



Cite this: *RSC Adv.*, 2025, 15, 30622

# Manganese catalyzed cross-coupling of allylic alcohols and indoles: an elegant route for access to $\gamma$ -hydroxyindole

Yanyan Shen,<sup>a</sup> Fangyuan Hu,<sup>b</sup> Yuhua Chen,<sup>b</sup> Dingguo Song,<sup>\*bc</sup> Fei Ling<sup>id</sup><sup>\*b</sup> and Weihui Zhong<sup>id</sup><sup>\*b</sup>

Alcohol and indole derivatives are widely recognized as versatile building blocks in both chemical and biochemical synthesis. The formal conjugate addition between these two classes of compounds provides a powerful and sustainable strategy for constructing  $\gamma$ -hydroxyindoles, owing to the reaction's 100% atom economy and the ready availability of starting materials. In this study, we report a redox-neutral cross-coupling reaction between indoles and allylic alcohols, catalyzed by a manganese(I) pincer complex, which enables the efficient synthesis of a broad range of  $\gamma$ -hydroxyindoles under mild conditions. The reaction featured broad substrate scope with good functional tolerance under simple conditions (24 examples, 60–83% yields).

Received 18th June 2025  
Accepted 19th August 2025

DOI: 10.1039/d5ra04342e

rsc.li/rsc-advances

## Introduction

Indoles represent a privileged class of nitrogen-containing heterocycles, widely recognized as ubiquitous structural motifs in synthetic chemistry and advanced materials science.<sup>1</sup> Among these,  $\gamma$ -hydroxyindole derivatives are of particular pharmacological significance, frequently serving as core pharmacophores in bioactive natural products, therapeutic agents, and alkaloid scaffolds (Fig. 1). For instance, vilazodone, a partial agonist of 5-HT<sub>1A</sub> receptors, functions by selectively inhibiting serotonin reuptake in the central nervous system.<sup>2</sup> Compound A is a potent neuraminidase inhibitor that exhibits

significant inhibitory activity against influenza virus.<sup>3</sup> In addition, compound B, a ligand with high  $\delta_2$  receptor affinity and selectivity, has exhibited promising antipsychotic properties.<sup>4</sup>

Given their relevance, significant efforts have been devoted to the efficient synthesis of  $\gamma$ -hydroxyindoles. While a one-pot synthesis from cyclic enol ethers and phenylhydrazine has been developed, its applicability is constrained by limited product diversity.<sup>5</sup> Currently, the base-mediated 1,4-Michael addition of indoles to  $\alpha,\beta$ -unsaturated carbonyl compounds, followed by carbonyl reduction, remains the predominant approach.<sup>6</sup> However, this strategy often involves multistep procedures and generates considerable chemical waste. Therefore, the pursuit of straightforward and sustainable synthetic methods, with simplified operations and minimal environmental impact, remains a compelling yet challenging goal.

The borrowing hydrogen (BH) strategy, first proposed by Williams and colleagues,<sup>7</sup> has recently witnessed a resurgence in organic chemistry. This approach leverages readily available alcohols as sustainable and safe coupling partners through simple metal catalysis, eliminating the need for stoichiometric oxidants, reducing agents, toxic bases, or multistep procedures. Over the past few decades, noble metals such as Ru, Rh, Ir, and Pd have proven to be highly efficient catalysts in BH reactions enabling the facile transformation of primary or secondary alcohols into green alkylating and arylating reagents.<sup>8</sup> A striking example of this utility is the BH-mediated cross-coupling of indoles and alcohols, which provides a powerful method for constructing functionalized indole derivatives. However, the limited availability and high cost associated with noble metals—along with the challenges of removing residual metals from the final products—have spurred interest in developing

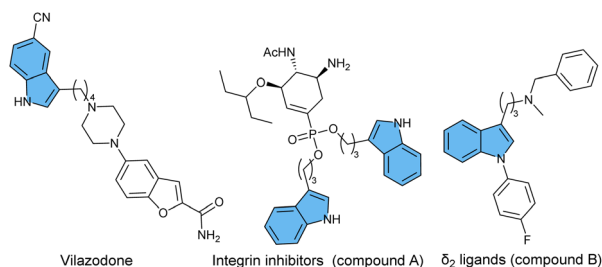


Fig. 1 Bioactive natural products.

<sup>a</sup>Zhejiang Institute of Economics and Trade, Hangzhou 310018, P. R. China

<sup>b</sup>College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, P. R. China. E-mail: lingfei@zjut.edu.cn; weihui.zhong@zjut.edu.cn

<sup>c</sup>Huzhou Key Laboratory of Medical and Environmental Applications Technologies, School of Life Sciences, Huzhou University, Huzhou 313000, P. R. China. E-mail: 03356@zjhu.edu.cn



alternative catalytic systems based on earth-abundant 3d transition metals.

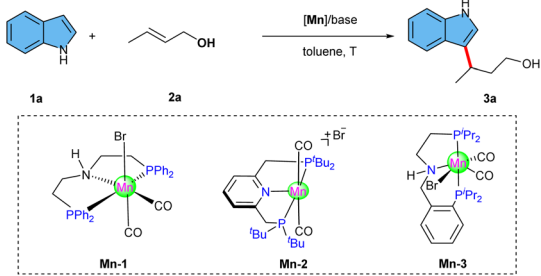
As the third most abundant transition metal in the Earth's crust, manganese has recently emerged as a valuable alternative for constructing indole scaffolds *via* borrowing hydrogen (BH) transformations.<sup>9</sup> In 2020, Rueping and co-workers demonstrated that a PNP–Mn complex could catalyze the regioselective dehydrogenative alkylation of indolines with readily available alcohols.<sup>10</sup> Subsequently, Srimani reported that a manganese NNS pincer complex enabled the catalytic  $\alpha$ -C3 alkylation of indoles (Scheme 1A).<sup>11</sup> In 2022, Shao and co-workers developed an elegant method for C3-alkylation and alkenylation of indoles using Mn-catalyzed dehydrogenative coupling of benzylic alcohols and 2-arylethanol, although the reaction was limited by substrate scope, as secondary alcohols and methanol could not be used as alkylating reagents.<sup>12</sup> Around the same time, Ruiter synthesized a new class of PCNHC–P Mn(i) pincer complexes and explored their activity in the  $\alpha$ -methylation of indoles.<sup>13</sup> Very recently, a novel base-catalyzed conjugate addition strategy for constructing indole derivatives from allylic alcohols was disclosed by Ke and co-workers.<sup>14</sup> However, this methodology demonstrates narrow substrate scope, particularly when indole substrates bear electron-withdrawing groups or when employing alkyl allylic alcohols instead of cinnamyl alcohol derivatives, without target product generation. Expanding base-metal-catalyzed BH processes to include a broader range of alkyl

and allylic alcohols, especially in formal conjugate addition reactions with indoles, remains a challenging yet desirable goal. In line with our continued interest in BH chemistry,<sup>15</sup> we envisioned a strategy involving the formal conjugate addition of allylic alcohols with indoles acting as carbon nucleophiles, coupled with regeneration of hydroxyl groups through hydrogenation of *in situ* generated carbonyl intermediates (Scheme 1B). A key challenge was the suppression of undesirable side reactions, such as aldol-type self-condensation of  $\alpha,\beta$ -unsaturated carbonyl compounds and competition between 1,2- and 1,4-addition of indoles to these intermediates. Herein, we report manganese pincer complex enabling the efficient synthesis of  $\gamma$ -hydroxyindoles *via* the formal conjugate addition of nitriles with allylic alcohols, achieving 100% atom economy (Scheme 1C). This protocol has a wide substrate scope with good functional tolerance under simple conditions (22 examples, 60–83% yields).

## Results and discussion

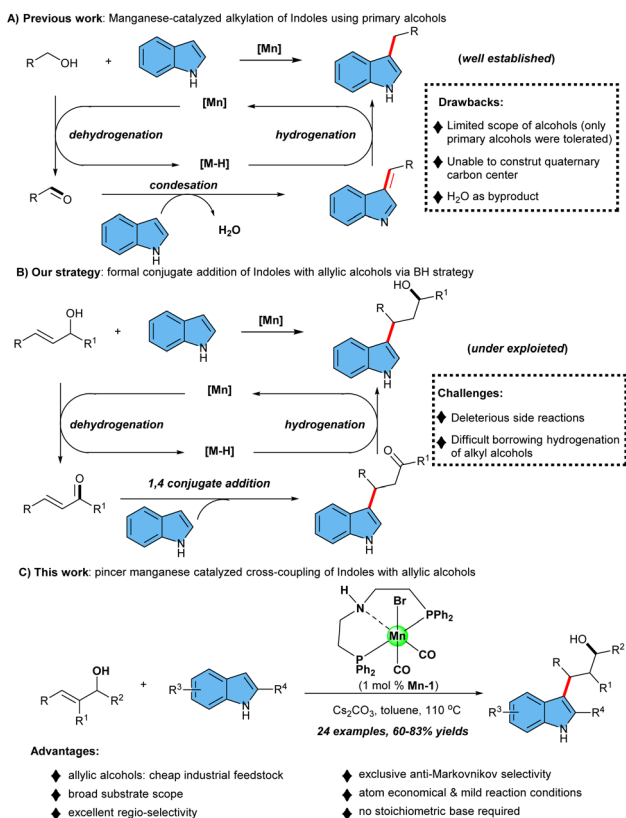
At the outset of our investigations, the reaction between model substrates indole (**1a**, 0.5 mmol, 1 equiv.) and crotonyl alcohol (**2a**, 1.0 mmol, 2 equiv.) was carried out using **Mn-1** (1 mol%) as the catalyst and KO<sup>t</sup>Bu (10 mol%) as the base at 110 °C (Table 1, entry 1). Gratifyingly, complete conversion of indole was

Table 1 Optimization of reaction conditions<sup>a</sup>



Entry	Cat.	Base	Temp (°C)	t (h)	Yield <sup>b</sup> (%)
1	<b>Mn-1</b>	KO <sup>t</sup> Bu	110	24	50
2	<b>Mn-2</b>	KO <sup>t</sup> Bu	110	24	38
3	<b>Mn-3</b>	KO <sup>t</sup> Bu	110	24	30
4	<b>Mn-1</b>	KO <sup>t</sup> Bu	90	24	Trace
5	<b>Mn-1</b>	KO <sup>t</sup> Bu	130	24	26
6	<b>Mn-1</b>	CS <sub>2</sub> CO <sub>3</sub>	110	24	82
7	<b>Mn-1</b>	K <sub>2</sub> CO <sub>3</sub>	110	24	60
8	<b>Mn-1</b>	Na <sub>2</sub> CO <sub>3</sub>	110	24	55
9 <sup>c,d</sup>	<b>Mn-1</b>	CS <sub>2</sub> CO <sub>3</sub>	110	24	40, 79
10	<b>Mn-1</b>	CS <sub>2</sub> CO <sub>3</sub>	110	24	35 <sup>e</sup> , 58 <sup>f</sup>
11 <sup>g</sup>	<b>Mn-1</b>	CS <sub>2</sub> CO <sub>3</sub>	110	24	70
12	—	CS <sub>2</sub> CO <sub>3</sub>	110	24	ND <sup>h</sup>

<sup>a</sup> Reaction conditions: **1** (0.5 mmol, 1 equiv.), **2** (1.0 mmol, 2 equiv.), toluene (1.0 mL), **[Mn]** (1 mol%), and base (10 mol%) at certain temperature under Ar. <sup>b</sup> Isolated yields. <sup>c</sup> 5 mol% of CS<sub>2</sub>CO<sub>3</sub> was used. <sup>d</sup> 15 mol% of CS<sub>2</sub>CO<sub>3</sub> was used. <sup>e</sup> *Tert*-amyl alcohol was used as solvent. <sup>f</sup> *i*-PrOH was used as solvent. <sup>g</sup> 0.5 mol% of **Mn-1** was used. <sup>h</sup> ND = not detected.

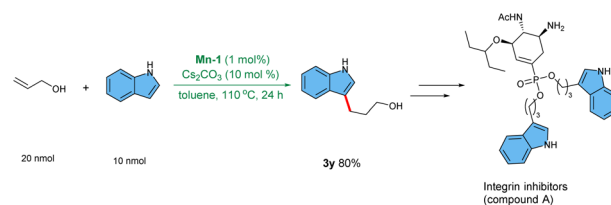


Scheme 1 Mn catalyzed borrowing hydrogen transformations of alcohols with indoles.



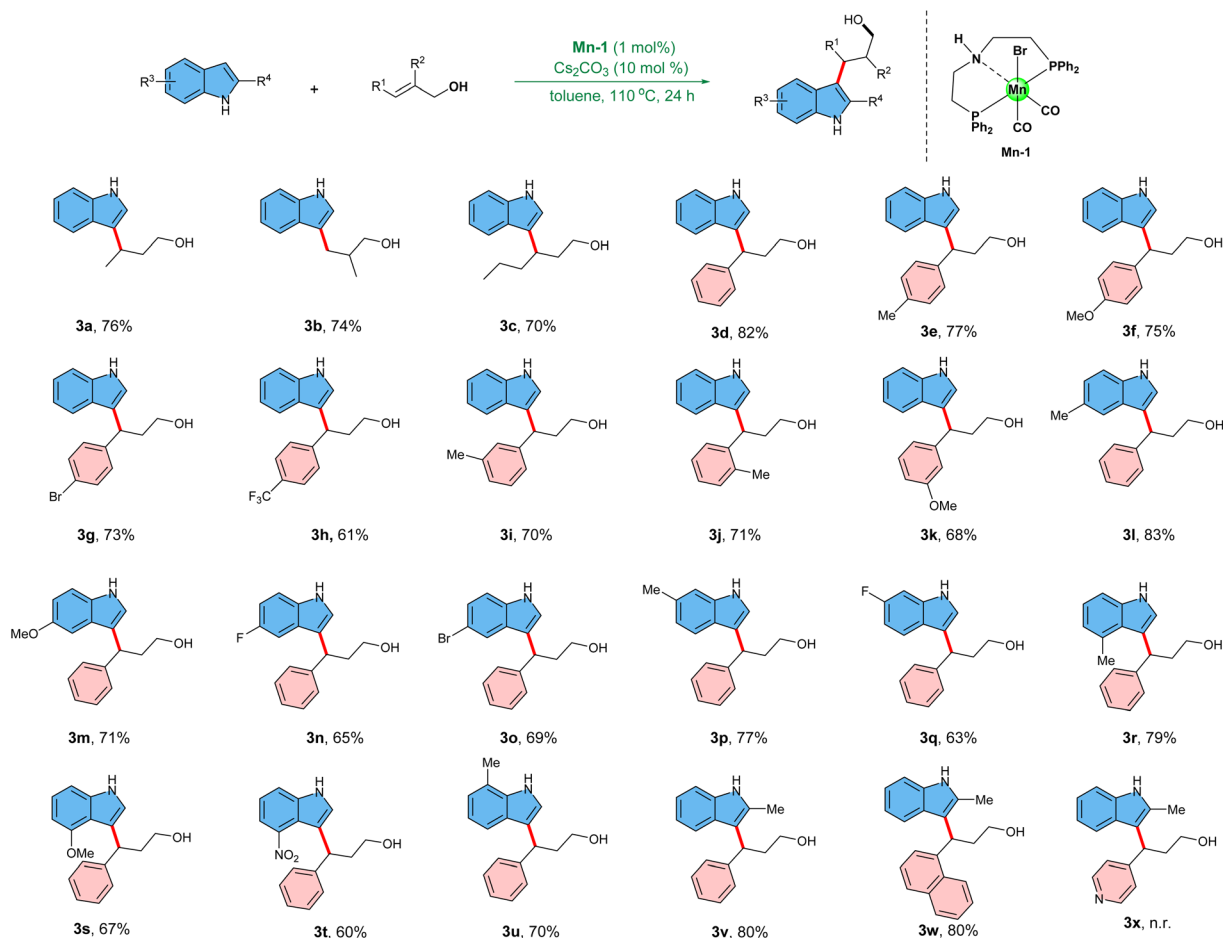
observed, and the desired conjugate addition product **3a** was isolated in 50% yield. Notably, no 3-alkylation product was detected under these conditions. In contrast, manganese complexes **Mn-2** (ref. 16) and **Mn-3** (ref. 17), bearing other tridentate ligands, exhibited significantly lower catalytic activity (Table 1, entries 2 and 3). Temperature screening revealed that decreasing the reaction temperature to 90 °C nearly shut down product formation, while increasing the temperature above 110 °C had no noticeable effect (Table 1, entries 4 and 5). Next, a series of bases were evaluated, among which Cs<sub>2</sub>CO<sub>3</sub> was identified as the optimal choice, affording product **3a** in 82% yield within 24 hours (Table 1, entries 6–8). Modifying the loading of Cs<sub>2</sub>CO<sub>3</sub> to either 5 mol% or 15 mol% did not lead to any improvement in yield (Table 1, entry 9). Further solvent optimization showed that conducting the reaction in *tert*-amyl alcohol or *i*-PrOH resulted in a decreased yield of product **3a** (Table 1, entry 10).

Notably, even with a reduced catalyst loading of 0.5 mol%, the reaction still proceeded smoothly, albeit with a slightly lower yield (Table 1, entry 11). As expected, omitting **Mn-1** from the reaction entirely led to no product formation, confirming the essential role of the catalyst (Table 1, entry 12).



Scheme 3 Gram-scale reaction.

With the optimized reaction conditions in hand, we next explored the substrate scope of the formal conjugate addition reactions (Scheme 2). Beyond crotyl alcohol, structurally diverse alkyl-substituted allylic alcohols, such as *iso*-but-2-en-1-ol and (*E*)-hex-2-en-1-ol, were demonstrated to be effective starting materials, affording the corresponding products in high yields under the optimized conditions. Subsequently, a variety of internal aryl-substituted allyl alcohols were examined. Electron-donating groups on the aryl ring, such as methyl and methoxy, led to relatively higher yields (**3e**, 77%; **3f**, 75%) compared to electron-withdrawing substituents like trifluoromethyl (**3h**, 50%). Notably, halogen substituents were well tolerated under



Scheme 2 Mn-catalyzed cross-coupling of allylic alcohols and indoles. Reaction conditions: **1** (0.5 mmol, 1 equiv.), **2** (1.0 mmol, 2 equiv.), toluene (1.0 mL), [**Mn**] (1 mol%), and base (10 mol%) at heated temperature under Ar. Reported yields were calculated for pure isolated products after column chromatography.



the reaction conditions; for example, the bromo-substituted substrate delivered the desired product **3g** in 73% yield. Furthermore, the position of the substituent on the aryl ring showed minimal influence on the reaction efficiency, as demonstrated by the formation of products **3i**, **3j**, and **3k** in 70%, 71%, and 68% yields, respectively. We then turned our attention to the indole component. Substituted indoles bearing groups at the C-2, C-4, C-5, C-6, and C-7 positions all underwent smooth transformation, providing the desired  $\gamma$ -hydroxyindoles in moderate to good yields (**3l–3v**, 60–83%). Interestingly, allyl alcohols bearing a naphthalene ring emerged as promising substrates, affording the corresponding alkylation products **3w** with an isolated yield of up to 80%. Unfortunately, when pyridyl-substituted allyl alcohols were used as starting materials, no desired product was detected. These results suggest that the reaction exhibits broad functional group tolerance and is compatible with various substitution patterns on both reaction partners.

To illustrate the scalability and practical value of this method, we conducted a gram-scale experiment. Specifically, a 10 mmol scale reaction of indoles with allyl alcohol proceeded smoothly, yielding 1.41 g of the target product **3y** (80% yield) after 36 hours (Scheme 3). Notably, **3y** serves as a key intermediate in the synthesis of compound A.

## Conclusions

In summary, we have established an efficient and straightforward method for the cross-coupling of indoles with allyl alcohols to synthesize  $\gamma$ -hydroxyindoles, catalyzed by a manganese(i) pincer complex. This protocol featured a broad substrate scope with a good functional tolerance under simple conditions (24 examples, 60–83% yields). Given the use of an earth-abundant metal and the hydrogen borrowing mechanism, this strategy holds significant potential for applications in both academic research and industrial settings.

## Experimental

### General procedure for the synthesis of $\gamma$ -hydroxyindoles

To a mixture of **Mn-1** catalyst (1 mol%), Cs<sub>2</sub>CO<sub>3</sub> (10 mol%), indoles (0.5 mmol) and cinnamyl alcohol (1.0 mmol), 1.0 mL of toluene was added. Then, the reaction was stirred at 110 °C for 4 h under Ar in a pressure tube (ACE pressure tube, 15 mL). After cooling to room temperature, the reaction was diluted with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (10 mL) for three times. The combined organic layers were washed by brine and dried over magnesium sulfate and the volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5 : 1–2 : 1) to give the desired product  $\gamma$ -hydroxyindoles.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

The authors confirm that all the data supporting the findings of this study are available within the article and its SI.

Experimental procedures and characterization data of all the compounds. See DOI: <https://doi.org/10.1039/d5ra04342e>.

## Acknowledgements

We thank the National Natural Science Foundation of China (No. 22178315 and 22378363), Natural Science Foundation of Zhejiang Province (No. LQ24B060008), Domestic Visiting Scholar Program for Teacher Professional Development of Zhejiang Province (No. FX2024154) for financial support.

## Notes and references

- (a) R. Dalpozzo, *Chem. Soc. Rev.*, 2015, **44**, 742–778; (b) M. Shiri, *Chem. Rev.*, 2012, **112**, 3508–3549; (c) M. Inman and C. J. Moody, *Chem. Sci.*, 2013, **4**, 29–41; (d) S. A. Patil, R. Patil and D. D. Miller, *Curr. Med. Chem.*, 2011, **18**, 615–637; (e) P. Dydio, D. Lichosyt and J. Jurczak, *Chem. Soc. Rev.*, 2011, **40**, 2971–2985.
- T. Heinrich, H. Bo ttcher, R. Gericke, G. D. Bartoszyk, S. Anzali, C. A. Seyfried, H. E. Greiner and C. van Amsterdam, *J. Med. Chem.*, 2004, **47**, 4684–4692.
- C. L. Chen, T. C. Lin, S. Y. Wang, J. J. Shie, K. C. Tsai, Y. S. E. Cheng, J. T. Jan, C. J. Lin, J. M. Fang and C. H. Wong, *Eur. J. Med. Chem.*, 2014, **81**, 106–118.
- M. G. Mamolo, D. Zampieri, C. Zanette, C. Florio, S. Collina, M. Urbano, O. Azzolina and L. Vio, *Eur. J. Med. Chem.*, 2008, **43**, 2073–2081.
- R. Campos, J. C. S. Woo, S. Lee and R. D. Tillyer, *Org. Lett.*, 2004, **6**, 79–82.
- X. Liang, S. Li and W. Su, *Tetrahedron Lett.*, 2012, **53**, 289–291.
- M. G. Edwards, R. F. R. Jazzar, B. M. Paine, D. J. Shermer, M. K. Whittlesey, J. M. J. Williams and D. D. Edney, *Chem. Commun.*, 2004, 90–91.
- (a) K. Motokura, D. Nishimura, K. Mori, T. Mizugaki, K. Ebitani and K. Kaneda, *J. Am. Chem. Soc.*, 2004, **126**, 5662–5663; (b) C. Loeffberg, R. Grigg, M. A. Whittaker, A. Keep and A. Derrick, *J. Org. Chem.*, 2006, **71**, 8023–8027; (c) F. Li, X. Zou and N. Wang, *Adv. Synth. Catal.*, 2015, **357**, 1405–1415; (d) A. Corma, T. Rodenas and M. J. Sabater, *J. Catal.*, 2011, **279**, 319–327; (e) M. L. Buil, M. A. Esteruelas, J. Herrero, S. Lzquierdo, I. M. Pastor and M. Yus, *ACS Catal.*, 2013, **3**, 2072–2075; (f) S. Thiagarajan and C. Gunanathan, *ACS Catal.*, 2017, **7**, 5483–5490; (g) Y. Tsukamoto, S. Itoh, M. Kobayashi and Y. Obora, *Org. Lett.*, 2019, **21**, 3299–3303; (h) S. Shee and S. Kundu, *J. Org. Chem.*, 2021, **86**, 6943–6951.
- Z. Wang and C. Wang, *Adv. Synth. Catal.*, 2021, **2**, 66–69.
- J. C. Borghs, V. Zubar, L. M. Azofra, J. Sklyaruk and M. Rueping, *Org. Lett.*, 2020, **22**, 4222–4227.
- A. Mondal, R. Sharma, B. Dutta, D. Pal and D. Srimani, *J. Org. Chem.*, 2022, **87**, 3989–4000.

- 12 M. Zhao, X. Li, X. Zhang and Z. Shao, *Chem.-Asian J.*, 2022, **17**, e202200483.
- 13 R. Thenarukandiyil, R. Kamte, S. Garhwal, P. Effnert, N. Fridman and G. de Ruiter, *Organometallics*, 2023, **42**, 62–71.
- 14 N. Wang, R. Chen, Z. Chen, W. Li, X. Wen, C. Zhao and Z. Ke, *Org. Chem. Front.*, 2024, **11**, 4794–4804.
- 15 (a) D. Song, L. Chen, Y. Li, T. Liu, X. Yi, L. Liu, F. Ling and W. Zhong, *Org. Chem. Front.*, 2021, **8**, 120–126; (b) X. Yi, Y. Chen, A. Huang, D. Song, J. He, F. Ling and W. Zhong, *Org. Chem. Front.*, 2021, **8**, 6830–6836; (c) S. Wang, D. Song, F. Shen, R. Chen, Y. Cheng, C. Zhao, Q. Shen, S. Yin, F. Ling and W. Zhong, *Green Chem.*, 2023, **25**, 357–364; (d) D. Song, S. Wang, W. Huang, R. Chen, F. Hu, L. Chen, X. Zhao, F. Ling and W. Zhong, *Org. Chem. Front.*, 2023, **10**, 5908–5915; (e) D. Song, R. Chen, W. Huang, P. Yang, L. Chen, J. Zhang, F. Ling and W. Zhong, *Adv. Synth. Catal.*, 2024, **366**, 1893–1898; (f) D. Song, S. Wang, W. Huang, R. Chen, F. Hu, L. Cheng, X. Zhao, F. Ling and W. Zhong, *Org. Chem. Front.*, 2023, **10**, 5908–5915.
- 16 M. V. Nerush, U. Gellrich, G. Leitius, Y. Ben-David and D. Milstein, *J. Am. Chem. Soc.*, 2016, **138**, 6985–6997.
- 17 (a) S. Chakraborty, U. K. Das, Y. Ben-David and D. Milstein, *J. Am. Chem. Soc.*, 2017, **139**, 11710–11713; (b) W. M. Dagnaw, Y. Lu, R. Zhao and Z.-X. Wang, *Organometallics*, 2019, **38**, 3590–3601; (c) U. K. Das, S. Chakraborty, Y. Diskin-Posner and D. Milstein, *Angew. Chem., Int. Ed.*, 2018, **57**, 13444–13448.

