and corresponding synthesis of a series of natural products and drugs. Moreover, this three-component strategy can be expanded to involve polycyclic aromatic hydrocarbons (PHAs) for synthesizing challenging and complex PHAs.

We initiated our studies of three-component reactions with commercially available naphthalene 1a, olefin 2a and fluoroalkyl bromide 3a. After extensive investigation of various

Table 1 Investigation of directing groups^a

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Entry	Variation from the optimal conditions	Yield (%) of 4a	Yield (%) of 5	Yield (%) of 6
1	No	85 ^b	<5	<5
2	Cy ₂ P- instead of Ph ₂ P-	0	0	0
3	Ph ₂ N- instead of Ph ₂ P-	0	0	0
4	PhO- instead of Ph ₂ P-	0	0	0
5	Py instead of Ph ₂ P-	0	0	0
6	PA instead of Ph ₂ P-	0	0	0
7	CH_2 = $CHCO_2Me$ instead of 2a	<5	<5	56
8	BrC(CH ₃) ₂ CO ₂ Et instead of 3a	<5	67	<5
9	Without $[RuCl_2(p\text{-cymene})]_2$	0	0	0
10	With $Pd(OAc)_2$ instead of $[RuCl_2(p\text{-cymene})]_2$	0	0	0
11	With Rh(Cp*)Cl ₂ instead of [RuC1 ₂ (p-cymene)] ₂	0	0	0

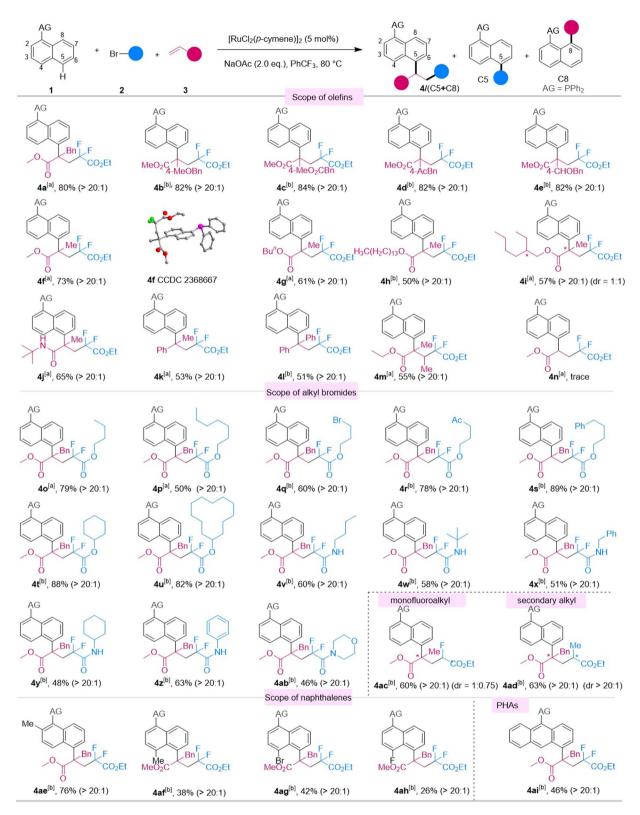
^a Reaction conditions: **1a** (0.10 mmol), **2a** (0.30 mmol), **3a** (0.30 mmol) 5 mol% [RuCl₂(p-cymene)]₂, NaOAc (2 equiv.), 1 mL PhCF₃, 80 °C in sealed Schlenk tubes, 12 h, under argon. Yields were determined using ¹H NMR, R=H or Bn. ^b Isolated yield.

reaction parameters (Table 1), the desired three-component C5tandem product (4a) was obtained in 85% yield with excellent site-selectivity (C5/C8 > 95:5) and chemoselectivity (C5/C5' > 95:5) when the reaction was assisted by the phosphine group and used [RuCl₂(p-cymene)]₂ (5 mol%) and NaOAc (2.0 equiv.) at 80 °C in (trifluoromethyl)benzene (see ESI† for detailed optimization) (entry 1). Other assisting groups such as Cy₂P-, Ph₂N-, PhO- and pyridine, as well as bidentate quinoline amide were also tested, but they were all ineffective for this reaction (entries 2–6), demonstrating the key role of the phosphine group in this transformation. Notably, only C8-hydroarylation product 6 was obtained when methyl acrylate was used (entry 7), proving the key role of alkene for the three-component tandem reaction of naphthalenes. When 2-bromoisobutyrate was selected as the coupling reagent (entry 8), the twocomponent C5-functionalized product 5 was obtained. This result may have been due to the tertiary alkyl radical having attacked the naphthalene faster than its having attacked the olefin. No product was detected without addition of [RuCl₂(pcymene)]₂ or with palladium and rhodium catalysts instead of $[RuCl_2(p\text{-cymene})]_2$ (entries 9–11), indicating the significant and unique ruthenium catalytic activity for this three-component remote C5-tandem reaction.

With the optimized conditions in hand, we probed the versatility of the three-component C5-tandem reaction of naphthalenes, olefins and alkyl bromides (Scheme 1). First, the olefin scope was investigated. Modified 2-benzylacrylate esters were evaluated and it turned out that electron-donating alkoxyl (3b) and electron-withdrawing ester (3c), acetyl (3d), and formyl (3e) groups were tolerated, affording the desired products 4b-e in 82-84% yields, respectively. Furthermore, an array

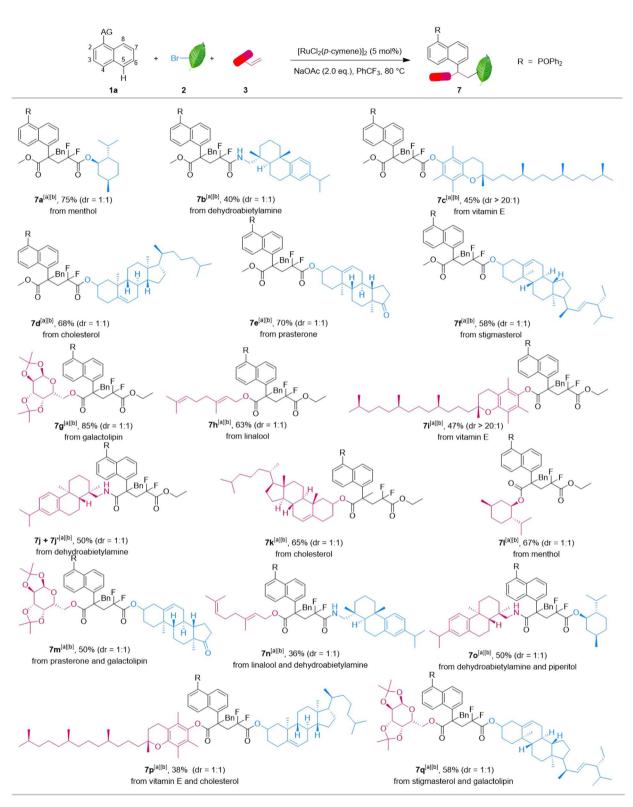
of 2-alkylacrylate esters could be converted smoothly into the corresponding products 4f-i, 4m in moderate to good yields. Moreover, acrylamide and styrenes (3j-l) were also accepted and delivered the products in 51-65% yields with excellent regio- and chemoselectivity levels (>20:1). However, monosubstituted and cyclic olefins were not suitable for the threecomponent reaction of naphthalenes. Next, we turned our attention to the scope of alkyl bromides. A variety of bromodifluoroacetates were applicable to the reaction and generated the desired products 4o-u in 50-89% yields, respectively. Additionally, a series of bromodifluoro acetamides underwent the reaction in the standard conditions, delivering products 4v-4ab, respectively, in 48-63% yields. Pleasingly, we also found that monofluoroalkyl and secondary alkyl bromides could be employed as the alkylating reagents, affording products 4ac and 4ad in good yields without diastereocontrol of the newly formed consecutive chiral centers, which proved these reaction to involve a radical addition process. Substituted naphthalenes and even anthracene were also investigated, giving the corresponding products 4ae-4ai in 38-76% yields, respectively. Given the excellent applicability of the threecomponent tandem transformation, diversification of bioactive molecules via this strategy was investigated (Scheme 2).

Reactions with modified bromodifluoroacetate and bromodifluoro acetamide derived from piperitol, dehydroabietylamine, vitamin E, etc. could proceed under the standard conditions, and afforded the corresponding products 7a-f in 40-75% yields. Moreover, diverse acrylate ester and acrylamide species were well tolerated, affording the coupling products 7g-l in moderate to good yields. Notably, modified alkyl bromides and diverse acrylate esters turned out to be suitable and reacted with



Scheme 1 Scope of three-component C5-tandem functionalization of naphthalenes with olefins and alkyl bromides. a Reaction conditions: 1 (0.10 mmol), 2 (0.30 mmol), 3 (0.30 mmol), 5 mol% [RuCl₂(p-cymene)]₂, NaOAc (2 equiv.), 1 mL PhCF₃, in sealed Schlenk tubes, 12 h, 80 °C, under argon; selectivity was determined using 31 P NMR. b Oxidized by H₂O₂.

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Scheme 2 Reaction with natural products and drugs. ^aReaction conditions: 1 (0.10 mmol), 2 (0.30 mmol), 3 (0.30 mmol), 5 mol% [RuCl₂(pcymene)]₂, NaOAc (2 equiv.), 1 mL PhCF₃, in sealed Schlenk tubes, 12 h, 80 °C, under argon, selectivity was determined by ³¹P NMR. ^bOxidized by H_2O_2 .

naphthalene **1a** in one pot smoothly to give **7m-q** in 36–58% yields, respectively. Therefore, this strategy may provide a serviceable way for achieving post-functionalization and modification of bioactive molecules in drug development and innovation.

To prove the practicability of this protocol, a scaled-up reaction, specifically on a 3 mmol scale, was conducted;

here, a mass of 1.37 g (75% yield) of product **4a** was obtained (Fig. 2a). The product **4a** could be further converted into valuable lactone product **8** *via* selective reduction of the ester group and a subsequent intramolecular esterification reaction (Fig. 2a).

Additionally, the product could be transformed into complicated and otherwise synthetically challenging fluorine-

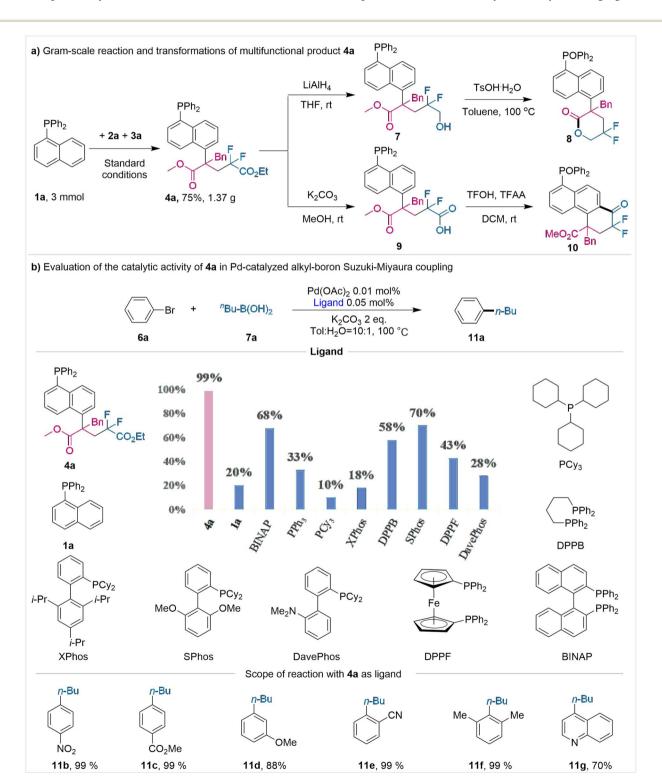


Fig. 2 Synthetic applications.

containing ketone 10 through hydrolysis and intramolecular Friedel-Crafts acylation steps (Fig. 2a) (see ESI† for detailed conditions). In consideration of the unique activity of phosphine ligands in Pd-catalyzed Suzuki-Miyaura cross-couplings (SMCs), control experiments were conducted (Fig. 2b). In comparison with the formation of $C(sp^2)$ – $C(sp^2)$, the $C(sp^3)$ – C(sp²) SMCs involving alkyl borons proved to be more challenging and less developed, as a result of the C(sp³)-Pd bond being more unstable thermodynamically.

We assumed that the modification of 1-naphthphosphine at the C5 position may enhance the stability of palladium intermediates, thereby improving the catalytic efficiency. Therefore, we tested the effect of product 4a on palladium-catalyzed Suzuki-Miyaura coupling of alkylboronic acids and aryl bromides with low catalyst loading. As shown in Fig. 2b, using 4a as the ligand, we obtained up to 99% yield of product (11a) in the coupling of bromobenzene (6a) with n-butylboronic acid (7a) at a concentration of 100 ppm of palladium catalyst. The good reactivity of product 4a was shown in the Suzuki crosscoupling reaction, probably owing to that the bulky and strong electron-donating alkyl substituent was introduced at the C-5 position of naphthalene phosphine, increasing the electron cloud density at the center of the P atom and promoting the catalytic activity of the palladium catalyst. However, only a low yield (20%) was observed using unmodified 1-naphthphosphine (1a), which indicated the importance of C5 substitution of 1-naphthphosphine. Other widely used commercial phosphine ligands, including dppb, PCy₃, and XPhos, were also tested. However, these ligands gave only low to moderate yields (10-70%) with 0.01 mol% of Pd(OAc)2. Then we investigated the scope of aryl bromides with *n*-butylboronic acid (7a) using 4a as ligand. Surprisingly, not only substituted bromobenzenes (11b-f) but the heterocycle bromide quinoline (11g) also could undergo the Suzuki-Miyaura coupling, generating the product in 70-99% yields, respectively. These results demonstrated the high performance of our C5-alkylated phosphines, which may have a wide application in the field of metal catalysis.

To shed light on the mechanism of this reaction, free radical verification experiments were first carried out (Fig. 3). When including 1.0 equivalents of radical trapping agent (TEMPO), the reaction was completely inhibited and a radical adduct product of 2a and TEMPO was observed (Fig. 3a) (see ESI† for detailed information), indicating that the reaction involved a radical process. Next, we conducted controlled experiments of auxiliary groups. The results showed that the diphenylamine (Ph₂N-) group and phenoxy (PhO-) group did not promote the three-component reaction, proving the key role of the tertiary phosphine auxiliary group in this design (Fig. 3b). Excitingly, Int A prepared using our previous method could react with 2a and 3a stoichiometrically under standard conditions and furnish product 4a in 20% yield. Moreover, examination of the catalytic reaction of Int A also suggested that it might be a viable intermediate for this transformation (Fig. 3c). Then, the kinetic isotope effect (KIE) of this transformation was investigated. High (1.9) and low (1.1) values of KIE were observed for the C5 and C8 positions, respectively (Fig. 3d), suggesting C5-H bond

activation to be the rate-determining step of this rutheniumcatalyzed three-component C5-functionalization of naphthalene. Next, an H/D exchange experiment of 1a was conducted with CD₃OD. A high level of deuterium was found at the C8 position of the product (55%) and recovered raw materials 1a (56%), but the C5-H bond was not deuterated (Fig. 3e). This result showed that C8-H activation was reversible while activation of the C5-H bond was an irreversible process. At last, a competition experiment was carried out (Fig. 3f). The results showed the electron-donating group to be more conducive than to the reaction.

Based on the above results and previous literature,12 a plausible process was derived, and is shown in Fig. 3g. According to this process, first substrate 1a coordinates with [RuCl₂(pcymene)], to generate ruthenium complex A, which then undergoes C8-H activation to form the five-membered cyclometalated complex Int A. Next, Int A is oxidized by alkyl bromides 2 via single-electron transfer to form trivalent ruthenium complex B and releases the first alkyl radical R, which is trapped by olefin 3 to form secondary alkyl radical species C. Subsequently, radical C attacks the para-position of the Ru-C8 bond of intermediate B to generate intermediate D. Then, intermediate D generates the C5-functionalized intermediate E via a dehydroaromatization process. Finally, intermediate E undergoes protonation reactions to afford product 4 and regenerates the catalyst $[RuX_2(p\text{-cymene})]_2$. During this process, insertion of alkene into the Ru-C bond in intermediate Int A followed by a protonation process could deliver the C8-alkylated by-product 6. Moreover, the alkyl radical may attack the paraposition of the Ru-C bond in intermediate B, producing C5alkylated by-product 5.

In summary, we have developed the first three-component tandem reaction of naphthalenes with olefins and alkyl bromides by using a phosphine-coordinated ruthenium catalytic system. This system overcomes the otherwise favorable two-component reaction, offering a modular and concise strategy for accessing complex and valuable multifunctional naphthalenes with high chemoselectivity and site-selectivity. Notably, this protocol features a broad substrate scope, wide functional group tolerance, mild reaction conditions and high universality including disubstituted olefins and trisubstituted olefins. The multifunctional products not only can serve as highly efficient ligands in Suzuki-Miyaura coupling reactions, but can also be further converted into fluorinated naphthohexacyclic ketones and fluorinated hexacyclic intramolecular lipids. Moreover, the synthetic value of this methodology was demonstrated by the synthesis of a series of complicated products including many natural products and drugs, which may contribute to research and discovery of new drugs containing naphthalene. Mechanistic studies disclosed that the C5-H bond activation is the rate-determining step in three-component radical tandem naphthyl functionalization, which is different from the previous twocomponent C5-functionalization. Further research on developing new types of multi-component C-H functionalization reactions is underway in our laboratory.

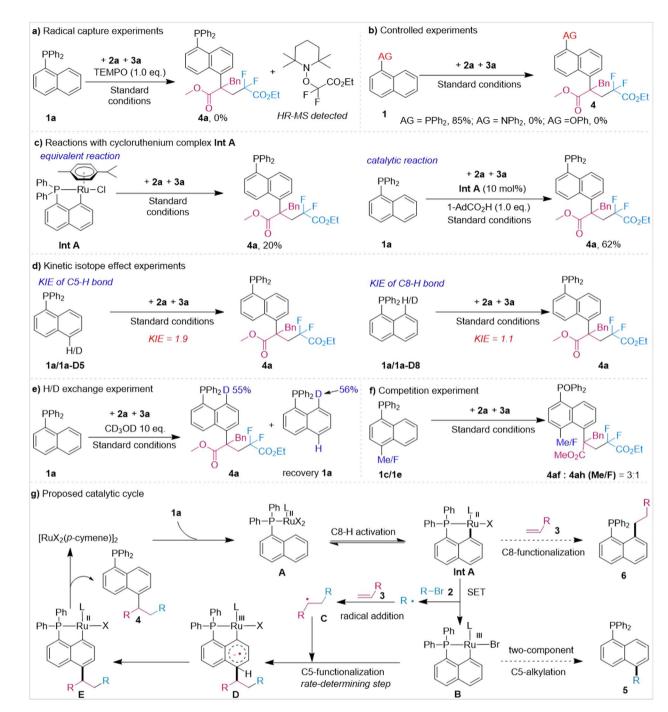


Fig. 3 Mechanistic investigations.

Data availability

The data underlying this study are available in the published article and its ESI. \dagger

Author contributions

Yue-Jin Liu conceived and directed the project and wrote the manuscript. Mao-Gui Huang conducted most of the experiments. Yue-Liu-Ting Fu performed preliminary experiments. Jia-Wei Li conducted nuclear magnetic resonance test. All the authors discussed the results, commented on and revised the manuscript.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

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- 1 (a) W. A. Ayer, M. Kamada and Y.-T. Ma, Can. J. Chem., 1989, 67, 2089–2094; (b) M. A. Kobaisi, S. V. Bhosale, K. Latham, A. M. Raynor and S. V. Bhosale, Chem. Rev., 2016, 116, 11685-11796.
- 2 (a) P. Ruiz-Castillo and S. L. Buchwald, Chem. Rev., 2016, 116, 12564-12649; (b) M. Han and S. G. Küçükgüzel, Mini Rev. Med. Chem., 2020, 20, 1300-1310.
- 3 M. Maheswari and N. Hussain, Synthesis, 2024, 56, 2145–2182. 4 (a) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, Chem. Soc. Rev., 2011, 40, 4740–4761; (b) C.-L. Sun, B.-J. Li and Z.-J. Shi, Chem. Rev., 2011, 111, 1293-1314; (c) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, Acc. Chem. Res., 2012, 45, 788-802; (d) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, Chem. Rev., 2012, 112, 5879-5918; (e) F. Zhang and D. R. Spring, Chem. Soc. Rev., 2014, 43, 6906-6919; (f) Z. Huang, H. N. Lim, F. Mo, M. C. Young and G. Dong, Chem. Soc. Rev., 2015, 44, 7764-7786; (g) H. Huang, X. Ji, W. Wu and H. Jiang, Chem. Soc. Rev., 2015, 44, 1155-1171; (h) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, Org. Chem. Front., 2015, 2, 1107-1295; (i) C. Sambiagio, D. Schönbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes and M. Schnürch, Chem. Soc. Rev., 2018, 47, 6603-6743; (j) S. Rej, Y. Ano and N. Chatani, Chem. Rev., 2020, 120, 1788-1887.
- 5 (a) S. Prévost, ChemPlusChem, 2020, 85, 476-486; (b) B. Large and D. Prim, Synthesis, 2020, 52, 2600-2612.
- 6 (a) A. Biafora, T. Krause, D. Hackenberger, F. Belitz and L. J. Gooßen, Angew. Chem., Int. Ed., 2016, 55, 14752–14755; (b) L. Zhang, L. Zhu, Y. Zhang, Y. Yang, Y. Wu, W. Ma, Y. Lan and J. You, ACS Catal., 2018, 8, 8324-8335; (c) X. Sun, G. Shan, Y. Sun and Y. Rao, Angew. Chem., Int. Ed., 2013, 52, 4440-4444; (d) R. Shi, L. Lu, H. Xie, J. Yan, T. Xu, H. Zhang, X. Qi, Y. Lan and A. Lei, Chem. Commun., 2016, 52, 13307-13310; (e) X. Luo, J. Yuan, C.-D. Yue, Z.-Y. Zhang, J. Chen, G.-A. Yu and C.-M. Che, *Org. Lett.*, 2018, **20**, 1810–1814; (f) S. Rej and N. Chatani, ACS Catal., 2018, 8, 6699-6706; (g) S. Moon, Y. Nishii and M. Miura, Org. Lett., 2019, 21, 233-236; (h) X. Yu, F. Yang and Y. Wu, Org. Lett., 2019, 21, 1726-1729; (i) J. Garrec, M. Cordier, G. Frison and S. Prévost, Chem. Eur J., 2019, 25, 14441–14446; (j) S. Lee, H. Lee and K. L. Tan, J. Am. Chem. Soc., 2013, 135, 18778–18781; (k) X.-C. Wang, W. Gong, L.-Z. Fang, R.-Y. Zhu, S. Li, K. M. Engle and J.-Q. Yu, *Nature*, 2015, **519**, 334–338; (*l*) M. Zhang, A. Luo, Y. Shi, R. Su, Y. Yang and J. You, ACS Catal., 2019, 9, 11802-11807; (m) J.-M. Li, Y.-H. Wang, Y. Yu, R.-B. Wu, J. Weng and G. Lu, ACS Catal., 2017, 7, 2661-2667; (n) C. Jing, X. Chen, K. Sun, Y. Yang, T. Chen, Y. Liu, L. Qu, Y. Zhao and B. Yu, Org. Lett., 2019, 21, 486–489; (o) Y. Fu, C.-H. Chen, M.-G. Huang, J.-Y. Tao, X. Peng, H.-B. Xu, Y.-J. Liu and M.-H. Zeng, ACS Catal., 2022, 12, 5036–5047; (p) C. Jing, X. Chen, K. Sun, Y. Yang, T. Chen, Y. Liu, L. Qu, Y. Zhao and B. Yu, Org. Lett., 2019, 21, 486-489; (q) W.-T. Ma,

- M.-G. Huang, Y. Fu, Z.-H. Wang, J.-Y. Tao, J.-W. Li, Y.-J. Liu and M.-H. Zeng, Chem. Commun., 2022, 58, 7152-7155.
- 7 (a) K. H. Jensen and M. S. Sigman, Org. Biomol. Chem., 2008, 6, 4083-4088; (b) R. I. McDonald, G. Liu and S. S. Stahl, Chem. Rev., 2011, 111, 2981-3019; (c) H. Egami and M. Sodeoka, Angew. Chem., Int. Ed., 2014, 53, 8294-8308; Angew. Chem., 2014, 126, 8434-8449; (d) E. Merino and C. Nevado, Chem. Soc. Rev., 2014, 43, 6598–6608; (e) J. R. Coombs and J. P. Morken, Angew. Chem., Int. Ed., 2016, 55, 2636-2649; Angew. Chem., 2016, 128, 2682-2696; (f) G. Yin, X. Mu and G. Liu, Acc. Chem. Res., 2016, 49, 2413–2423; (g) X.-W. Lan, N.-X. Wang and Y. Xing, Eur. J. Org Chem., 2017, 2017, 5821-5851; (h) J. Derosa, V. A. van der Puyl, V. T. Tran, M. Liu and K. M. Engle, Chem. Sci., 2018, 9, 5278-5283; (i) R. Giri and S. Kc, J. Org. Chem., 2018, 83, 3013-3022; (i) J. S. Zhang, L. Liu, T. Chen and L. B. Han, Chem.-Asian J., 2018, 13, 2277-2291; (k) Z.-X. Wang, X.-Y. Bai and B.-J. Li, Chin. J. Chem., 2019, 37, 1174-1180.
- 8 (a) N. Huang, J. Luo, L. Liao and X. Zhao, J. Am. Chem. Soc., 2024, 146, 7029-7038; (b) Y.-T. Zheng and H.-C. Xu, Angew. Chem., Int. Ed., 2024, 63, e202313273; (c) C. Coudret and S. Fraysse, Chem. Commun., 1998, 663-664; (d) X. Hu, I. Cheng-Sánchez, W. Kong, G. A. Molander and C. Nevado, Nat. Catal., 2024, 7, 655-665.
- 9 (a) X.-L. Lai and H.-C. Xu, J. Am. Chem. Soc., 2023, 145, 18753-18759; (b) X.-G. Wang, Y. Li, H.-C. Liu, B.-S. Zhang, X.-Y. Gou, Q. Wang, J.-W. Ma and Y.-M. Liang, *J. Am. Chem. Soc.*, 2019, 141, 13914-13922; (c) S. Neogi, S. Bhunya, A. K. Ghosh, B. Sarkar, L. Roy and A. Hajra, ACS Catal., 2024, 14, 4510-4522; (d) Y.-Y. Luan, J.-Y. Li, W.-Y. Shi, Z. Zhang, R.-Q. Jiao, X. Chen, X.-Y. Liu and Y.-M. Liang, Org. Lett., 2024, 26, (e) J. Wu, W. Wei, J. Pöhlmann, 3213-3217; R. Purushothaman and L. Ackermann, Angew. Chem., Int. Ed., 2023, **62**, e202219319; (f) S. Chen, B. Yuan, Y. Wang and L. Ackermann, Angew. Chem., Int. Ed., 2023, 62, e202301168.
- 10 (a) N. Hofmann and L. Ackermann, J. Am. Chem. Soc., 2013, 135, 5877-5884; (b) J. Li, S. Warratz, D. Zell, S. De Sarkar, E. E. Ishikawa and L. Ackermann, J. Am. Chem. Soc., 2015, 137, 13894–13901; (c) J. Li, K. Korvorapun, S. D. Sarkar, T. Rogge, D. Burns, S. Warratz and L. Ackermann, Nat. Commun., 2017, 8, 15430–15438; (d) O. Saidi, J. Marafie, A. E. Ledger, P. M. Liu, M. F. Mahon, G. Kociok-Kohn, M. K. Whittlesey and C. G. Frost, J. Am. Chem. Soc., 2011, 133, 19298–19301; (e) F. Julia-Hernandez, M. Simonetti and I. Larrosa, Angew. Chem., Int. Ed., 2013, 52, 11458-11460; (f) A. Sagadevan and M. F. Greaney, Angew. Chem., Int. Ed., 2019, 58, 9826–9830; (g) J. Wu, N. Kaplaneris, J. Pöhlmann, T. Michiyuki, B. Yuan and L. Ackermann, Angew. Chem., Int. Ed., 2022, 61, e202208620.
- 11 (a) X. Lv, M. Wang, Y. Zhao and Z. Shi, J. Am. Chem. Soc., 2024, **146**, 3483–3491; (b) Z. Li, W. Xu, S. Song, M. Wang, Y. Zhao and Z. Shi, Angew. Chem., Int. Ed., 2024, 63, e202316035.
- 12 (a) R. Sun, X. Chu, S. Zhang, T. Li, Z. Wang and B. Zhu, Eur. J. *Inorg. Chem.*, 2017, **2017**, 3174–3183; (b) T. Kuwabara, T. Kato, K. Takano, S. Kodama, Y. Manabe, N. Tsuchida, K. Takano, Y. Minami, T. Hiyama and Y. Ishii, Chem. Commun., 2018, **54**, 5357–5360; (c) K. Korvorapun, R. Kuniyil and L. Ackermann, ACS Catal., 2020, 10, 435-440.