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Regioselective Ru(II)-catalyzed C–H alkenylation and annulation of indoles: a direct approach to fused lactone scaffolds

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In this work, we offer a method for selectively alkenylating C5–H and then annulating indole-4-carboxylic acid derivatives using ruthenium(II) as a catalyst. Our approach facilitates the effective formation of fused lactone structures by employing a weakly coordinating carboxylic acid group at the C4 position as a guiding group. The reaction process starts with an alkenylation at the C5 position of the indole ring, followed by an intramolecular Michael addition to produce annulated lactones in high yields. This is the first report of ruthenium-catalyzed lactone synthesis at the C5 position of indoles *via* a carboxylic acid directing group. We anticipate that because of its simplicity, high regioselectivity, and use of readily available starting materials, this process will open up new options for constructing functionalized lactone scaffolds that could be immensely valuable in medical and pharmacological studies.

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Introduction

Lactones and their derivatives are important heterocyclic motifs widely found in natural products and bioactive molecules (Fig. 1).[1–11] For instance, γ-rubromycin exhibits activity against HIV-1 reverse transcriptase and telomerase, overexpressed in cancer cells; purpuromycin is a potential topical agent for treating vaginal infections. Thunberginol F and its analogues show anti-allergic and antimicrobial effects, while cattienoid B, a steroid from *Tomophagus cattienensis*, demonstrates cytotoxicity against KB carcinoma cells. These frameworks also serve as versatile building blocks and intermediates in organic synthesis.[4,12–16] Lactone-based compounds exhibit diverse bioactivities, including antibacterial, anti-HIV, antifungal, antibiotic, antitumor, and immunosuppressive properties.[17–21] Although several synthetic strategies for phthalides have been reported,[22–33] many involve multistep procedures. Thus, developing efficient and direct methods for constructing phthalide scaffolds remains a critical goal.

In parallel, indole frameworks represent one of the most valuable and ubiquitous heterocycles in nature, playing a pivotal role in medicinal chemistry.[34–37] Their unique reactivity has driven extensive efforts toward selective functionalization at various positions.[38–41] The indole nucleus contains six distinct reactive sites, but selectively targeting the less reactive benzenoid ring—especially over the more reactive C2 and C3 positions—remains challenging.[42–46]

Indoles and their fused analogues exhibit a broad spectrum of pharmacological properties, including anti-inflammatory, antitubercular, antidiabetic, anti-HIV, and anticonvulsant activities (Fig. 1).[47] Among these, indole-fused lactones are particularly intriguing due to the potential synergistic enhancement of biological and chemical properties.[48] These hybrid molecules may open new avenues in drug discovery and material science.[49,50] Despite their promise, synthetic strategies for constructing indole–lactone hybrids, particularly *via* direct C–H activation, remain limited.[51–54]

Transition-metal-catalyzed C–H activation has emerged as a precise method for site-selective modification of (hetero) arenes.[55–59] Ruthenium, in particular, offers advantages such as high efficiency, broad functional group tolerance, and mild reaction conditions.[60–63] Ru(II)-catalyzed annulation of indoles has garnered significant interest,[62,63] yet selective annulation at the C5 position to construct lactone rings is underexplored.[64] Transition-metal-catalyzed annulations *via* C–H activation have revolutionized cyclic compound synthesis.[65,66] While Rh(III) catalysts are effective, their high cost limits widespread use, prompting interest in Ru(II) complexes as cost-effective alternatives.[67–69]

Selective functionalization at the indole C5 position is particularly challenging due to electronic and steric factors. Typically, indoles favour reactions at the more reactive C2 or C3 positions, making selective C5 activation difficult.[70–74] The planar structure and stability of the indole ring contribute to the low reactivity of the C5–H bond. Traditional methods often require harsh conditions, risking degradation.[75] Despite recent advances, achieving high selectivity and yield at C5 remains elusive.[76,77] Selective C5-functionalization is vital for accessing

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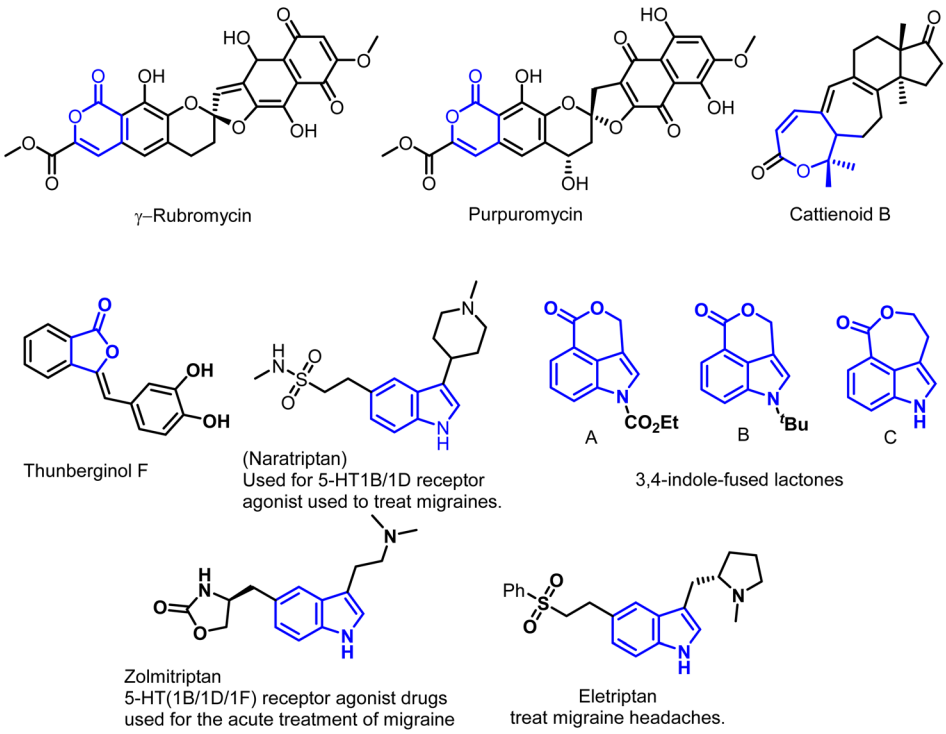


Fig. 1 Pharmaceutically active compounds containing indole and lactone derivatives.

bioactive derivatives with potential therapeutic applications.[57,78,79] Even with directing groups, selective activation is complicated when similarly reactive C–H bonds are nearby.[25,80–85] In particular, directing C5 activation from a C4 position is difficult due to the higher reactivity of adjacent C3. As a result, C5-selective functionalization remains underdeveloped.

Satoh and Miura reported a Rh-catalyzed reaction between benzoic acids and acrylates producing 7-vinylphthalides (Scheme 1a).[26] Zhao and Su observed mixed products *via* Rh-catalyzed C–H olefination of benzoic acids (Scheme 1b).[86] Ackermann's group demonstrated Ru-catalyzed synthesis of phthalides from benzoic acids and conjugated alkenes (Scheme 1c).[87] Breit and co-workers reported a Rh(III)-catalyzed *ortho*-C–H olefination of carboxylic acids using a urea-functionalized Cp* ligand (Scheme 1d), where non-covalent interactions with the substrate enhanced reactivity and enabled efficient functionalization of less reactive substrates.[93]

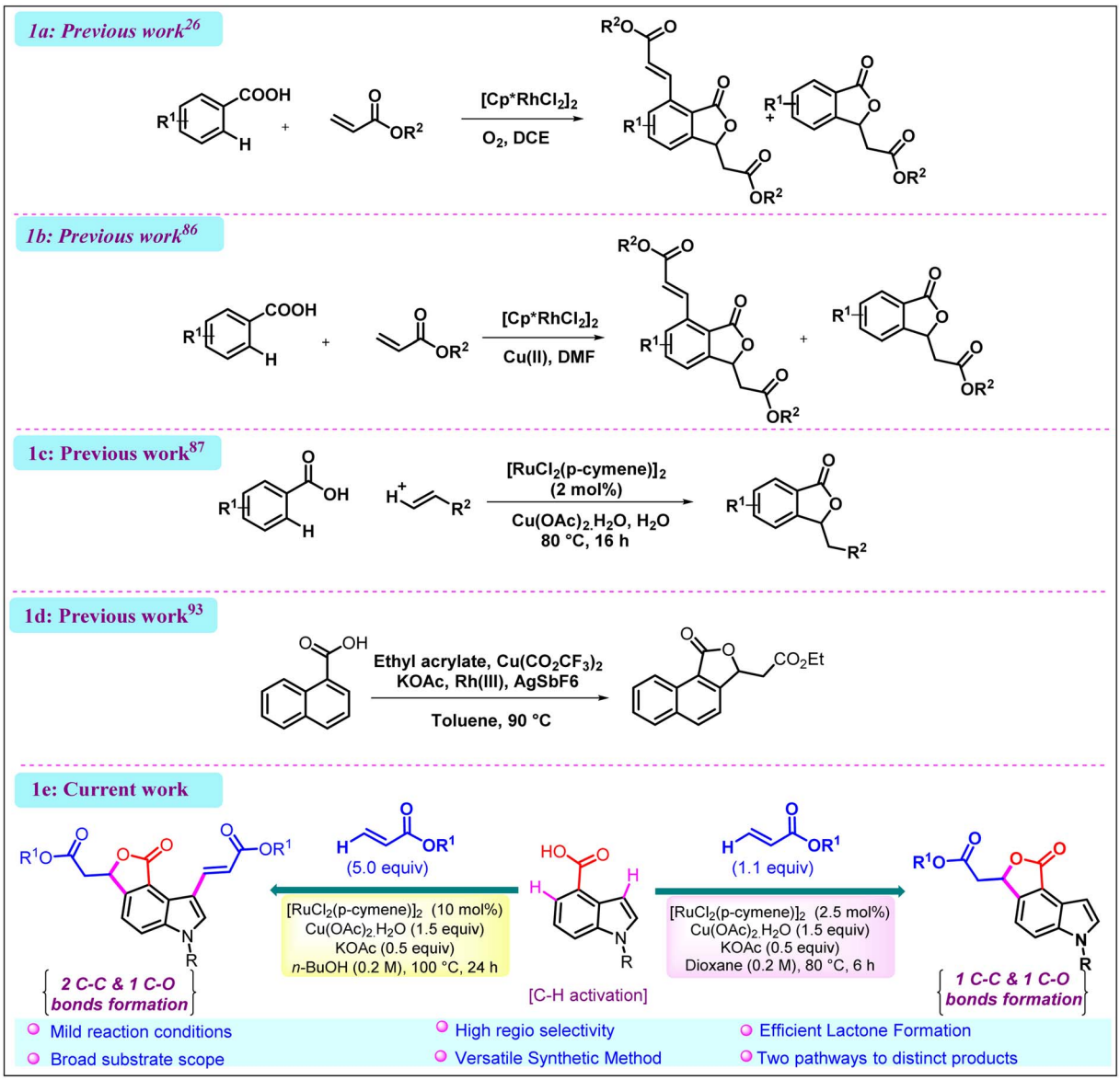
Building on our previous work on indole functionalization,[88–92] we now report a Ru(II)-catalyzed strategy for site-selective annulation at the indole C5 position to construct five-membered lactone rings and achieve C3 olefination (Scheme 1e). Employing a C4 carboxylic acid as a directing group under mild conditions, our method offers high regioselectivity and broad functional group tolerance.

Results and discussion

Initially, the reaction of 1*H*-indole-4-carboxylic acid (**1a**) with ethyl acrylate (**2b**) was examined as the model reaction. The results of screening various reaction conditions are shown in Table 1 (for detailed optimization of reaction conditions and corresponding results, please refer to SI Section 2). Initially, we investigated the effect of selected oxidants, additives, and solvents on the ruthenium-catalyzed cross-dehydrogenative alkenylation of 1*H*-indole-4-carboxylic acid (**1a**), followed by annulation with olefin **2b** to as synthesized products **3ab** and **4ab**. We observed that the desired products **3ab** and **4ab** were not formed in the absence of either the oxidant or the ruthenium catalyst (entries **1** and **2**).

We initiated our study by examining the model reaction of 1*H*-indole-4-carboxylic acid (**1a**, 1.0 equiv.) and ethyl acrylate (**2b**, 1.1 equiv.) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%) and $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv.) as the oxidant, in dioxane at 80 °C for 12 hours to establish optimal conditions.

Under the initial conditions, product **3ab** was obtained in 42% yield (entry **3**). The yield significantly improved to 76% upon the addition of potassium acetate (KOAc, 0.5 equiv.) (entry **4**). However, extending the reaction time to 24 hours led to a slight decrease in yield (entry **5**). Additionally, we found that substituting KOAc with other metal acetates resulted in lower yields (entries **6–8**). Interestingly, a shorter reaction time of 6 hours led to a further improvement in yield, providing **3ab** in 86% yield (entry **9**). We then examined the effect of solvent polarity by evaluating various solvents, including DCE, DME, MeOH, *t*-AmOH, and THF (entries **10–15**). We observed that dioxane was the most efficient solvent, providing the maximum yield of 86% (entry **9**) whereas DMF produced the lowest yield of **3ab**, at 18% (entry **13**). It reveals that increasing the equivalents of **2a** enhanced the yield of product **4ab**, while the yield of **3ab**



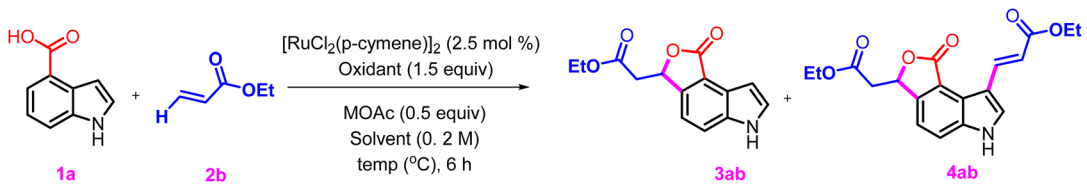
Scheme 1 Comparison with previous works.

decreased (Table 1, entry **16**). Furthermore, higher catalyst loading improved the yield to 58% of **4ab**, indicating that both increased catalyst loading and excess **2b** favour the formation of **4ab**. Additionally, prolonging the reaction time and increasing the reaction temperature to 120 °C further improved the yield of **4ab** (entries **19** & **20**). Among the solvents tested (Table 1, entries **3–7**), *n*-BuOH provided the highest yield of **4ab** (84%). Thus, the optimal reaction conditions for C5 alkenylation–annulation of **1a** involve the use of 2.5 mol% of $[RuCl_2(p\text{-cymene})]_2$, 1.5 equiv. of $Cu(OAc)_2 \cdot H_2O$, 0.5 equiv. of KOAc, and 1.1 equiv. of **2** in 0.2 M dioxane at 80 °C for 6 hours. Additionally, the optimal conditions for C5 alkenylation–annulation followed by C3 alkenylation of **1a** involve the use of 10 mol% of $[RuCl_2(p\text{-cymene})]_2$, 1.5 equiv. of $Cu(OAc)_2 \cdot H_2O$, 0.5 equiv. of KOAc, and 5 equiv. of **2** in 0.2 M *n*-BuOH at 120 °C for 24 hours.

After optimizing the reaction conditions, we explored the substrate scope and generality of the reaction for the C5 alkenylation–annulation of various indole derivatives (**1**) with different acrylates (**2**), which furnished products in good to excellent yields (Scheme 2). The results are summarized in Scheme 2 (for the general reaction protocol, please refer to SI Section 3.2).

The reaction of indole derivative **1a** with sterically distinct acrylates produced the corresponding products **3aa–3ad** in yields ranging from 73% to 86%. However, no product was observed when using acrylic acid as the substrate. Similarly,

Table 1 Optimization of the Ru-catalyzed alkenylation/annulation[a]



Entry	2b (equiv.)	Oxidant (equiv.)	MOAc	Solvent	Temp. (°C)	Time (h)	Yield (%)[b] 3ab	4ab
1[c]	1.1	—	—	Dioxane	80	12	nd	
2[d]	1.1	$Cu(OAc)_2 \cdot H_2O$	—	Dioxane	80	12	nd	
3	1.1	$Cu(OAc)_2 \cdot H_2O$	—	Dioxane	80	12	42	—
4	1.1	$Cu(OAc)_2 \cdot H_2O$	KOAc	Dioxane	80	12	76	—
5	1.1	$Cu(OAc)_2 \cdot H_2O$	KOAc	Dioxane	80	24	61	Trace
6	1.1	$Cu(OAc)_2 \cdot H_2O$	LiOAc	Dioxane	80	12	68	—
7	1.1	$Cu(OAc)_2 \cdot H_2O$	NaOAc	Dioxane	80	12	61	—
8	1.1	$Cu(OAc)_2 \cdot H_2O$	CsOAc	Dioxane	80	12	52	—
9	1.1	$Cu(OAc)_2 \cdot H_2O$	KOAc	Dioxane	80	6	86	—
10	1.1	$Cu(OAc)_2 \cdot H_2O$	KOAc	THF	80	6	61	—
11	1.1	$Cu(OAc)_2 \cdot H_2O$	KOAc	DME	80	6	68	—
12	1.1	$Cu(OAc)_2 \cdot H_2O$	KOAc	DCE	80	6	52	—
13	1.1	$Cu(OAc)_2 \cdot H_2O$	KOAc	DMF	80	6	18	—
14	1.1	$Cu(OAc)_2 \cdot H_2O$	KOAc	MeOH	80	6	48	Trace
15	1.1	$Cu(OAc)_2 \cdot H_2O$	KOAc	*t*-AmOH	80	6	56	6
16	3.0	$Cu(OAc)_2 \cdot H_2O$	KOAc	Dioxane	80	6	16	46
17[e]	3.0	$Cu(OAc)_2 \cdot H_2O$	KOAc	Dioxane	80	6	12	51
18[e]	5.0	$Cu(OAc)_2 \cdot H_2O$	KOAc	Dioxane	80	6	7	58
19[e]	5.0	$Cu(OAc)_2 \cdot H_2O$	KOAc	Dioxane	80	24	—	68
20[e]	5.0	$Cu(OAc)_2 \cdot H_2O$	KOAc	Dioxane	120	24	—	75
20[e]	5.0	$Cu(OAc)_2 \cdot H_2O$	KOAc	*t*-AmOH	120	24	—	77
21[e]	5.0	$Cu(OAc)_2 \cdot H_2O$	KOAc	*n*-BuOH	120	24	—	84

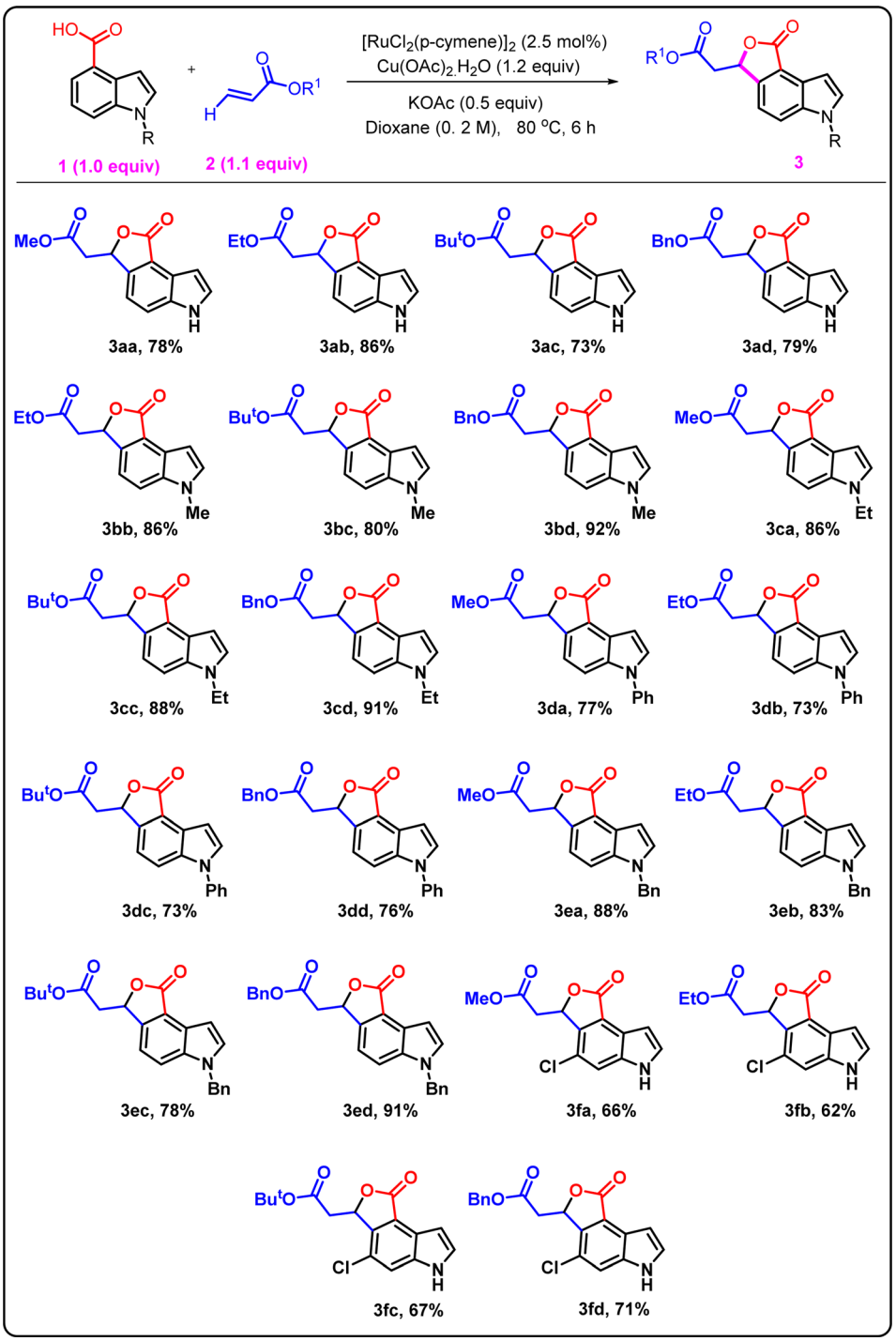
[a] Reaction conditions: **1a** (1.0 equiv.), **2b** (1.1 equiv.), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%), $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv.), KOAc (0.5 equiv.), solvent (0.2 M), *x* °C, time (*x* h). [b] Isolated yields. [c] Without $[RuCl_2(p\text{-cymene})]_2$ and $Cu(OAc)_2 \cdot H_2O$. [d] Without $[RuCl_2(p\text{-cymene})]_2$. [e] $[RuCl_2(p\text{-cymene})]_2$ (10 mol%). nd = not detected.

indole derivative **1b** underwent alkenylation with acrylates to afford products **3bb–3bd** in 80–92% yields. Next, the reactivity of **1c** with acrylates was examined, yielding products **3ca–3cd** in 86–91% yields. The effect of electron-withdrawing substituents on the indole ring was also investigated. Alkenylation of **1d** with acrylates afforded products **3da–3dd** in moderate yields (73–77%), with the yields decreasing upon the introduction of phenyl substituent. To explore the influence of benzyl substituent on the indole ring in alkenylation–annulation, we performed reactions on **1e**, which resulted in products **3ea–3ed** in moderate to good yields (78–91%). Additionally, we evaluated the reactivity of indole derivative with a chloro substituent at the C6 position, which resulted in relatively low yields compared to other substituents.

The scope of the protocol was not limited to acrylic acid esters (**2**) as olefinic substrates but was also extended to a variety of other alkenes (Scheme 3). We investigated the reactivity of acrylonitrile (**2e**), (methylsulfonyl)ethene (**2f**), *N*,*N*-dimethylacrylamide (**2g**), and methyl vinyl ketone (**2h**) with indole derivatives (**1**) under standard conditions (Scheme 3).

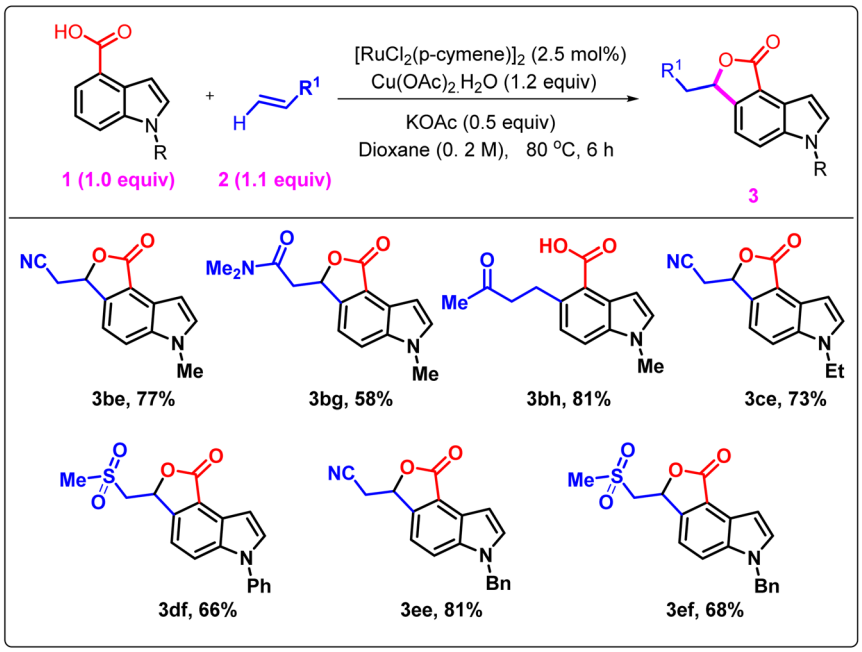
When acrylonitrile (**2e**) reacted with indole derivatives **1b**, **1c**, and **1e**, products **3be**, **3ce**, and **3ee** were obtained in good yields. The reaction of (methylsulfonyl)ethene (**2f**) with **1d** and **1e** afforded products **3df** and **3ef** in yields of 66% and 68%, respectively. Similarly, *N*,*N*-dimethylacrylamide (**2g**) reacted with indole derivative **3b** to yield product **3bg** in 58% yield. However, when methyl vinyl ketone (**2h**) was employed as the coupling partner with indole derivative (**1b**), the alkylated product **3bh** was obtained in 81% yield.

We further explored the substrate scope and generality of the reaction for the C5 alkenylation–annulation followed by C3 alkenylation of various indole derivatives (**1**) with different acrylates (**2**), which furnished products in good to excellent yields (Scheme 4a) (for the general reaction protocol, please refer to SI Section 3.3). The reaction of indole derivative **1a** with acrylates **2b** and **2c** afforded the corresponding products **4ab**



Scheme 2 Scope of indole derivatives and acrylates[a,b]. [a]Reaction conditions: **1** (1.0 equiv.), **2** (1.1 equiv.), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%), $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv.), KOAc (0.5 equiv.), dioxane (0.2 M), 80 °C, 6 h. [b]Isolated yields; (Me = methyl, Et = ethyl, *t*Bu-*t*-butyl, Bn = benzyl, Ph = phenyl).

with 82% yield and **4ac** with 70% yield. Similarly, indole derivative **1b** underwent alkenylation with acrylates (**2b–2d**) to yield products **4bb–4bd** in 79–88% yields. Next, the reactivity of **1c** with acrylates was investigated, yielding products **4ca**, **4cc**, and **4cd** in yields ranging from 79% to 88%. The effect of electron-withdrawing substituents on the indole ring was also examined. Alkenylation of 1d with acrylates (**2a–2d**) resulted in the formation of products **4da–4dd** in moderate yields (68–77%). Notably, the yields were observed to decrease upon the introduction of phenyl substituent. To explore the influence of the benzyl substituent on the indole ring in alkenylation–annulation, we performed reactions on indole derivative (**1e**),



Scheme 3 C5-alkenyation–annulation of indole derivatives with various alkenes. [a]Reaction conditions: **1** (1.0 equiv.), **2** (1.1 equiv.), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%), $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv.), KOAc (0.5 equiv.), dioxane (0.2 M), 80 °C, 6 h. [b]Isolated yields; (Me = methyl, Et = ethyl, *t*Bu-*t*-butyl, Bn = benzyl, Ph = phenyl).

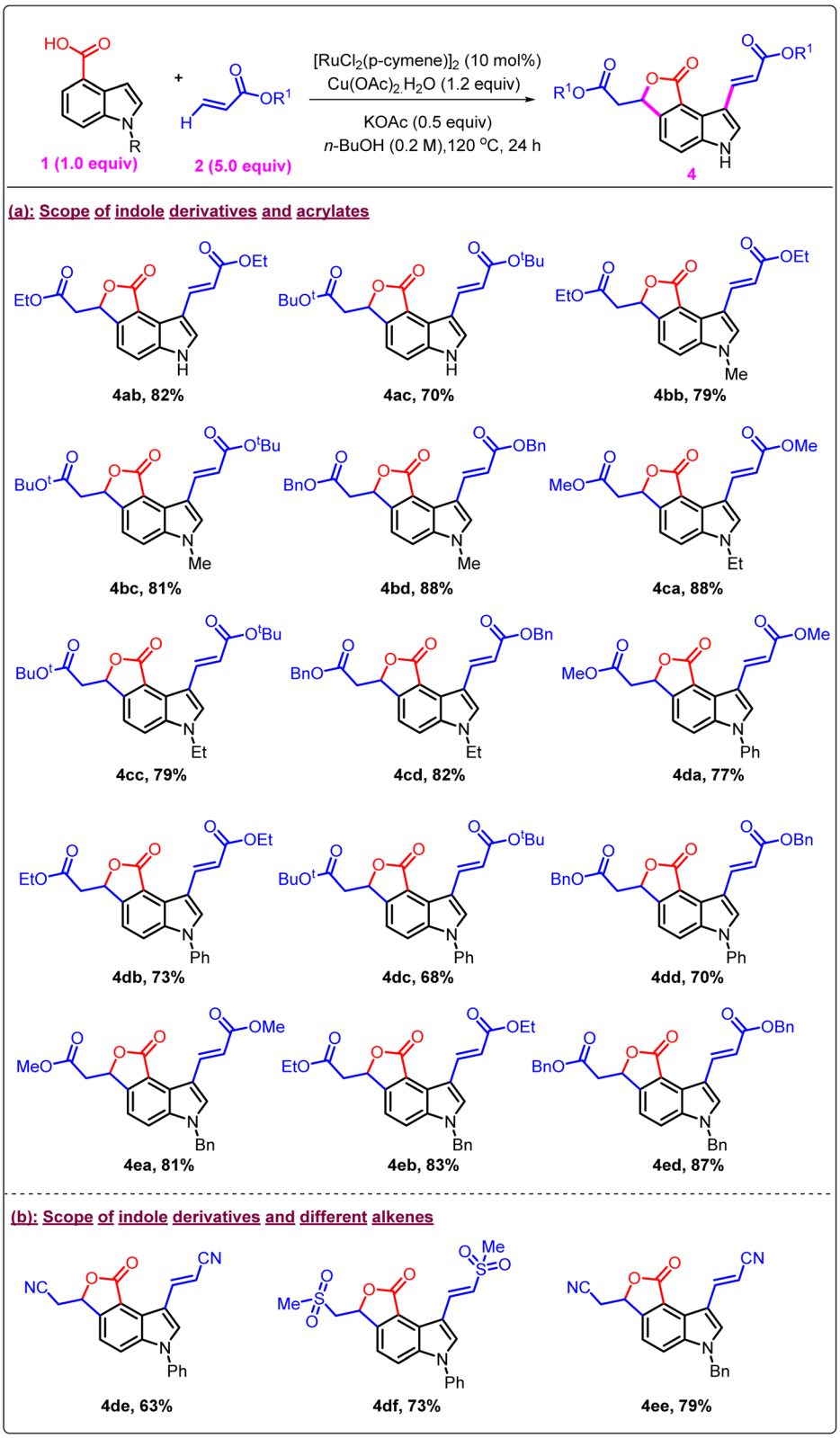
which resulted in products **4ea–4ed** in good yields (81–87%). These results suggest that the benzyl group at the C2 position is well tolerated and does not significantly hinder the reactivity under the standard conditions.

We also investigated the reactivity of acrylonitrile (**2e**) and (methylsulfonyl)ethene (**2f**) with indole derivatives (**1d** and **1e**) under standard conditions (Scheme 4b). When acrylonitrile (**2e**) reacted with indole derivative **1d**, product **4de** was obtained in 63% yield. Similarly, the reaction of indole derivative **1e** with acrylonitrile (**2e**) afforded product **4ee** in 79% yield. Additionally, indole derivative **1d** reacted with (methylsulfonyl)ethene (**2f**), yielding product **4df** in 73% yield.

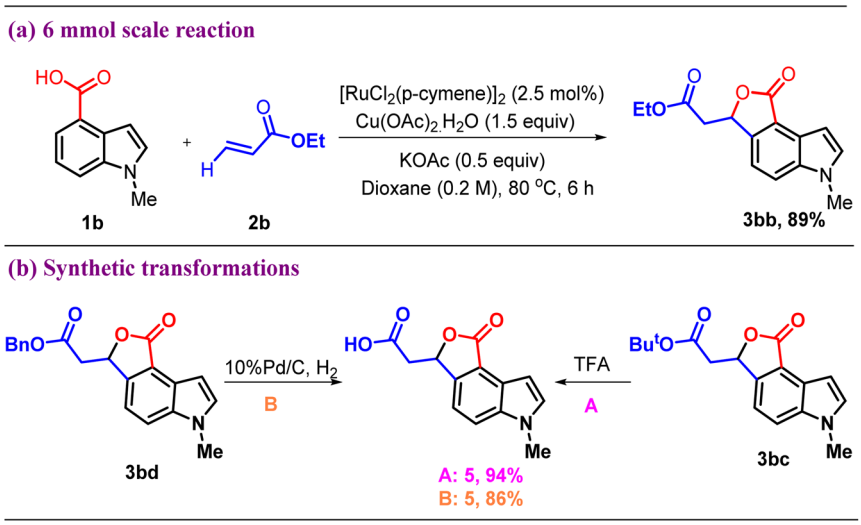
^{1}H NMR studies revealed that only the *trans*-alkenylated products were formed in the C3 alkenylation products (**4**). As demonstrated in Scheme 5a, a scale-up reaction was performed at a 6 mmol scale to assess the feasibility of this approach, yielding compound **3bb** in 89% yield (detailed reaction protocol and results are provided in the SI Section 3.4).

To validate the utility of C5-functionalized indoles, we attempted the conversion of the C5-annulated indoles into further modifications (Scheme 5b) (SI Section 5 of the SI provides extensive experimental techniques and results). The C5 annulated indole derivatives were successfully transformed into their corresponding acids, which serve as versatile intermediates for the synthesis of a wide range of valuable organic substrates. The C5 annulated indole derivative **3bc** was selectively hydrolyzed to give compound **5** in 94% yield using TFA (Route-**A**). Additionally, the benzyl group of **3bd** was deprotected to generate compound **5** in 86% yield, utilizing hydrogen gas under 1 atm pressure in the presence of 10% Pd/C as a catalyst in dioxane (Route-**B**). The modified acid derivative can be further transformed into valuable organic molecules, and the resulting products hold vast potential as scaffolds for the design of next-generation bioactive compounds, offering valuable opportunities in drug discovery and the development of therapies for diseases ranging from cancer to infections and beyond.

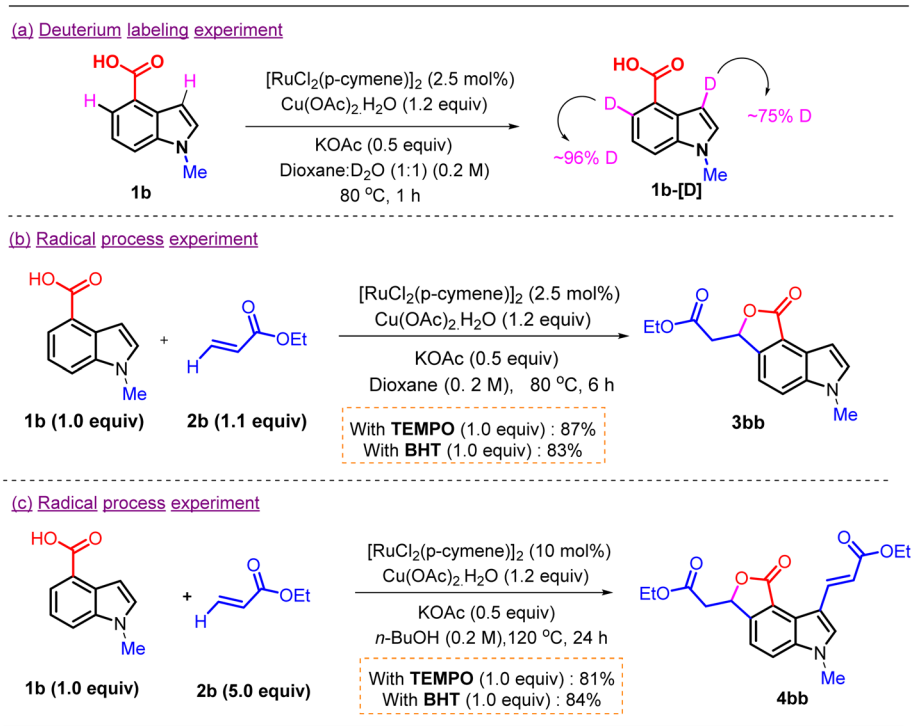
To explain the origin of the site-selectivity of the ruthenium catalysed C–H functionalization, deuterium incorporation experiments were conducted under standard reaction conditions (Scheme 6a). The analysis of the product revealed that methyl-1*H*-indole-4-carboxylate (**1b**) in the absence of alkene resulted in indole, **1b-[D]**, with 96% deuterium incorporation at the C5 position and 75% at the C3 position, strongly supported by the observed regioselectivity (for the detailed reaction protocol and results, please refer to SI Section 4.1). 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 **3bb** (87% and 83%, Scheme 6b) and **4bb** (81% and 84%, Scheme 6c). These findings suggest that the reaction proceeds through a non-radical pathway (for the detailed reaction protocol and results, please refer to SI Section 4.2). Scheme 7 illustrates a workable multistep catalytic cycle that has been proposed based on previous literature studies.[1–7] In the presence of $Cu(OAc)_2 \cdot H_2O$ and KOAc, an active catalyst, labelled as **A**, is formed. The first step involves the coordination of **1**, with an active ruthenium catalyst, followed by C–H



Scheme 4 C5-annulation and C3-olefination of indole derivatives with different acrylates and various alkenes [a,b]. [a]Reaction conditions: **1** (1.0 equiv.), **2** (5.0 equiv.), $[RuCl_2(p\text{-cymene})]_2$ (10 mol%), $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv.), KOAc (0.5 equiv.), *n*-BuOH (0.2 M), 120 °C, 24 h. [b]Isolated yields; (Me = methyl, Et = ethyl, *t*Bu-*t*-butyl, Bn = benzyl, Ph = phenyl).

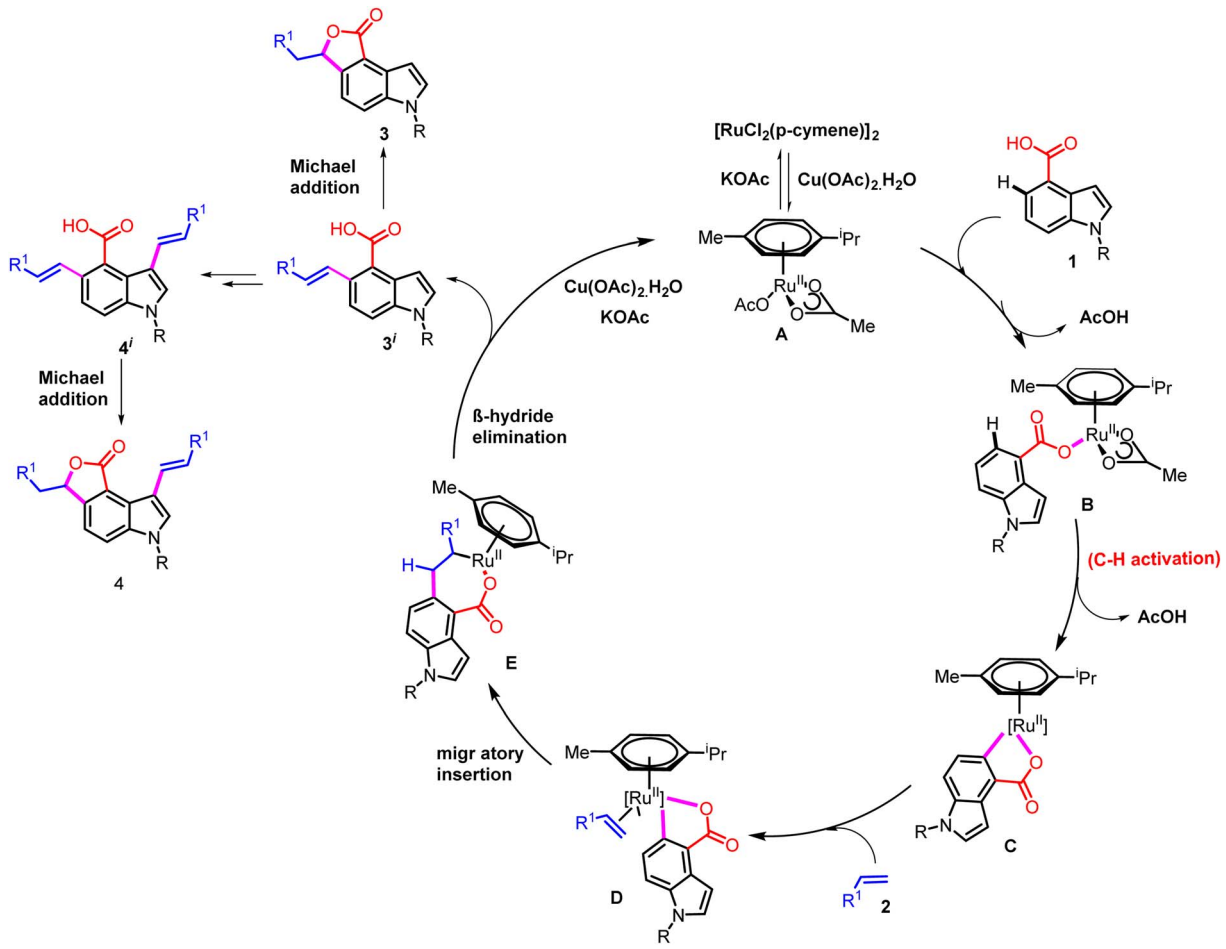


Scheme 5 Synthetic transformations of C5-annulated indole derivatives.



Scheme 6 Mechanistic studies of site-selectivity of the ruthenium-catalysed C–H functionalization.

metalation and release of AcOH, leading to the formation of a five-membered ruthenium complex **C**. Subsequent coordination followed by insertion of an olefine **2** with intermediate **C** gave rise to the intermediate **E**. Finally, β-hydride elimination, led to the formation of **3**^{i}, which undergo subsequent intramolecular michael addition to form the desired products **3** and **4**, and the active catalyst **A** was regenerated by reoxidation using $Cu(OAc)_2 \cdot H_2O$ and KOAc. This shows that experiments with deuterium labeling and radical scavengers suggest that the ruthenium-catalyzed C–H functionalization happens through a non-radical process with specific metal attachment, backed by a suggested catalytic cycle that includes olefin insertion and β-hydride elimination. The observed C5-selectivity over C3 in the Ru(II)-catalyzed C–H activation of indole derivatives can be rationalized by both coordination geometry and substrate electronics. Although the C3 position of indole is inherently more reactive due to higher electron density, in our system, the presence of a C4-directing group (acid) guides the Ru(II) center



Scheme 7 Plausible mechanism.

selectively toward the C5 position *via* formation of a five-membered cyclometalated intermediate, enabling regioselective activation.

Conclusion

In conclusion, we've developed an efficient ruthenium-catalyzed method for the oxidative C–H alkenylation of indole derivatives, followed by an intramolecular annulation to form fused lactone rings. This strategy highlights the remarkable chemoselectivity of ruthenium catalysis and offers a versatile route to access structurally diverse indole-lactone frameworks. The transformation proceeds through a cross-dehydrogenative alkenylation, followed by an intramolecular oxa-Michael addition, showcasing a streamlined reaction sequence with broad substrate compatibility. Overall, our findings expand the synthetic potential of ruthenium-based catalysis and offer promising avenues for constructing functionalized molecules of interest in medicinal and pharmaceutical chemistry.

Conflicts of interest

The authors declare no competing financial interest.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary (SI) materials.

A comprehensive study comprising general information on the reaction system, followed by optimization details to establish the best conditions. It includes experimental procedures and an in-depth section on mechanistic studies, covering deuterium labelling experiments, radical process investigations, and the proposed catalytic cycle. The work further highlights synthetic applications and provides complete experimental characterization data for the obtained products, along with copies of the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra. A list of references is included to support the study. See DOI: **https://doi.org/10.1039/d5ra03671b**.

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References

1 C. P. Mason, K. R. Edwards, R. E. Carlson, J. Pignatello, F. K. Gleason and J. M. Wood, *Science*, 1982, **215**, 400–402.
2 S. Richter and M. Palumbo, *Mini Rev. Med. Chem.*, 2003, **3**, 37–49.
3 A. N. Pearce, E. W. Chia, M. V. Berridge, G. R. Clark, J. L. Harper, L. Larsen, E. W. Maas, M. J. Page, N. B. Perry, V. L. Webb, *et al.*, *J. Nat. Prod.*, 2007, **70**, 936–940.
4 J. J. Beck and S. C. Chou, *J. Nat. Prod.*, 2007, **70**, 891–900.
5 A. Trani, C. Dallanoce, G. Panzone, F. Ripamonti, B. P. Goldstein and R. Ciabatti, *J. Med. Chem.*, 1997, **40**, 967–971.
6 T. Nomura, T. Kushiro, T. Yokota, Y. Kamiya, G. J. Bishop and S. Yamaguchi, *J. Biol. Chem.*, 2005, **280**, 17873–17879.
7 B. T. T. Hien, L. T. P. Hoa, L. X. Tham and D. N. Quang, *Fitoterapia*, 2013, **91**, 125–127.
8 M. Yoshikawa, E. Uchida, N. Chatani, H. Kobayashi, Y. Naitoh, Y. Okuno, H. Matsuda, J. Yamahara and N. Murakami, *Chem. Pharm. Bull.*, 1992, **40**, 3352–3354.
9 A. Kurume, Y. Kamata, M. Yamashita, Q. Wang, H. Matsuda, M. Yoshikawa, I. Kawasaki and S. Ohta, *Chem. Pharm. Bull.*, 2008, **56**, 1264–1269.
10 T. Ueno, H. Takahashi, M. Oda, M. Mizunuma, A. Yokoyama, Y. Goto, Y. Mizushina, K. Sakaguchi and H. Hayashi, *Biochemistry*, 2000, **39**, 5995–6002.
11 L.-J. Zhu, C.-L. Zhuang, N. Lei, C.-Q. Sheng, W. Guo, Z.-Y. Miao, W.-F. Liu, J.-Z. Yao and W.-N. Zhang, *Aust. J. Chem.*, 2011, **64**, 1390–1396.
12 M. Singh and N. P. Argade, *J. Org. Chem.*, 2010, **75**, 3121–3124.
13 K. Tianpanich, S. Prachya, S. Wiyakrutta, C. Mahidol, S. Ruchirawat and P. Kittakoop, *J. Nat. Prod.*, 2011, **74**, 79–81.
14 K. Yoshikawa, N. Kokudo, T. Hashimoto, K. Yamamoto, T. Inose and T. Kimura, *Biol. Pharm. Bull.*, 2010, **33**, 1355–1359.
15 Z. Ye, G. Lv, W. Wang, M. Zhang and J. Cheng, *Angew. Chem., Int. Ed.*, 2010, **49**, 3671–3674.
16 M. C. Willis, *Angew. Chem., Int. Ed.*, 2010, **49**, 6026–6027.
17 G. Strobel, E. Ford, J. Worapong, J. K. Harper, A. M. Arif, D. M. Grant, P. C. Fung and R. M. W. Chau, *Phytochemistry*, 2002, **60**, 179–183.
18 T. H. Chou, I. S. Chen, T. L. Hwang, T. C. Wang, T. H. Lee, L. Y. Cheng, Y. C. Chang, J. Y. Cho and J. J. Chen, *J. Nat. Prod.*, 2008, **71**, 1692–1695.
19 A. Arnone, G. Assante, G. Nasini, S. Strada and A. Vercesi, *J. Nat. Prod.*, 2002, **65**, 48–50.
20 L. P. Logrado, C. O. Santos, L. A. Romeiro, A. M. Costa, J. R. Ferreira, B. C. Cavalcanti, O. M. de Moraes, L. V. Costa-Lotufo, C. Pessoa and M. L. dos Santos, *Eur. J. Med. Chem.*, 2010, **45**, 3480–3489.
21 R. Karmakar, P. Pahari and D. Mal, *Chem. Rev.*, 2014, **114**, 6213–6284.
22 C. Kanazawa and M. Terada, *Tetrahedron Lett.*, 2007, **48**, 933–935.
23 D. Mal, P. Pahari and S. R. De, *Tetrahedron*, 2007, **63**, 11781–11792.
24 F. Wang, G. Song and X. Li, *Org. Lett.*, 2010, **12**, 5430–5433.
25 L. Ackermann and J. Pospech, *Org. Lett.*, 2011, **13**, 4153–4155.
26 K. Ueura, T. Satoh and M. Miura, *Org. Lett.*, 2007, **9**, 1407–1409.
27 M. Uchiyama, H. Ozawa, K. Takuma, Y. Matsumoto, M. Yonehara, K. Hiroya and T. Sakamoto, *Org. Lett.*, 2006, **8**, 5517–5520.
28 S. Mochida, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2011, **76**, 3024–3033.
29 S. Mochida, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2009, **74**, 6295–6298.
30 M. C. Miura, T. Tsuda, T. Satoh, S. Pivsa-Art and M. Nomura, *J. Org. Chem.*, 1998, **63**, 5211–5215.
31 K. Ueura, T. Satoh and M. Miura, *J. Org. Chem.*, 2007, **72**, 5362–5367.
32 D. Parmar, M. S. Maji and M. Rueping, *Chem. Eur J.*, 2014, **20**, 83–86.
33 L. Chen, H. Li, F. Yu and L. Wang, *Chem. Comm.*, 2014, **50**, 14866–14869.
34 M. Somei and F. Yamada, *Nat. Prod. Rep.*, 2004, **21**, 278–311.
35 M. Ishikura, T. Abe, T. Choshi and S. Hibino, *Nat. Prod. Rep.*, 2013, **30**, 694–752.
36 S. A. Patil, P. Renukadevi and D. D. Miller, *Future Med. Chem.*, 2012, **4**, 2085–2115.
37 T. V. Sravanthi and S. L. Manju, *Eur. J. of Pharm. Sci.*, 2016, **91**, 1–10.
38 S. P. Roche, J.-J. Youte Tendoung and B. Tréguier, *Tetrahedron*, 2015, **71**, 3549–3591.
39 G. R. Humphrey and J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875–2911.
40 S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2005, **105**, 2873–2920.
41 M. Bandini and A. Eichholzer, *Angew Chem., Int. Ed. Engl.*, 2009, **48**, 9608–9644.
42 Z. Song, R. Samanta and A. P. Antonchick, *Org. Lett.*, 2013, **15**, 5662–5665.
43 S. R. Neufeldt, C. K. Seigerman and M. S. Sanford, *Org. Lett.*, 2013, **15**, 2302–2305.
44 C. G. Hartung, A. Fecher, B. Chapell and V. Snieckus, *Org. Lett.*, 2003, **5**, 1899–1902.
45 S. Paul, G. A. Chotana, D. Holmes, R. C. Reichle, R. E. Maleczka, Jr. and M. R. Smith 3rd, *J. Am. Chem. Soc.*, 2006, **128**, 15552–15553.
46 L. Ping, D. S. Chung, J. Bouffard and S.-g. Lee, *Chem. Soc. Rev.*, 2017, **46**, 4299–4328.
47 P. V. Thanikachalam, R. K. Maurya, V. Garg and V. Monga, *Eur. J. Med. Chem.*, 2019, **180**, 562–612.
48 M. D. Burke and S. L. Schreiber, *Angew Chem., Int. Ed. Engl.*, 2004, **43**, 46–58.
49 C. W. Murray and D. C. Rees, *Nat. Chem.*, 2009, **1**, 187–192.

50 C. A. Lipinski, F. Lombardo, B. W. Dominy and P. J. Feeney, *Adv. Drug. Deliv. Rev.*, 2001, **46**, 3–26.
51 T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, *Chem. Soc. Rev.*, 2016, **45**, 2900–2936.
52 Y. Park, Y. Kim and S. Chang, *Chem. Rev.*, 2017, **117**, 9247–9301.
53 P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879–5918.
54 G. He, B. Wang, W. A. Nack and G. Chen, *Acc. Chem. Res.*, 2016, **49**, 635–645.
55 J. Rallabandi and I. Shown, *Chem. Sel.*, 2025, **10**, e202406066.
56 L. Yang and H. Huang, *Chem. Rev.*, 2015, **115**, 3468–3517.
57 T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147–1169.
58 L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315–1345.
59 J. F. Hartwig, *Acc. Chem. Res.*, 2017, **50**, 549–555.
60 R. K. Chinnagolla, S. Pimparkar and M. Jeganmohan, *Org. Lett.*, 2012, **14**, 3032–3035.
61 L. Ackermann, *Acc. Chem. Res.*, 2014, **47**, 281–295.
62 J. R. Hummel, J. A. Boerth and J. A. Ellman, *Chem. Rev.*, 2017, **117**, 9163–9227.
63 R. K. Chinnagolla, S. Pimparkar and M. Jeganmohan, *Chem. Comm.*, 2013, **49**, 3703–3705.
64 T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal and S. W. Krska, *Chem. Soc. Rev.*, 2016, **45**, 546–576.
65 Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, *Org. Chem. Front.*, 2015, **2**, 1107–1295.
66 X. X. Guo, D. W. Gu, Z. Wu and W. Zhang, *Chem. Rev.*, 2015, **115**, 1622–1651.
67 S. I. Kozhushkov and L. Ackermann, *Chem. Sci.*, 2013, **4**, 886–896.
68 P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879–5918.
69 L. Ackermann, *Acc. Chem. Res.*, 2014, **47**, 281–295.
70 L. Li, Z.-W. Hou, P. Li and L. Wang, *Org. Lett.*, 2021, **23**, 5983–5987.
71 V. Pirovano, *Eur. J. Org Chem.*, 2018, **2018**, 1925–1945.
72 A. K. Sinha, D. Equbal and M. R. Uttam, *Chem. Het. Compd.*, 2018, **54**, 292–301.
73 B. Prabagar, Y. Yang and Z. Shi, *Chem. Soc. Rev.*, 2021, **50**, 11249–11269.
74 J. Ma, R. Feng and Z.-B. Dong, *Asian J. Org. Chem.*, 2023, **12**, e202300092.
75 O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074–1086.
76 R. A. Jagtap and B. Punji, *Asian J. Org. Chem.*, 2020, **9**, 326–342.
77 J. A. Leitch, Y. Bhonoah and C. G. Frost, *ACS Catal.*, 2017, **7**, 5618–5627.
78 S. R. Neufeldt and M. S. Sanford, *Acc.Chem. Res.*, 2012, **45**, 936–946.
79 K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem.Res.*, 2012, **45**, 788–802.
80 P. Zhao, R. Niu, F. Wang, K. Han and X. Li, *Org. Lett.*, 2012, **14**, 4166–4169.
81 K. Padala and M. Jeganmohan, *Org. Lett.*, 2012, **14**, 1134–1137.
82 K. Padala and M. Jeganmohan, *Org. Lett.*, 2011, **13**, 6144–6147.
83 X. Kuang, S. Chen, L. Meng, J. Chen, X. Wu, G. Zhang, G. Zhong, T. Hu, Y. Li and C. Z. Lu, *Chem. Commun. (Camb)*, 2019, **55**, 1643–1646.
84 M. Bakthadoss and P. V. Kumar, *Adv. Synth. Catal.*, 2018, **360**, 2650–2658.
85 R. Manikandan, P. Madasamy and M. Jeganmohan, *ACS Catal.*, 2016, **6**, 230–234.
86 Q. Jiang, C. Zhu, H. Zhao and W. Su, *Chem.–Asian J.*, 2016, **11**, 356–359.
87 L. Ackermann and J. Pospech, *Org. Lett.*, 2011, **13**, 4153–4155.
88 J. Rallabandi, S. Mohanty and I. Shown, *RSC Adv.*, 2024, **14**, 37788–37796.
89 K. Graczyk, W. Ma and L. Ackermann, *Org. Lett.*, 2012, **14**, 4110–4113.
90 V. S. Thirunavukkarasu, M. Donati and L. Ackermann, *Org. Lett.*, 2012, **14**, 3416–3419.
91 A. Bechtoldt, C. Tirler, K. Raghuvanshi, S. Warratz, C. Kornhaaß and L. Ackermann, *Angew. Chem., Int. Ed.*, 2016, **55**, 264–267.
92 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.
93 D. Maurer and B. Breit, *Chem. - Eur. J.*, 2021, **27**, 2643.