


Cite this: *RSC Adv.*, 2024, 14, 37788

Ruthenium(II) catalyzed C-3 site selective alkenylation of indole derivatives via C–H activation†

Jithender Rallabandi,^{ab} Smrutiranjana Mohanty^b and Indrajit Shown^{ab}  [✉]

An efficient synthetic method has been developed for C-3 site-selective alkenylation of indole derivatives under ruthenium(II) catalysis with an ester as a directing group. Besides the presence of two potential C(sp²)–H sites available for functionalization in the substrates, exclusive C3 selectivity was achieved in a selective manner as only mono-functionalized products were formed. The high site selectivity is attributed to the formation of an uncommon six-membered metallacycle intermediate between the ruthenium catalyst and ester directing group, enabled by the selective alkenylation at the C3 position of indole derivatives. This protocol features high site selectivity, operational simplicity, broad substrate scope, and moderate to high yields.

Received 28th August 2024
Accepted 13th November 2024

DOI: 10.1039/d4ra06210h

rsc.li/rsc-advances

Introduction

The indole ring system is one of the most prevalent heterocycles found in nature, playing a crucial role in medicinal chemistry.¹ Numerous studies have demonstrated that its importance arises from the wide range of biological properties exhibited by compounds with various substituent patterns around the indole nucleus.² Over the last decade, several studies have highlighted the diverse biological activities of molecules containing the indole moiety. These activities encompass a broad spectrum, including but not limited to anti-HIV,^{3a} anticancer,^{3b} anti-inflammatory,^{3c} antiviral,^{3d} and antipsychotic^{3e} effects, among others (Fig. 1).

Among various approaches, C–H activation has emerged as a pivotal strategy for the functionalization of a diverse array of organic molecules, serving as a common route for the formation of C–C bonds.⁴ Although a vast number of activation methods utilizing different metal catalysts, ligands, reaction conditions, and reagents have been discovered, achieving selective functionalization remains to be a challenging task.⁵ Moreover, even when directing groups are employed, achieving selective activation can be difficult, particularly when multiple C–H bonds are nearby, each with a similar likelihood of undergoing activation.⁶ The Ru(II) complexes have attracted a lot of interest in this context because of their great selectivity and affordability. They are extensively employed for the selective *ortho* C–H bond

activation and oxidative Heck-type alkenylation of (hetero) aromatics with a wide range of alkenes.^{7,8}

In 2005, the Gaunt group reported a palladium-catalyzed C2/C3 alkenylation of indoles, where they controlled the regioselectivity by employing different solvents⁹ (Scheme 1a). Additionally, independent studies conducted by Xu *et al.*,^{10a} Carretero *et al.*,^{10b} Choudhury *et al.*,^{10c} Tanaka *et al.*,^{10d} Zhu *et al.*^{10e} and Walsh *et al.*^{10f} have revealed that altering the reaction conditions can influence the reaction pathways. Furthermore, the generation of side products like over-olefination, annulation, and polymerization byproducts is a problem with metal-catalyzed C3-olefination of indoles, especially when palladium catalysts are used.¹¹ Over the last two decades, Ru(II) catalysis has gained increasing attention for C–H functionalization due to its cost-effectiveness compared to metals such as Pd, Rh, and Ir.¹² It has been reported that Ru catalysts have emerged as highly efficient and promising agents for the formation of C–C bonds using a directing group strategy.¹³ Although various strategies have been described for the regioselective insertion of functional groups at indole C-2, C-4, and C-7 positions.¹⁴ However, there have been no reports of selective alkenylation of indole derivatives at the C-3 position using a Ru catalyst and a directing group at the C-4 position, such as an ester. Therefore, our focus lies in achieving alkenylation at the C3 position using a Ru catalyst, a task that presents a significant challenge.

Previous studies have shown that Ru(II)-catalyzed C–H activation using an amide directing group proceeds through a rare 6-membered metallacycle, rather than the typical 5-membered metallacycle.¹⁵ Additionally, it has been reported that a stable 5-membered metallacycle, rather than a 6-membered one, can also promote Ru(II)-catalyzed C–H activation.⁷ In our research, we revealed that Ru(II)-catalyzed C–H activation can proceed

^aDepartment of Chemistry, Hindustan Institute of Technology and Science, Chennai 603103, India. E-mail: indrajits@hindustanuniv.ac.in; shownindrajit@gmail.com

^bSyngene International Ltd, Genome Valley, Hyderabad, Telangana 500078, India

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d4ra06210h>

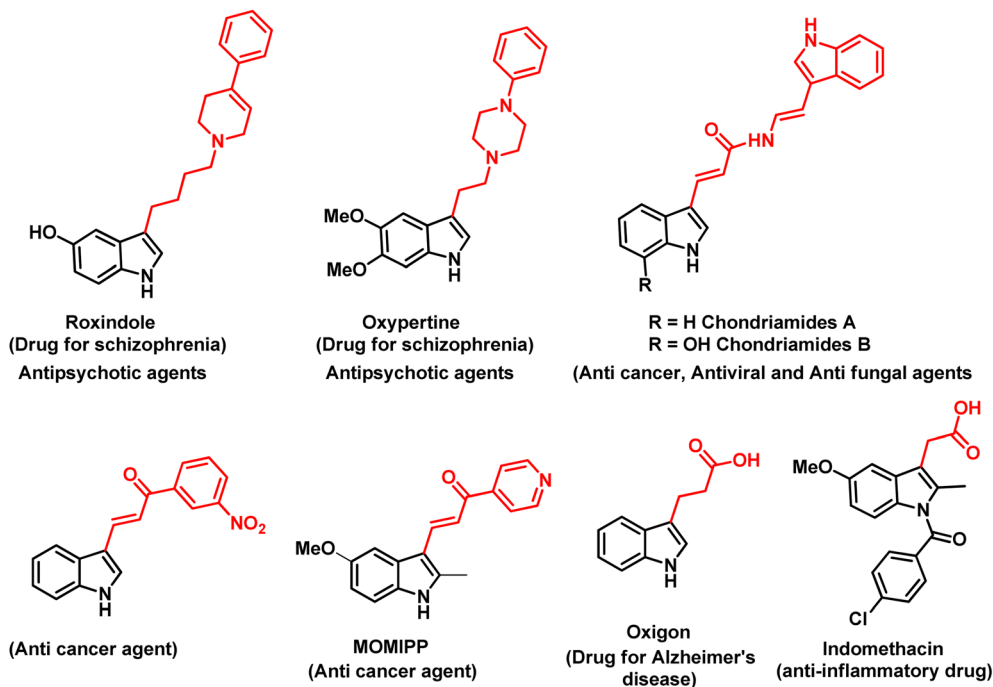



Fig. 1 Pharmaceutically active compounds of 3-substituted indole derivatives.

through both 5- and 6-membered metallacycle intermediates, depending on the reaction conditions and the nature of the directing group used. As illustrated in Scheme 1b, the reaction of Ru-catalyzed C–H activation using an ester as a directing group with acrylates generally leads to the product through a five-membered metallacycle instead of six-membered metallacycle.¹⁶ Herein, we describe our recent finding (Scheme 1c) of a highly regioselective alkenylation of indole derivatives at the C-3 position, utilizing the ester functional group as a directing group at the C4 position and Ru(II) as a catalyst. Notably, unlike other known methods (Scheme 1c), our study reveals that the reaction proceeds *via* an uncommon six-membered metallacycle intermediate instead of a 5-membered metallacycle, resulting in the formation of selective C-3 alkenylated indole derivatives.

Selective functionalization of C-3 with a directing group at C-4 presents a challenging due to the presence of a substantially more reactive C-5 position. This is because activation at C-3 must proceed *via* a rare 6-membered metallacycle, whereas the activation at C-5 can proceed *via* a well-known stable 5-membered metallacycle, as shown in Scheme 1d.^{7,16} Hence, an appropriate C4-tethered directing group (DG) is in great demand to compete with C5-metalation and achieve C3-selectivity. In catalytic alkenylations, the presence of AgSbF₆ and Cu(OAc)₂ is crucial for ensuring the success of the reaction.¹⁷

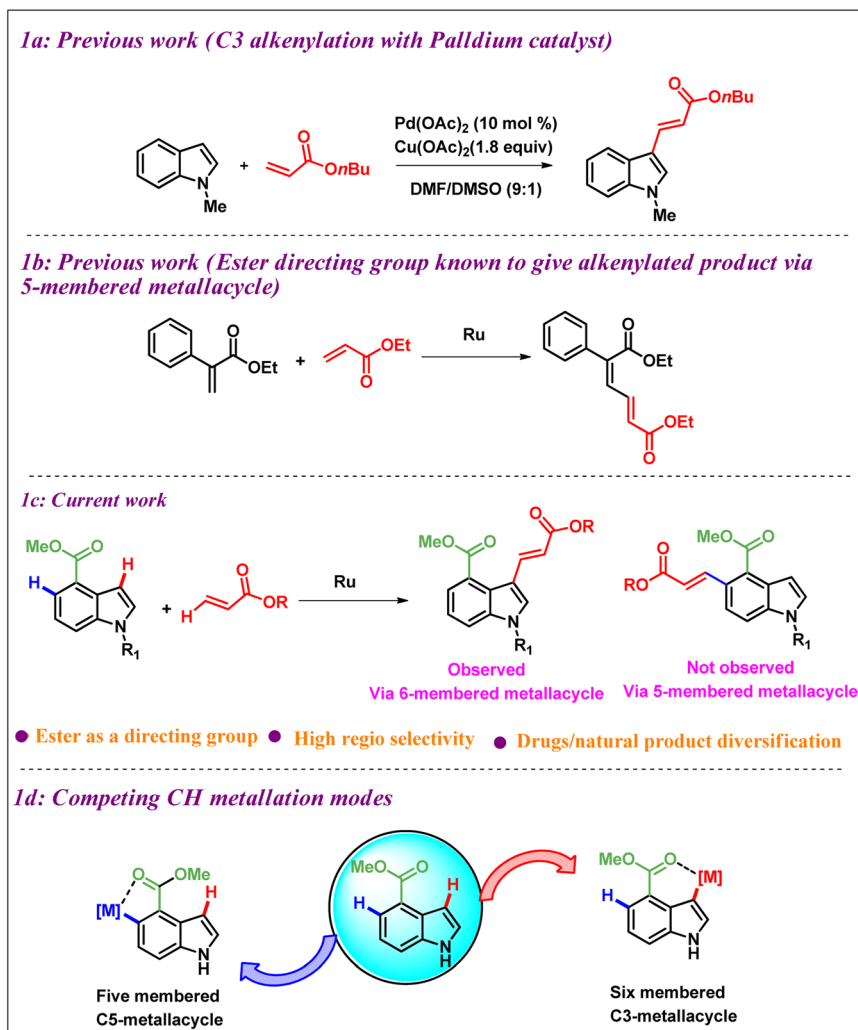
Results and discussion

In this study, we initiated the optimization of the C-3 alkenylation of indole derivative **1a** and methyl acrylate **2a** as model

substrates. Using methyl ester as a directing group, AgSbF₆ as an additive, and Cu(OAc)₂·H₂O (1.2 equiv) as an oxidant in DMF solvent, the desired product, **3aa**, was obtained with only a 17% yield (Table 1, entry 1). Our initial investigations revealed that substituting the ester group at the C-4 position of indole **1a** with either an aldehyde or alcohol as the directing group resulted in no product formation.

We proceeded to screen various reaction conditions to verify the effect of solvent polarity by using solvents such as DCE, 1,4-dioxane, and THF (refer to Table 1, entries 2–4). We observed a 52% yield using THF as the solvent (Table 1, entry 4). Furthermore, we observed that when the reaction temperature was lowered to 50 °C, the product yield was enhanced. To explore this, we attempted the same reaction by decreasing the temperature to 50 °C with a variety of solvents, resulting in the product yield being raised to 81% with THF as a solvent (Table 1, entries 5–8). It was also found that the yield of the product was disfavoured (16%, entry 9) when the reaction was performed at room temperature. By keeping other parameters fixed, when the equivalents of AgSbF₆ were increased to 40 mol%, the yield of the product increased, reaching around 88% (Table 1, entry 10). We then examined different additives, such as AgOTf, KPF₆, and AgBF₄, and found that they all yielded less than AgSbF₆ (Table 1, entries 11–13). Finally, to the effect of oxidants on product yield was explored by using a variety of oxidants: Ag₂CO₃, Ag₂O, Na₂S₂O₈, and PhI(OAc)₂. These reactions displayed inferior results in all cases (Table 1, entries 14–17). The desired product did not form in the absence of the catalyst (Table 1, entries 18). The additive, oxidant, and catalyst were found to be essential in this process, as revealed by these control experiments. Thus, the optimal reaction condition for





Scheme 1 Comparative overview of reported catalytic alkenylation approaches for indoles, (1a). Palladium-catalyzed C2/C3 alkenylation of indoles, (1b). Ru-catalyzed C–H activation using an ester as a directing group, (1c). Ru(II)-catalyzed highly regioselective alkenylation of indole derivatives at the C–3 position, utilizing the ester functional group, (1d). Activation at C–3 must continue via a rare 6-membered metallacycle.

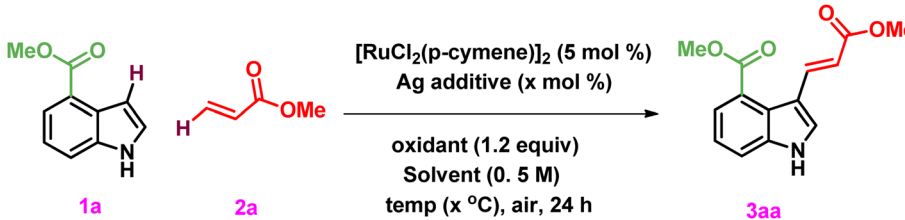
the C3 alkenylation of **1a** involves the use of 5.0 mol% [RuCl₂(p-cymene)]₂, 40 mol% AgSbF₆, and Cu(OAc)₂·H₂O (1.2 equiv.) in 0.5 M THF at 50 °C (Table 1, entry 10).

After obtaining the optimum reaction conditions, we explored the substrate scope and generality of the reaction for the C3 alkenylation of various indole derivatives, **1**, with different acrylates, **2**, resulting in good yields (Table 2). The reaction of methyl indole-4-carboxylate, **1a**, with sterically distinct acrylates furnished products, **3aa**, **3ab**, **3ac**, and **3ad**, with yields ranging from 69 to 88%. However, no product was observed with acrylic acid. Similarly, methyl-1-methyl-1H-indole-4-carboxylate (**3b**) underwent alkenylation reactions with acrylates to afford products, **3ba–3bd**, in 78–83% yield. Furthermore, the alkenylation reaction of methyl-1-ethyl-1H-indole-4-carboxylate with acrylates resulted in the corresponding products, **3ca–3cd**, in 72–82% yields.

To investigate the effect of benzyl substituents on N-H indoles on alkenylation, we performed alkenylation on methyl-1-

benzyl-1H-indole-4-carboxylate and methyl-1-(4-methoxybenzyl)-1H-indole-4-carboxylate, resulting in products, **3da–3dd**, in moderate to good yields (69–76%). Additionally, we examined the reactivity of methyl-1-(4-methoxybenzyl)-1H-indole-4-carboxylate with different acrylates, which resulted in products, **3ea–3ec**, in 68–81%. The effect of electron-withdrawing substituents present on indole toward alkenylation was studied by the alkenylation of methyl-1-phenyl-1H-indole-4-carboxylate, yielding products, **3fa–3fd**, in moderate yields (59–68%). To investigate the influence of various esters at the C-4 position on the indole framework, we performed an alkenylation reaction with ethyl 1H-indole-4-carboxylate as the starting material. This process produced the intended product **3gd** with an 82% yield. ¹H NMR study indicated that only the *trans*-alkenylated product was formed. Additionally, as shown in Scheme 4c, a scale-up reaction was carried out on a 3 mmol scale to illustrate the feasibility of this approach, yielding **3aa** in a 78% yield. Furthermore, we explored the reactivity of a useful olefin partner, such as methyl



Table 1 Optimization of Reaction Conditions^a


Entry	Solvent	Conditions	Yield 3aa ^b
1	DMF	AgSbF ₆ /Cu(OAc) ₂ ·H ₂ O/100 °C	17%
2	DCE	AgSbF ₆ /Cu(OAc) ₂ ·H ₂ O/100 °C	28%
3	Dioxane	AgSbF ₆ /Cu(OAc) ₂ ·H ₂ O/100 °C	33%
4	THF	AgSbF ₆ /Cu(OAc) ₂ ·H ₂ O/100 °C	52%
5 ^c	DMF	AgSbF ₆ /Cu(OAc) ₂ ·H ₂ O/50 °C	24%
6 ^c	DCE	AgSbF ₆ /Cu(OAc) ₂ ·H ₂ O/50 °C	34%
7 ^c	Dioxane	AgSbF ₆ /Cu(OAc) ₂ ·H ₂ O/50 °C	73%
8 ^c	THF	AgSbF ₆ /Cu(OAc) ₂ ·H ₂ O/50 °C	81%
9 ^d	THF	AgSbF ₆ /Cu(OAc) ₂ ·H ₂ O/RT	16%
10 ^e	THF	AgSbF ₆ /Cu(OAc) ₂ ·H ₂ O/50 °C	88%
11 ^e	THF	AgOTf/Cu(OAc) ₂ ·H ₂ O/50 °C	21%
12 ^e	THF	KPF ₆ /Cu(OAc) ₂ ·H ₂ O/50 °C	63%
13 ^e	THF	AgBF ₄ /Cu(OAc) ₂ ·H ₂ O/50 °C	56%
14 ^e	THF	AgSbF ₆ /Ag ₂ CO ₃ /50 °C	51%
15 ^e	THF	AgSbF ₆ /Ag ₂ O/50 °C	22%
16 ^e	THF	AgSbF ₆ /Na ₂ S ₂ O ₈ /50 °C	26%
17 ^{e,f}	THF	AgSbF ₆ /Cu(OAc) ₂ ·H ₂ O/50 °C	n.d.
18 ^e	THF	AgSbF ₆ /PhI(OAc) ₂ /50 °C	n.d.

^a Reaction conditions: **1a** (1 equiv, 0.2 mmol), **2b** (3 equiv, 0.6 mmol), [RuCl₂(*p*-cymene)]₂ (5.0 mol%), additive (20 mol%), oxidant (1.2 equiv, 0.24 mmol), Solvent (0.5 M), temperature as mentioned, under air for 24 h. ^b Isolated yield. ^c Reaction was carried out at 50 °C. ^d Reaction was carried out at room temperature. ^e additive (40 mol%). ^f Reaction without catalyst. RT = room temperature. n.d. = not detected.

vinyl ketone (**2e**), with methyl 1*H*-indole-4-carboxylate (**3a**) under standard conditions (Scheme 2). Surprisingly, this resulted in the corresponding C-3 alkylated product, **3ae**, with a yield of 76%. Similarly, indole derivatives, **3d** and **3e**, yielded the C3-alkylated products, **3de** and **3ee**, respectively with good yields of 66% and 69%.

3-alkenylated and alkylated indole derivatives represent attractive synthetic targets due to their pharmacological activity and their role precursors for many drugs, such as Roxindole, Oxypertine and Oxigon. To demonstrate the utility of C3-functionalized indoles, we attempted the conversion of the C3 alkenyl indoles into further modifications (Scheme 3).

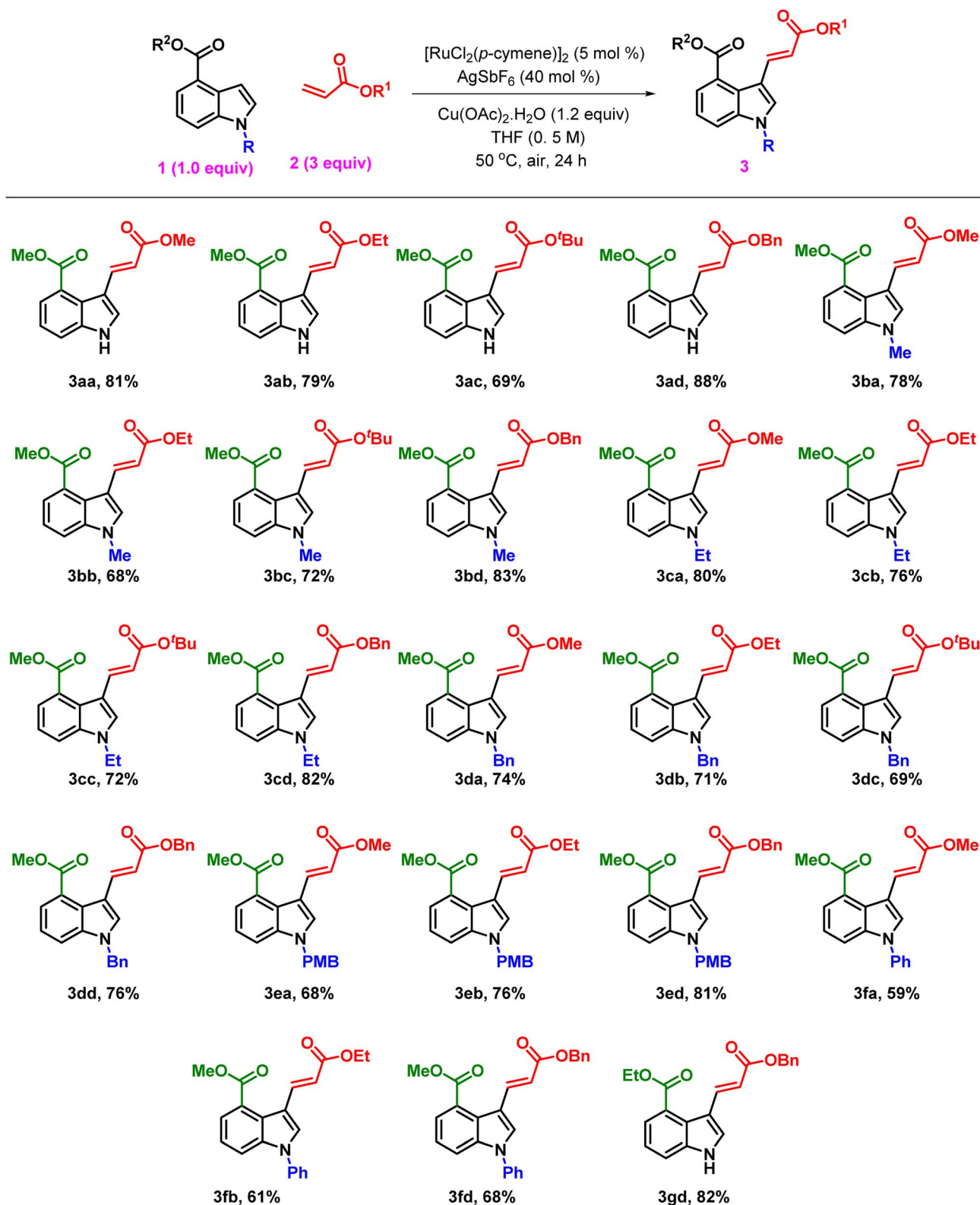
The C-3 alkenylated indole derivatives were further modified into analogues of drug molecules to evaluate the feasibility of their synthesis (Scheme 3b). The C-3 alkenyl indole derivative, **3ac**, was selectively reduced to the C-3 alkylated indole derivative **4** with an 88% yield, using hydrogen gas under 1 atm pressure in the presence of 10% Pd/C as a catalyst in dioxane. Further hydrolysis of **4** resulted in the generation of compound **5**, a derivative of Oxigon (drug for Alzheimer's) and Tryptophan (natural amino acid). Consequent amide formation of **5** yielded **6a**, a derivative of Oxypertine (antipsychotic agent), and **6b**,

a derivative of Roxindole (antipsychotic agent), with yields of 80% and 83% respectively.

To explain the origin of the site-selectivity of the ruthenium-catalysed C–H functionalization, deuterium incorporation experiments were conducted under standard reaction conditions (Scheme 4a). The analysis of the product revealed that methyl-1*H*-indole-4-carboxylate **1a** in the absence of alkene resulted in indole, **1a**-(D), with 50% deuterium incorporation at the C3 position, strongly supported by the observed regioselectivity (Scheme 4a). To ascertain whether the reaction proceeds through a radical pathway, the reaction was performed in the presence of 1 equiv. of TEMPO ((2,2,6,6-Tetramethylpiperidin-1-yl)oxyl) and BHT (2,6-di-*tert*-butyl-4-methylphenol). In both the cases, we obtained a good yield of the product **3ab** (68% and 63%, Scheme 4b). These findings suggest that the reaction proceeds through a non-radical pathway.

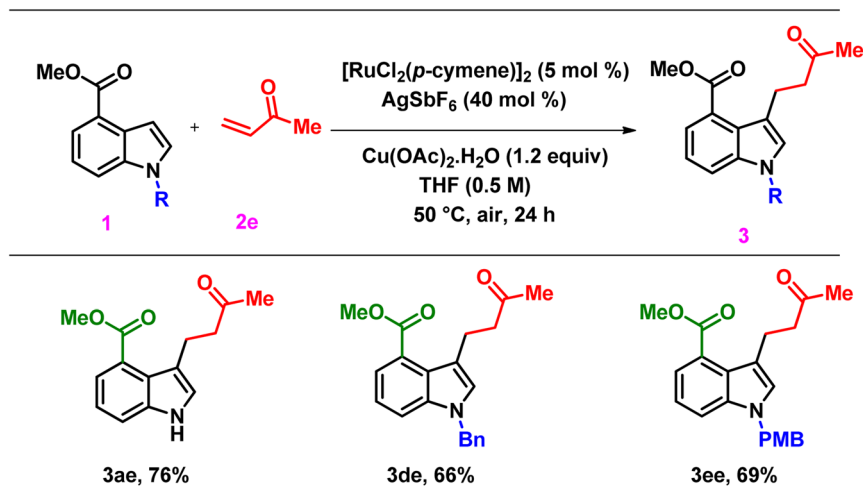
Scheme 5 illustrates a workable multistep catalytic cycle that has been proposed based on previous literature studies.¹⁸ In the presence of Cu(OAc)₂·H₂O and AgSbF₆, an active catalyst, labelled as **I**, is formed. The first step involves the coordination of methyl-1*H*-indole-4-carboxylate, **1a**, with an active ruthenium catalyst, followed by C–H metalation and release of AcOH,



Table 2 Scope of indoles and acrylates^{a,b}

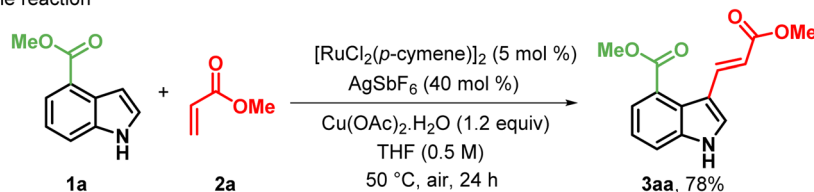
^a Reaction conditions: 1 (1 equiv, 0.2 mmol), 2 (3 equiv, 0.6 mmol), $[\text{RuCl}_2(p\text{-cymene})]_2$ (5.0 mol %), AgSbF_6 (20 mol %), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1.2 equiv, 0.24 mmol), THF (0.5 M), 50 °C, 24 h. ^b Isolated yield; (Me = methyl, Et = ethyl, Bn = benzyl, Ph = Phenyl, PMB = *p*-methoxybenzyl).



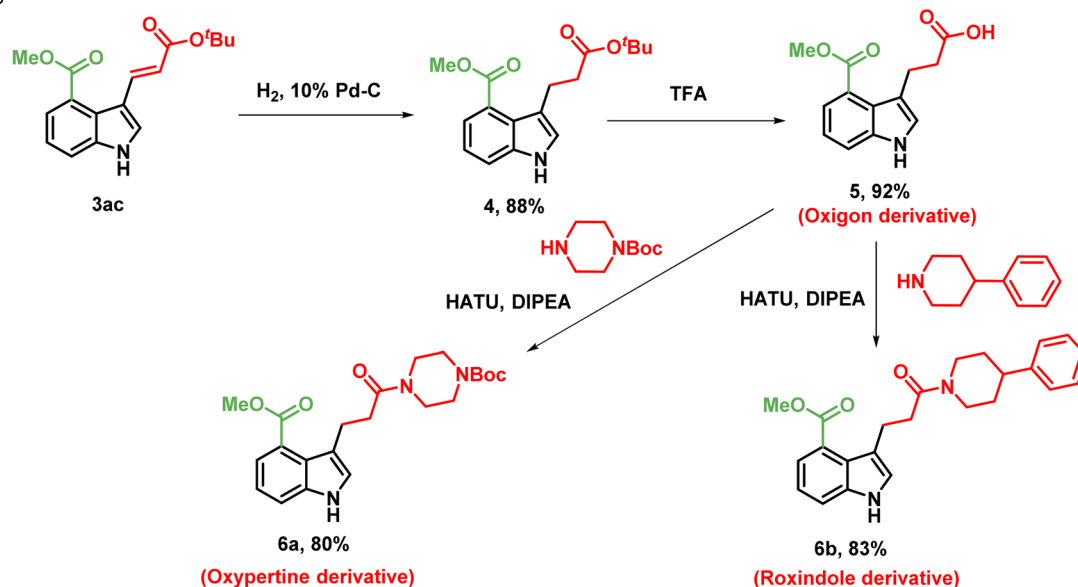


Scheme 2 C3 alkylation with vinyl methyl ketone.^{a,b} Reaction conditions: **1** (1 equiv, 0.2 mmol), **2** (3 equiv, 0.6 mmol), [RuCl₂(*p*-cymene)]₂ (5.0 mol%), AgSbF₆ (20 mol%), Cu(OAc)₂·H₂O (1.2 equiv, 0.24 mmol), THF (0.5 M), 50 °C, 24 h. ^bIsolated yield.

(a) 3 mmol scale reaction



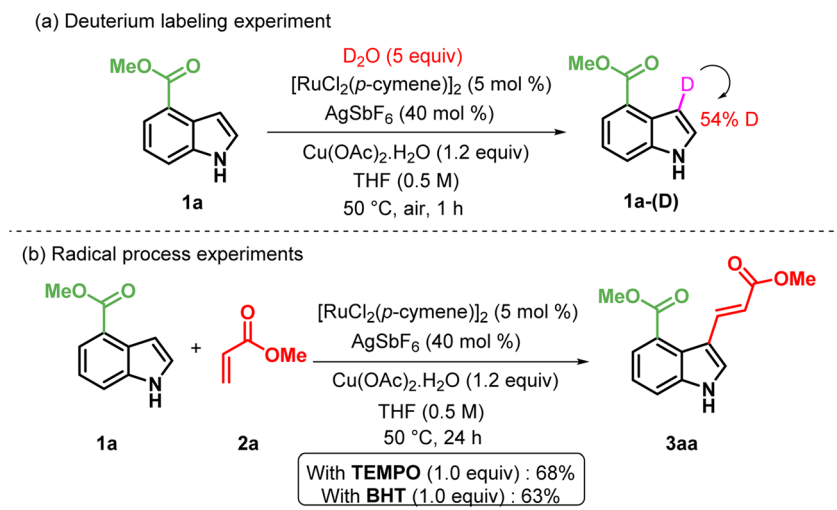
(b) Synthetic transformations



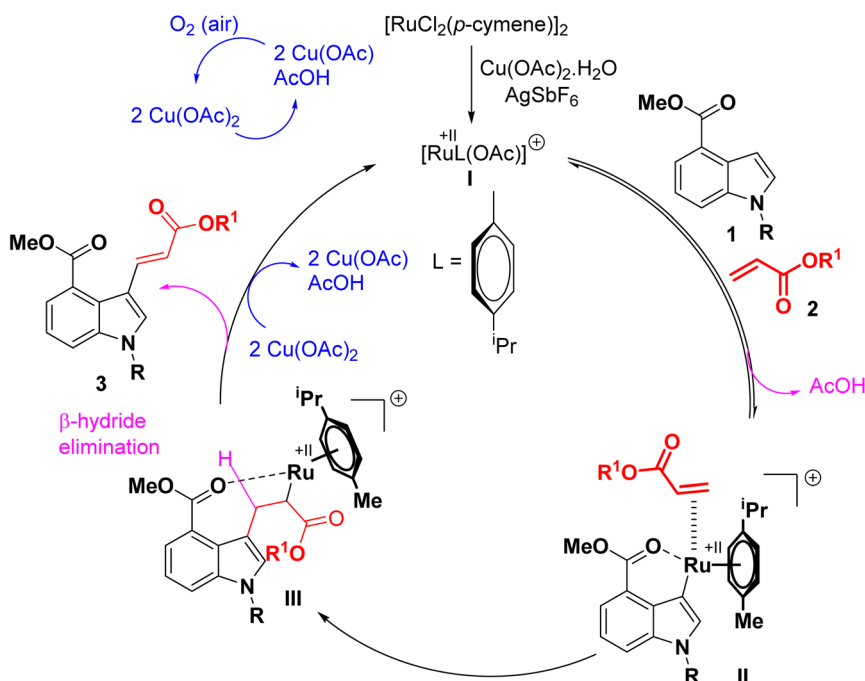
Scheme 3 Synthetic Transformations of C3 Alkenyl Indoles.

leading to the formation of a six-membered ruthenium complex **II**. Subsequent coordination followed by insertion of acrylate **2** with intermediate **II** gave rise to the intermediate **III**. Finally, β -

hydride elimination followed by release of AczH, led to the formation of the desired product **3**, and the active catalyst was regenerated by reoxidation using Cu(OAc)₂·H₂O and air.



Scheme 4 Mechanistic studies of site-selectivity of the ruthenium-catalysed C–H functionalization.



Scheme 5 Mechanism of ruthenium-catalyzed site-selective C-3 alkenylation of indole derivatives.

$\text{Cu}(\text{OAc})_2$ act as a source of AcOH and air act as a terminal oxidant.¹⁶⁰

Conclusions

In summary, we have developed a ruthenium-catalyzed site-selective C-3 alkenylation of indole derivatives by utilizing a directing group strategy *via* the formation of a 6-membered metallacycle. This method holds significance as it facilitates the formation of valuable 3-substituted indoles, a crucial class of molecules in medicinal chemistry, chemical biology, drug discovery, and related heterocyclic compounds. This method

not only ensures high site selectivity but also offers mild reaction conditions, and broad substrate scope, making it a valuable approach for the functionalization of indole derivatives.

Data availability

Experimental procedures and the characterization data for reaction products, copies of NMR and additional information underlying this study are available in the published article and its ESI.† The authors confirm that the data supporting the findings of this study are available within the article [and/or] its ESI materials.†



Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors are thankful to Dr Chandrasekhar Korapala, Dr Sathya Shanker and Dr Tonykurissery Anthappan of Syngene Intl. Ltd for their help and support during this research work. IS gratefully acknowledges the Department of Science and Technology (DST) and SERB for research grants (GITA/DST/TWN/P-103/2022) and (CRG/2021/003355) New Delhi, India.

References

- (a) Y. Ban, Y. Murakami, Y. Iwasawa, M. Tsuchiya and N. Takano, *Org. Biomol. Chem.*, 1988, **8**, 231; (b) U. Pindur and T. Lemster, *Curr. Med. Chem.*, 2001, **8**, 1681; (c) A. Ramirez and S. Garcia-Rubio, *Curr. Med. Chem.*, 2003, **10**, 1891; (d) A. J. Kochanowska-Karamyan and M. T. Hamann, *Chem. Rev.*, 2010, **110**, 4489.
- (a) Y. Meng, B. Yu, H. Huang, Y. Peng, E. Li, Y. Yao, C. Song, W. Yu, K. Zhu, K. Wang, D. Yi, J. Du and J. Chang, *J. Med. Chem.*, 2021, **64**, 925; (b) G. M. Ziarani, R. Moradi, T. Ahmadi and N. Lashgari, *RSC Adv.*, 2018, **8**, 12069; (c) V. Sharma, P. Kumar and D. Pathak, *J. Heterocycl. Chem.*, 2010, **47**, 491; (d) H. Xu and M. Lv, *Curr. Pharm. Des.*, 2009, **15**, 2120–2148; (e) V. Sharma, P. Kumar and D. Pathak, *J. Heterocycl. Chem.*, 2010, **47**, 491; (f) S. Lal and T. J. Snape, *Curr. Med. Chem.*, 2012, **19**, 4828.
- (a) Q. Chen, C. Wu, J. Zhu, E. Li and Z. Xu, *Med. Chem.*, 2022, **22**, 993; (b) Y. Wang, Y. Li, C. Yu, Y. Mi and Z. Tian, *Eur. J. Med. Chem.*, 2019, **183**, 111691; (c) K. Hemalatha, G. Madhumitha and S. M. Roopan, *Chem. Sci. Rev. Lett.*, 2013, **2**, 287; (d) M. Z. Zhang, Q. Chen and G. F. Yang, *Eur. J. Med. Chem.*, 2015, **89**, 421–441; (e) N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma and E. H. Choi, *Molecules*, 2013, **18**, 6620.
- (a) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879; (b) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315; (c) K. M. Engle, T.-S. Mei, M. Wasa and J. Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788; (d) X. Chen, K. M. Engle, D. H. Wang and J. Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (e) V. S. Thirunavukkarasu, S. I. Kozhushkov and L. Ackermann, *Chem. Commun.*, 2014, **50**, 29; (f) S. R. Neufeldt and M. S. Sanford, *Acc. Chem. Res.*, 2012, **45**, 936–946; (g) J. F. Hartwig, *Acc. Chem. Res.*, 2017, **50**, 549–555; (h) T. Brandhofer and O. García Mancheño, *Eur. J. Org. Chem.*, 2018, **2018**(44), 6050–6067; (i) V. K. Tiwari and M. Kapur, *Org. Biomol. Chem.*, 2019, **17**(5), 1007–1026; (j) R. Das, N. P. Khot, A. S. Deshpande and M. Kapur, *Chem.–Eur. J.*, 2019, **26**(4), 927–938; (k) T. Iwai and M. Sawamura, *ACS Catal.*, 2015, **5**(9), 5031–5040; (l) K. Hirano and M. Miura, *Chem. Sci.*, 2018, **9**(1), 22–32; (m) W. Wang, M. M. Lorion, J. Shah, A. R. Kapdi and L. Ackermann, *Angew. Chem.*, 2018, **57**(45), 14700–14717; (n) W. Ma, P. Gandeepan, J. Li and L. Ackermann, *Org. Chem. Front.*, 2017, **4**(7), 1435–1467.
- (a) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740; (b) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315; (c) V. Ritleng, C. Sirlin and M. Pfeffer, *Chem. Rev.*, 2002, **102**, 1731; (d) K. Padala and M. Jeganmohan, *Org. Lett.*, 2011, **13**, 6144; (e) D. Colby, A. Tsai, R. Bergman and J. Ellman, *Acc. Chem. Res.*, 2012, **45**, 814.
- (a) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (b) K. M. Engle, T.-S. Mei, M. Wasa and J. Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788; (c) S. R. Neufeldt and M. S. Sanford, *Acc. Chem. Res.*, 2012, **45**, 936.
- (a) L. Ackermann and J. Pospech, *Org. Lett.*, 2011, **13**, 4153; (b) K. Padala and M. Jeganmohan, *Org. Lett.*, 2011, **13**, 6144; (c) K. Padala and M. Jeganmohan, *Org. Lett.*, 2012, **14**, 1134; (d) X. Lu, C. Shen, K. Meng, L. Zhao, T. Li, Y. Sun, J. Zhang and G. Zhong, *Chem. Commun.*, 2019, **55**, 826; (e) R. Manikandan, P. Madasamy and M. Jeganmohan, *ACS Catal.*, 2016, **6**, 230; (f) G. D. Dias, T. A. Nascimento, K. A. Andresa, D. Almeida, A. C. S. Bombaça, F. S. Rubem, M. Barreto, C. Jacob, S. Warratz, N. Eufânio, D. S. Júnior and L. Ackermann, *Eur. J. Org. Chem.*, 2019, **13**, 2344; (g) P. Zhao, R. Niu, F. Wang, K. Han and X. Li, *Org. Lett.*, 2012, **14**, 4166; (h) M. Bakthadoss and P. V. Kumara, *Adv. Synth. Catal.*, 2018, **360**, 1.
- (a) H. Liang and J. Wang, *Chem.–Eur. J.*, 2022, **29**, 7; (b) H. E. Ketcham, M. T. Bennett, C. W. Reid and T. B. Gunnoe, *Adv. Organomet. Chem.*, 2023, **93**, 93–176; (c) P. Singh, K. K. Chouhan and A. Mukherjee, *Chem.–Asian J.*, 2021, **16**, 2392–2412; (d) G.-F. Zha, H.-L. Qin and E. A. B. Kantchev, *RSC Adv.*, 2016, **6**, 30875–30885; (e) C. Shan, L. Zhu, L.-B. Qu, R. Bai and Y. Lan, *Chem. Soc. Rev.*, 2018, **47**, 7552–7576; (f) S. I. Kozhushkov and L. Ackermann, *Chem. Sci.*, 2013, **4**, 886–896.
- N. P. Grimster, C. Gauntlett, C. R. A. Godfrey and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2005, **20**, 3125.
- (a) X. Zhang, Y. Li, H. Shi, L. Zhang, S. Zhang, X. Xu and Q. Liu, *Chem. Commun.*, 2014, **50**, 7306; (b) A. M. Martinez, J. Echavarren, I. Alonso, N. Rodriguez, R. G. Arrayas and J. C. Carretero, *Chem. Sci.*, 2015, **6**, 5802; (c) D. Ghorai, C. Dutta and J. Choudhury, *ACS Catal.*, 2016, **6**, 709; (d) T. Yamada, Y. Shibata and K. Tanaka, *Chem.–Eur. J.*, 2019, **25**, 16022; (e) S. Wu, Z. Wang, D. Ma, C. Chen and B. Zhu, *Org. Chem. Front.*, 2020, **7**, 1158; (f) X. Xu, C. Luo, H. Zhao, Y. Pan, L. Zhang, J. Li, L. Xu, M. Lei and P. J. Walsh, *Chem.–Eur. J.*, 2021, **27**, 8811.
- (a) J. Sim, B. Ryou, M. Choi, C. Lee and C.-M. Park, *Org. Lett.*, 2022, **24**(23), 4264–4269; (b) C. Tan, H. Jiang, M. Zeng, K. Li, Z. Chen and G. Yin, *Org. Biomol. Chem.*, 2022, **20**(7), 1425–1435; (c) C.-J. Wu, W.-X. Cao, B. Chen, C.-H. Tung and L.-Z. Wu, *Org. Lett.*, 2021, **23**(6), 2135–2139; (d) X.-R. Wu, H.-L. Peng, L.-Q. Wei, L.-P. Li, S.-Y. Yao and B.-H. Ye, *Catal. Commun.*, 2019, **124**, 12–18; (e) F. G. Cirujano, P. Leo, J. Vercammen, S. Smolders, G. Orcajo and D. E. De Vos, *Adv. Synth. Catal.*, 2018, **360**, 3872–3876; (f) A. K. Verma, A. K. Danodia, R. K. Saunthwal, M. Patel and



- D. Choudhary, *Org. Lett.*, 2015, **17**, 3658–3661; (g) R. K. Saunthwal, M. Patel, S. Kumar, A. K. Danodia and A. K. Verma, *Chem.–Eur. J.*, 2015, **21**, 18601–18605.
- 12 (a) C. Bruneau and R. Gramage-Doria, *Coord. Chem. Rev.*, 2021, **428**, 213602; (b) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879.
- 13 X. Cui, X. Xu, S. J. McClain, B. Donnadiou, Z. Zhu, X. Qian, H. H. C. Lakmal and Z. U. Li, *J. Am. Chem. Soc.*, 2019, **141**, 15730.
- 14 (a) Y. Zhang, J. Zheng and S. Cui, *J. Org. Chem.*, 2014, **79**, 6490; (b) H. Ikemoto, T. Yoshino, K. Sakata, S. Matsunaga and M. Kanai, *J. Am. Chem. Soc.*, 2014, **136**, 5424; (c) Z. Q. Song, R. Samanta and A. P. Antonchick, *Org. Lett.*, 2013, **15**, 5662; (d) B. Li, J. Ma, W. Xie, H. Song, S. Xu and B. Wang, *J. Org. Chem.*, 2013, **78**, 9345; (e) X. F. Yang, X. H. Hu, C. Feng and T. P. Loh, *Chem. Commun.*, 2015, **51**, 2532; (f) J. Shi, Y. Yan, Q. Li, H. E. Xu and W. Yi, *Chem. Commun.*, 2014, **50**, 6483; (g) V. Lanke and K. R. Prabhu, *Org. Lett.*, 2013, **15**, 6262; (h) Q. Liu, Q. Li, Y. Ma and Y. Jia, *Org. Lett.*, 2013, **15**, 4528.
- 15 (a) Y.-H. Sun, T.-Y. Sun, Y.-D. Wu, X. Zhang and Y. Rao, *Chem. Sci.*, 2016, **7**, 2229–2238; (b) Y. C. Yuan, C. Bruneau, V. Dorcet, T. Roisnel and R. Gramage-Doria, *J. Org. Chem.*, 2019, **84**, 1898–1907; (c) Y. C. Yuan, C. Bruneau, T. Roisnel and R. Gramage-Doria, *Org. Biomol. Chem.*, 2019, **17**, 7517–7525; (d) Y. C. Yuan, C. Bruneau, T. Roisnel and R. Gramage-Doria, *Catal. Sci. Technol.*, 2019, **9**, 4711–4717; (e) Y. C. Yuan, C. Bruneau, T. Roisnel and R. Gramage-Doria, *J. Org. Chem.*, 2019, **84**, 12893–12903; (f) Y. Hashimoto, K. Hirano, T. Satoh, F. Kakiuchi and M. Miura, *Org. Lett.*, 2012, **14**, 2058–2061; (g) Y. Hashimoto, K. Hirano, T. Satoh, F. Kakiuchi and M. Miura, *J. Org. Chem.*, 2013, **78**, 638–646; (h) K. D. Collins, F. Lied and F. Glorius, *Chem. Commun.*, 2014, **50**, 4459–4461; (i) W. Liu and L. Ackermann, *Chem. Commun.*, 2014, **50**, 1878–1881; (j) Y. C. Yuan, Q. L. Lu, X. T. Zhu, S. Posada-Pérez, M. Solà, A. Poater and R. Gramage-Doria, *Org. Chem. Front.*, 2023, **10**, 42–53; (k) J. Park, J. Lee and S. Chang, *Angew. Chem.*, 2017, **129**, 4320–4324; (l) P. G. Chirila, L. Skibinski, K. Miller, A. Hamilton and C. J. Whiteoak, *Adv. Synth. Catal.*, 2018, **360**, 2324–2332; (m) R. Gramage-Doria, *Chem.–Eur. J.*, 2020, **26**, 9688–9709; (n) Y. C. Yuan, M. Goujon, C. Bruneau, T. Roisnel and R. Gramage-Doria, *J. Org. Chem.*, 2019, **84**, 16183–16191.
- 16 (a) X. H. Hu, J. Zhang, X. F. Yang, Y. H. Xu and T. P. Loh, *J. Am. Chem. Soc.*, 2015, **137**, 3169; (b) K. Padala, S. Pimparkar, P. Madasamy and M. Jeganmohan, *Chem. Commun.*, 2012, **48**, 7140; (c) Y. Hatamoto, S. Sakaguchi and Y. Ishii, *Org. Lett.*, 2004, **6**, 4623–4625; (d) Y. H. Xu, W. J. Wang, Z. K. Wen, J. J. Hartley and T. P. Loh, *Tetrahedron Lett.*, 2010, **51**, 3504–3507; (e) J. Zhang and T. P. Loh, *Chem. Commun.*, 2012, **48**, 11232–11234; (f) X. H. Hu, J. Zhang, X. F. Yang, Y. H. Xu and T. P. Loh, *J. Am. Chem. Soc.*, 2015, **137**, 3169–3172; (g) T. Zhu, Z. Li, F. Xiao and W. L. Duan, *Tetrahedron Lett.*, 2018, **59**, 3238–3241; (h) C. Yu, F. Li, J. Zhang and G. Zhong, *Chem. Commun.*, 2017, **53**, 533–536; (i) F. Li, C. Yu, J. Zhang and G. Zhong, *Org. Lett.*, 2016, **18**, 4582–4585; (j) R. Lekkala, R. Lekkala, B. Moku and H. L. Qin, *Org. Chem. Front.*, 2019, **6**, 796–800; (k) M. Bakthadoss, T. T. Reddy, V. Agarwal and D. S. Sharada, *Chem. Commun.*, 2022, **58**, 1406–1409; (l) H. Sindhe, A. Kamble, M. M. Reddy, A. Singh and S. Sharma, *Org. Biomol. Chem.*, 2024, **22**, 1162–1166; (m) A. Aloia, M. Casiello, A. Nacci and A. Monopoli, *Eur. J. Org. Chem.*, 2024, **27**, e202400111; (n) P. Sand and B. Schmidt, *Eur. J. Org. Chem.*, 2021, **2021**(40), 5497–5506; (o) K. Graczyk, W. Ma and L. Ackermann, *Org. Lett.*, 2012, **14**, 4110–4113.
- 17 (a) R. Giri, A. T. Brusoe and B. M. Trost, *Org. Biomol. Chem.*, 2011, **9**, 6496–6500; (b) D. C. Powers and T. Ritter, *Acc. Chem. Res.*, 2012, **45**, 840–850; (c) J. Q. Yu and Z. Shi, *Chem. Rev.*, 2016, **116**, 4648–4682; (d) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147–1169; (e) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792–9826.
- 18 (a) S. R. Mohanty, N. Prusty, T. Nanda, S. K. Banjare and P. C. Ravikumar, *J. Org. Chem.*, 2022, **87**, 6189; (b) P. P. Jadhav, N. M. Kahar and S. G. Dawande, *Org. Lett.*, 2021, **23**, 8673; (c) J. Smith, A. Johnson, B. Lee and C. Wong, *Catal. Sci. Technol.*, 2021, **11**, 5772; (d) K. Graczyk, W. Ma and L. Ackermann, *Org. Lett.*, 2012, **14**, 4110–4113; (e) J. A. Leitch, P. B. Wilson, C. L. McMullin, M. F. Mahon, Y. Bhonoah, I. H. Williams and C. G. Frost, *ACS Catal.*, 2016, **6**, 5520–5529.

