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## Rhodium-catalysed decarbonylative C(sp<sup>2</sup>)-H alkylation of indolines with alkyl carboxylic acids and carboxylic anhydrides under redox-neutral conditions†

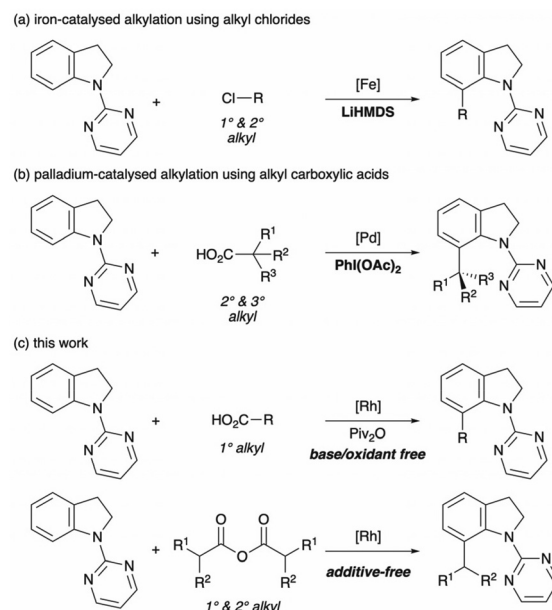
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We developed a rhodium-catalysed decarbonylative C(sp<sup>2</sup>)-H alkylation method for indolines. This reaction facilitates the use of alkyl carboxylic acids and their anhydrides as a cheap, abundant and non-toxic alkyl source under redox-neutral conditions, featuring the introduction of a primary alkyl chain, which cannot be addressed by previous radical-mediated decarboxylative reaction. Through a mechanistic investigation, we revealed that an initially formed C-7 acylated indoline was transformed into the corresponding alkylated indoline via a decarbonylation process.

Indoles and their derivatives are ubiquitous structural motifs found in various natural products and pharmaceuticals.<sup>1</sup> As such, efficient synthetic methods to access densely functionalised indoles have been extensively developed.<sup>2</sup> Among them, site-selective C-H functionalisation of indoles allows the forging of new chemical bonds directly from a simple starting material for the rapid assembly of molecular complexity.<sup>3</sup> However, selective activation of the C(7)-H bond is still challenging because the reactivity of the benzenoid moiety is lower than that of the pyrrole one.<sup>4</sup> Consequently, ligand-directed C-7 functionalisation of indolines has emerged as a promising alternative to the corresponding functionalisation of indoles.<sup>5,6</sup>

The C-7 alkylation has also attracted considerable attention within the field of C-H functionalisation of indolines, utilising a series of alkylating reagents: activated alkenes,<sup>7</sup> diazo compounds bearing an electron-withdrawing group,<sup>8</sup> cyclopropanols<sup>9</sup> and aziridines.<sup>10,11</sup> However, these alkylating reagents cannot yield indolines bearing a simple alkyl chain without using any specific functional groups. Recently, Punji *et al.* addressed this problem by using simple primary and secondary alkyl chlorides in their iron-catalysed alkylation, but its highly basic conditions might narrow the substrate scope (Scheme 1a).<sup>12</sup>

Alkyl carboxylic acids have recently garnered significant attention as an alkylating reagent owing to their advantages, such as being inexpensive, abundant in nature, stable under benchtop conditions and easy to handle.<sup>13,14</sup> Despite these advantages, only one precedent of C-7 alkylation of indolines has been reported to date: the palladium-catalysed oxidative decarboxylative alkylation of indolines with alkyl carboxylic acids (Scheme 1b).<sup>15</sup> In this method, primary alkyl carboxylic acids could not be coupled with indolines because of the low stability of the primary alkyl radical species. Moreover, the oxidative conditions sometimes reduce the generality of the reaction and complicate the isolation procedure. Considering these limitations, we developed the redox-neutral decarbonylative alkylation of indolines by employing (*in situ*-formed) carboxylic anhydrides (Scheme 1c).<sup>16</sup>



Scheme 1 Transition metal-catalysed C-7 alkylation of indolines.

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Inspired by previous work on decarbonylative alkylation,<sup>13</sup> we began our investigation by employing 1-(pyrimidin-2-yl)indoline (**1a**), propionic acid (**2a**) and pivalic anhydride with various rhodium salts as a catalyst (Table 1). An initial experiment was performed in 1,4-dioxane at 130 °C for 18 h in the presence of [RhCl(CO)<sub>2</sub>]<sub>2</sub> (2.5 mol%), producing the desired 7-ethyl-1-(pyrimidin-2-yl)indoline (**3a**) in good yield (entry 1). Other rhodium catalysts, namely [RhCl(cod)]<sub>2</sub>, [Rh(OAc)(cod)]<sub>2</sub>, [Rh(cod)<sub>2</sub>BF<sub>4</sub>], [Rh(cod)<sub>2</sub>OTf] and RhCl(PPh<sub>3</sub>)<sub>3</sub>, yielded little of the desired C-7 alkylated product (entries 2–6). Among the solvents tested, 1,2-dichloroethane (DCE) was proved to be the best choice (entries 7–10). Other anhydrides, acetic anhydride, di-*tert*-butyl dicarbonate (Boc<sub>2</sub>O) and the combination of Boc<sub>2</sub>O and pivalic acid, decreased the yield (entries 11–13). Lower reaction temperature (110 °C) was inadequate for the reaction to promote (entry 14). Increasing the amount of **2a** and pivalic anhydride resulted in an improved yield of the coupling product (entry 15). A control experiment showed that both the rhodium catalyst and pivalic anhydride are essential for the reaction to proceed (entries 16 and 17).

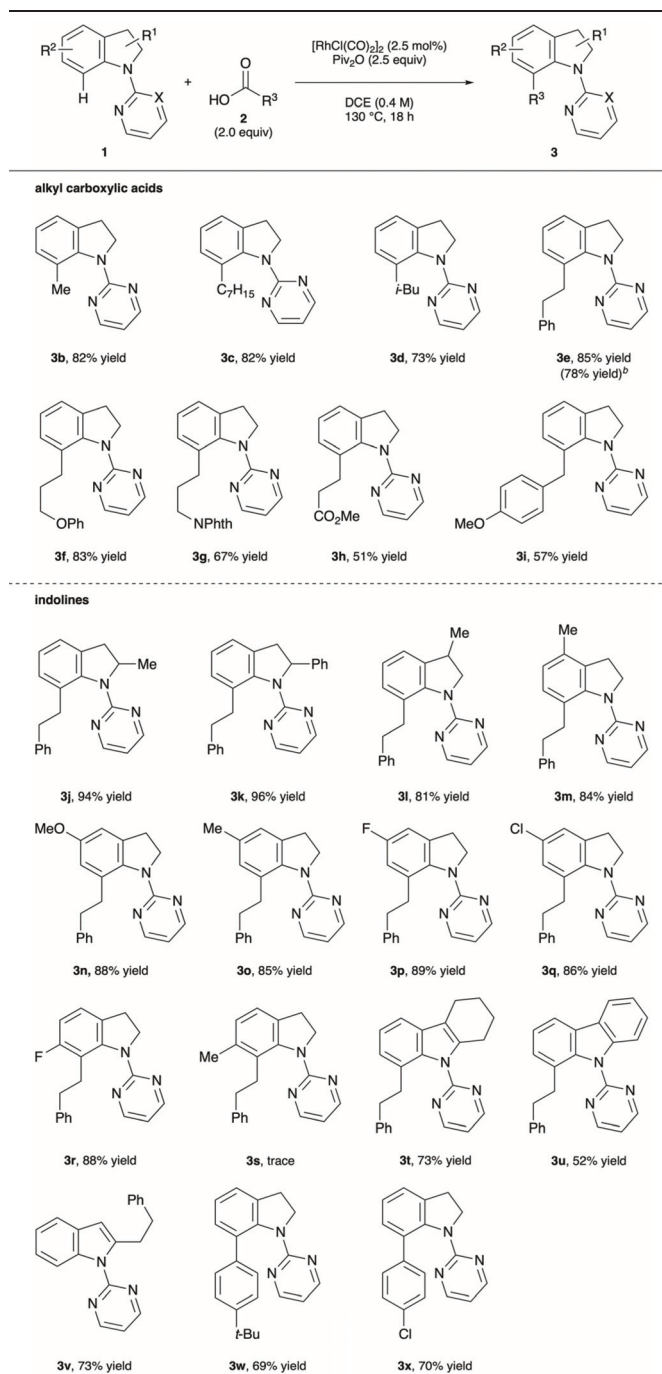
Having determined the optimised reaction conditions, we explored the decarbonylative alkylation of various alkyl carboxylic acids **2** with **1a** (Table 2).<sup>17</sup> Acetic acid, *n*-octanoic acid, isovaleric acid and 3-phenylpropionic acid delivered the corresponding C-7 alkylated indolines **3b–e** in 73–85% yields. Moreover, the reaction with 3-phenylpropionic acid proceeded smoothly on 1 mmol scale, showing the feasibility for a large

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

Entry	Rh catalyst	Solvent	Anhydride	Yield (%) <sup>b</sup>
1	[RhCl(CO) <sub>2</sub> ] <sub>2</sub>	1,4-Dioxane	Piv <sub>2</sub> O	69
2	[RhCl(cod)] <sub>2</sub>	1,4-Dioxane	Piv <sub>2</sub> O	0
3	[Rh(OAc)(cod)] <sub>2</sub>	1,4-Dioxane	Piv <sub>2</sub> O	8
4	[Rh(cod) <sub>2</sub> BF <sub>4</sub> ]	1,4-Dioxane	Piv <sub>2</sub> O	Trace
5	[Rh(cod) <sub>2</sub> OTf]	1,4-Dioxane	Piv <sub>2</sub> O	Trace
6	RhCl(PPh <sub>3</sub> ) <sub>3</sub>	1,4-Dioxane	Piv <sub>2</sub> O	Trace
7	[RhCl(CO) <sub>2</sub> ] <sub>2</sub>	Toluene	Piv <sub>2</sub> O	59
8	[RhCl(CO) <sub>2</sub> ] <sub>2</sub>	DCE	Piv <sub>2</sub> O	83
9	[RhCl(CO) <sub>2</sub> ] <sub>2</sub>	MeCN	Piv <sub>2</sub> O	24
10	[RhCl(CO) <sub>2</sub> ] <sub>2</sub>	DMF	Piv <sub>2</sub> O	Trace
11	[RhCl(CO) <sub>2</sub> ] <sub>2</sub>	1,4-Dioxane	Ac <sub>2</sub> O	50
12	[RhCl(CO) <sub>2</sub> ] <sub>2</sub>	1,4-Dioxane	Boc <sub>2</sub> O	31
13	[RhCl(CO) <sub>2</sub> ] <sub>2</sub>	1,4-Dioxane	Boc <sub>2</sub> O + PivOH	16
14 <sup>c</sup>	[RhCl(CO) <sub>2</sub> ] <sub>2</sub>	1,4-Dioxane	Piv <sub>2</sub> O	41
15 <sup>d</sup>	[RhCl(CO) <sub>2</sub> ] <sub>2</sub>	DCE	Piv <sub>2</sub> O	91(92)
16	–	DCE	Piv <sub>2</sub> O	0
17	[RhCl(CO) <sub>2</sub> ] <sub>2</sub>	DCE	Piv <sub>2</sub> O	Trace

<sup>a</sup> Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), Rh catalyst (5 mol% of [Rh]) and Piv<sub>2</sub>O (0.3 mmol) were reacted in solvent (0.5 mL) at 130 °C for 18 h, unless otherwise noted. <sup>b</sup> Yield was determined by <sup>1</sup>H NMR analysis using 1,2,4,5-tetramethylbenzene as an internal standard. The value in parentheses indicates isolated yield. <sup>c</sup> At 110 °C. <sup>d</sup> **2a** (0.4 mmol) and Piv<sub>2</sub>O (0.5 mmol) were used.

Table 2 Substrate scope<sup>a</sup>



<sup>a</sup> Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), [RhCl(CO)<sub>2</sub>]<sub>2</sub> (2.5 mol%) and Piv<sub>2</sub>O (0.75 mmol) were reacted in DCE (0.75 mL) at 130 °C for 18 h. <sup>b</sup> 1 mmol scale. At 150 °C.

scale synthesis (**3e**). Alkyl substituents bearing phenoxide, phthalimide and methyl ester moieties were tolerated, providing the corresponding alkylated indolines in moderate to good yields (**3f–h**). 2-(4-Methoxyphenyl)acetic acid afforded an acceptable yield of **3i**. Subsequently, the substrate scope of the indoline derivatives was examined. The reaction of 2- and

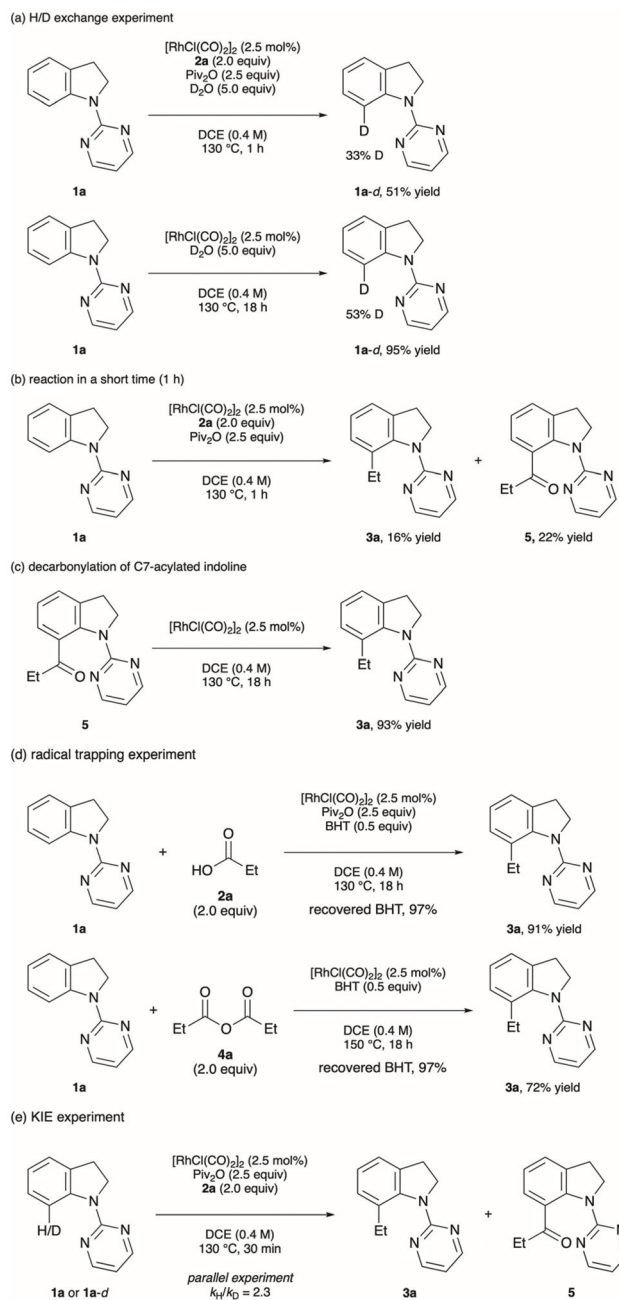
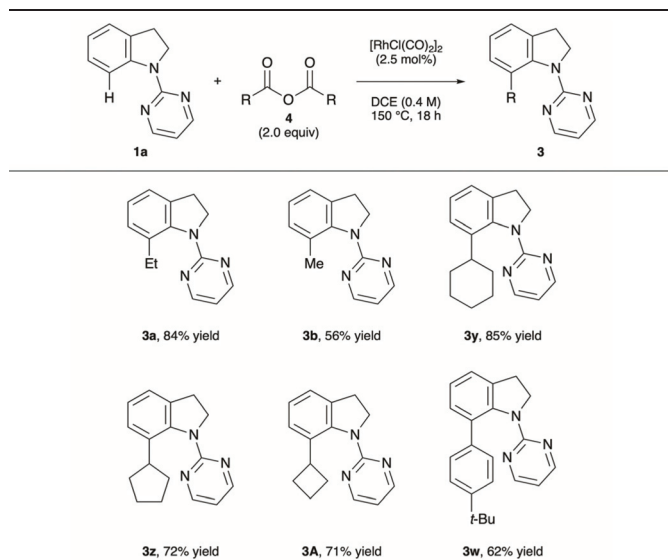


3-substituted indolines produced the desired alkylated indolines **3j–l** in 81–96% yields. 4-Methylindoline rendered the desired product **3m** in high yield. Indolines bearing an electron-donating and -withdrawing group at the 5-position, including methoxy, methyl, fluoro and chloro groups, underwent the alkylation with high yields (**3n–q**). 6-Fluoroindoline was compatible with the reaction conditions (**3r**), while 6-methylindoline failed to react with 3-phenylpropionic acid. Notably, the reaction was not restricted to indolines; a 2-substituted indole and a carbazole reacted with an alkyl carboxylic acid in a similar fashion to yield **3t** and **3u** in 73% and 52%, respectively. Further, C-2 alkylation proceeded with 1-(pyrimidin-2-yl)indole, furnishing 73% of **3v**. The decarbonylative arylation of **1a** proceeded smoothly by subjecting benzoic acids to the optimised reaction conditions (**3w** and **3x**).

Alkyl carboxylic anhydrides underwent this decarbonylative alkylation reaction in a similar manner (Table 3). The alkylation of propionic and acetic anhydrides with **1a** proceeded smoothly to provide the corresponding products in moderate to high yields (**3a** and **3b**, respectively). To our delight, branched carboxylic anhydrides participated in the reaction to furnish the products **3y–A** in 71–85% yields. Application of the reaction conditions to benzoic anhydride derivative successfully led to the formation of the C-7 arylated indoline **3w**.

A series of control experiments were performed to gain insight into the reaction mechanism (Scheme 2). Initially, a set of H/D exchange experiments was conducted in the presence/absence of **2a** and pivalic anhydride (Scheme 2a). The addition of D<sub>2</sub>O to the standard reaction conditions resulted in the incorporation of deuterium into the recovered starting material. Moreover, H/D exchange of **1a** was observed by heating **1a**, [RhCl(CO)<sub>2</sub>]<sub>2</sub> and D<sub>2</sub>O (5.0 equiv.) in DCE at

Table 3 Decarbonylative alkylation using carboxylic anhydrides<sup>a</sup>



Scheme 2 Control experiments.

130 °C. These results indicate that the C(sp<sup>2</sup>)-H bond activation step is reversible. When the alkylation reaction was halted after 1 h, a significant amount of 7-acylated indoline **5** was detected (Scheme 2b). As ketone **5** appears to be a putative intermediate in the formation of **3a**, **5** was subjected to the standard reaction conditions without an alkyl carboxylic acid and pivalic anhydride (Scheme 2c). The clean conversion of **5** into **3a** was confirmed, indicating that **3a** arose from the catalytic decarbonylation of **5**.<sup>18</sup> In the radical trapping experiment with BHT, no significant decrease of the yield was observed in both alkyl carboxylic acid and anhydride cases,<sup>19</sup> suggesting



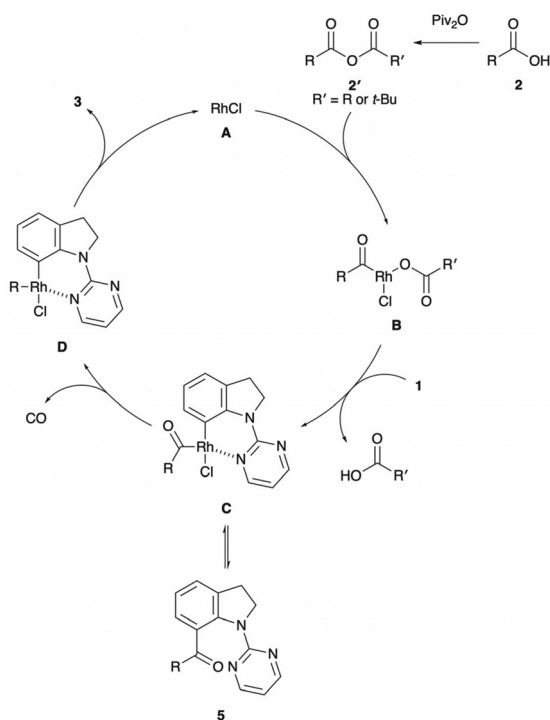


Fig. 1 Proposed reaction mechanism.

the involvement of an alkyl radical species is unlikely (Scheme 2d). Moreover, the kinetic isotope effect experiment revealed that the C–H bond cleavage step is likely to be the rate-determining step (Scheme 2e).

Based on the aforementioned experimental results and previous reports,<sup>13,14,16</sup> we propose the reaction mechanism depicted in Fig. 1. The reaction starts with the formation of mixed anhydride 2' followed by oxidative addition of the C–O bond to rhodium(i) A to furnish acylrhodium(III) carboxylate B. Coordination of the indoline 1 to B promotes a C-7 selective C–H activation, which might proceed *via* an electrophilic mechanism,<sup>13c</sup> yielding six-membered rhodacycle C. Reductive elimination from C affords the acylated product 5. Besides, acylrhodium(III) C undergoes deinsertion of CO and subsequent reductive elimination, leading to the formation of the C-7 alkylated indole 3 along with the regeneration of active Rh(i) catalyst A.

## Conclusions

In conclusion, we developed a rhodium-catalysed decarbonylative alkylation approach for indolines under redox-neutral conditions. Alkyl carboxylic acids, which are cheap, abundant and stable, function as ideal alkylating reagents with the assistance of pivalic anhydride to provide the C-7 alkylated indolines in good to high yields. Additionally, a related decarbonylative alkylation reaction with symmetrical carboxylic anhydrides is achieved under acid/base- and redox-neutral conditions. Our reaction facilitates the use of primary carboxylic

acids, which are difficult to use in the previous radical-mediated decarboxylative process, as alkylating reagents. Further investigation of decarbonylative alkylation is currently underway in our laboratory.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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## Notes and references

- (a) W. Xu, D. J. Gavia and Y. Tang, *Nat. Prod. Rep.*, 2014, **31**, 1474; (b) M.-Z. Zhang, Q. Chen and G.-F. Yang, *Eur. J. Med. Chem.*, 2015, **89**, 421; (c) V. M. Norwood and R. W. Huigens, *ChemBioChem*, 2019, **20**, 2273.
- (a) K. Krueger, A. Tillack and M. Beller, *Adv. Synth. Catal.*, 2008, **350**, 2153; (b) D. F. Taber and P. K. Tirunahari, *Tetrahedron*, 2011, **67**, 7195; (c) S. Kotha and C. Chakkapalli, *Chem. Rec.*, 2017, **17**, 1039; (d) S. W. Youn and T. Y. Ko, *Asian J. Org. Chem.*, 2018, **7**, 1467; (e) A. K. Clarke, H. E. Ho, J. A. Rossi-Ashton, R. J. K. Taylor and W. P. Unsworth, *Chem. – Asian J.*, 2019, **14**, 1900.
- (a) J. A. Leitch, Y. Bhonoah and C. G. Frost, *ACS Catal.*, 2017, **7**, 5618; (b) D. V. Vorobyeva and S. N. Osipov, *Synthesis*, 2018, **50**, 227; (c) T. A. Shah, D. Bhusan, S. Pradhan and T. Punniyamurthy, *Chem. Commun.*, 2019, **55**, 572; (d) S. Pradhan, P. B. De, T. A. Shah and T. Punniyamurthy, *Chem. – Asian J.*, 2020, **15**, 4184; (e) J. Wen and Z. Shi, *Acc. Chem. Res.*, 2021, **54**, 1723; (f) P. Bhattacharjee and U. Bora, *Org. Chem. Front.*, 2021, **8**, 2343.
- For selected examples on C(7)–H selective functionalisation of indoles, see: (a) A. J. Borah and Z. Z. Shi, *J. Am. Chem. Soc.*, 2018, **140**, 6062; (b) X. D. Qiu, P. P. Wang, D. Y. Wang, M. Y. Wang, Y. Yuan and Z. Z. Shi, *Angew. Chem., Int. Ed.*, 2019, **58**, 1504; (c) C. N. Kona, Y. Nishii and M. Miura, *Angew. Chem., Int. Ed.*, 2019, **58**, 9856; (d) X. W. Han, Y. Yuan and Z. Z. Shi, *J. Org. Chem.*, 2019, **84**, 12764; (e) S. J. Fang, G. B. Jiang, M. Li, Z. Y. Liu, H. F. Jiang and W. Q. Wu, *Chem. Commun.*, 2019, **55**, 13769; (f) P. Chen, Y. H. Hao, X. X. Wang, D. Yuan, Y. M. Yao and L. Ackermann, *Chem. – Eur. J.*, 2019, **25**, 7292; (g) I. Choi, A. M. Messinis and L. Ackermann, *Angew. Chem., Int. Ed.*, 2020, **59**, 12534.
- For recent reviews on C(7)–H selective functionalisation of indolines, see: (a) T. A. Shah, P. B. De, S. Pradhan and T. Punniyamurthy, *Chem. Commun.*, 2019, **55**, 572; (b) R. A. Jagtap and B. Punji, *Asian J. Org. Chem.*, 2020, **9**,



- 326; (c) S. Pradhan, P. B. De, T. A. Shah and T. Punniyamurthy, *Chem. – Asian J.*, 2020, **15**, 4184.
- 6 For recent examples on C(7)–H selective functionalisation of indolines, see: (a) P.-L. Wang, Y. Li, L. Ma, C.-G. Luo, Z.-Y. Wang, Q. Lan and X.-S. Wang, *Adv. Synth. Catal.*, 2016, **358**, 1048; (b) Z. Q. Song and A. P. Antonchick, *Org. Biomol. Chem.*, 2016, **14**, 4804; (c) H. Q. Luo, H. D. Liu, Z. P. Zhang, Y. F. Xiao, S. H. Wang, X. Z. Luo and K. J. Wang, *RSC Adv.*, 2016, **6**, 39292; (d) S. Maiti, L. Burgula, G. Chakraborti and J. Dash, *Eur. J. Org. Chem.*, 2017, **2017**, 332; (e) H. Jo, J. Park, N. K. Mishra, M. Jeon, S. Sharma, H. Oh, S.-Y. Lee, Y. H. Jung and I. S. Kim, *Tetrahedron*, 2017, **73**, 1725; (f) T. Jeong, S. H. Lee, N. K. Mishra, U. De, J. Park, P. Dey, J. H. Kwak, Y. H. Jung, H. S. Kim and I. S. Kim, *Adv. Synth. Catal.*, 2017, **359**, 2329; (g) M. K. Manna, G. Bairy and R. Jana, *Org. Biomol. Chem.*, 2017, **15**, 5899; (h) A. E. Hande and K. R. Prabhu, *J. Org. Chem.*, 2017, **82**, 13405; (i) P. B. De, S. Pradhan, S. Banerjee and T. Punniyamurthy, *Chem. Commun.*, 2018, **54**, 2494; (j) Y. Q. Dong, S. Sun, J. T. Yu and J. Cheng, *Tetrahedron Lett.*, 2019, **60**, 1349; (k) R. Du, K. Zhao, J. Liu, F. Han, C. Xia and L. Yang, *Org. Lett.*, 2019, **21**, 6418; (l) H. Q. Luo, Q. Xie, K. Sun, J. B. Deng, L. Xu, K. J. Wang and X. Z. Luo, *RSC Adv.*, 2019, **9**, 18191; (m) S. K. Banjare, P. Biswal and P. C. Ravikumar, *J. Org. Chem.*, 2020, **85**, 5330; (n) Q. K. Yan, H. Huang, H. Zhang, M. H. Li, D. D. Yang, M. P. Song and J. L. Niu, *J. Org. Chem.*, 2020, **85**, 11190; (o) G. Xie, Y. Zhao, C. Cai, G.-J. Deng and H. Gong, *Org. Lett.*, 2021, **23**, 410; (p) S. Maiti, T. Mandal, B. P. Dash and J. Dash, *J. Org. Chem.*, 2021, **86**, 1396.
- 7 (a) S. G. Pan, N. Ryu and T. Shibata, *Adv. Synth. Catal.*, 2014, **356**, 929; (b) H. Oh, J. Park, S. H. Han, N. K. Mishra, S. H. Lee, Y. Oh, M. Jeon, G.-J. Seong, K. Y. Chung and I. S. Kim, *Tetrahedron*, 2017, **73**, 4739; (c) C. Pan, Y. Wang, C. Wu and J.-T. Yu, *Org. Biomol. Chem.*, 2018, **16**, 693; (d) S. K. Banjare, R. Chebolu and P. C. Ravikumar, *Org. Lett.*, 2019, **21**, 4049.
- 8 (a) W. Ai, X. Yang, Y. Wu, X. Wang, Y. Li, Y. Yang and B. Zhou, *Chem. – Eur. J.*, 2014, **20**, 17653; (b) I. E. Iagafarova, D. V. Vorobyeva, D. A. Loginov, A. S. Peregudov and S. N. Osipov, *Eur. J. Org. Chem.*, 2017, **2017**, 840.
- 9 X. Zhou, S. Yu, Z. Qi, L. Kong and X. Li, *J. Org. Chem.*, 2016, **81**, 4869.
- 10 P. B. De, S. Atta, S. Pradhan, S. Banerjee, T. A. Shah and T. Punniyamurthy, *J. Org. Chem.*, 2020, **85**, 4785.
- 11 For recent examples on C(sp<sup>2</sup>)–H alkylation, see: (a) H. Tian, H. Yang, C. Tian, G. An and G. Li, *Org. Lett.*, 2020, **22**, 7709; (b) Y. Cheng, Y. He, J. Zheng, H. Yang, J. Liu, G. An and G. Li, *Chin. Chem. Lett.*, 2021, **32**, 1437.
- 12 R. A. Jagtap, P. P. Samal, C. P. Vinod, S. Krishnamurthy and B. Punji, *ACS Catal.*, 2020, **10**, 7312.
- 13 (a) H. Yang, C. Tian, D. Qiu, H. Tian, G. An and G. Li, *Org. Chem. Front.*, 2019, **6**, 2365; (b) H. Zhao, X. Xu, H. Yu, B. Li, X. Xu, H. Li, L. Xu, Q. Fan and P. J. Walsh, *Org. Lett.*, 2020, **22**, 4228; (c) H. Yu, H. Zhao, X. Xu, X. Zhang, Z. Yu, L. Li, P. Wang, Q. Shi and L. Xu, *Asian J. Org. Chem.*, 2021, **10**, 879; (d) Y. He, H. Yang, D. Gao, J. Ma, Y. Shao, G. An and G. Li, *Chin. J. Org. Chem.*, 2021, **41**, 4725.
- 14 For selected examples on C(sp<sup>2</sup>)–H arylations and alkenylations with (in situ formed) carboxylic anhydrides, see: (a) W. Jin, Z. Yu, W. He, W. Ye and W.-J. Xiao, *Org. Lett.*, 2009, **11**, 1317; (b) H. Zhao, X. Xu, Z. Luo, L. Cao, B. Li, H. Li, L. Xu, Q. Fan and P. J. Walsh, *Chem. Sci.*, 2019, **10**, 10089.
- 15 C. Premi, A. Dixit and N. Jain, *Org. Lett.*, 2015, **17**, 2598.
- 16 For our recent works on rhodium-catalysed C–H functionalisation of (hetero)arenes with anhydrides, see: (a) H. Suzuki, Y. Liao, Y. Kawai and T. Matsuda, *Eur. J. Org. Chem.*, 2021, **2021**, 4938; (b) H. Suzuki, F. Sasamori and T. Matsuda, *Org. Lett.*, 2022, **24**, 1141–1145.
- 17 The use of  $\alpha$ -branched carboxylic acids suffered from the formation of **3d** (~1(0%)) as an inseparable byproduct owing to the unselective C–O bond cleavage and the rearrangement of a *tert*-butyl group.
- 18 For chelation-assisted decarbonylation of unstrained ketones, see: (a) Z.-Q. Lei, H. Li, Y. Li, X.-S. Zhang, K. Chen, X. Wang, J. Sun and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2012, **51**, 2690; (b) T.-T. Zhao, W.-H. Xu, Z.-J. Zheng, P.-F. Xu and H. Wei, *J. Am. Chem. Soc.*, 2018, **140**, 586; (c) T.-Y. Yu, W.-H. Xu, H. Lu and H. Wei, *Chem. Sci.*, 2020, **11**, 12336.
- 19 Acylation of BHT has not been observed in crude <sup>1</sup>H NMR analysis.

