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Cobalt-catalysed reductive C–H alkylation of indoles using carboxylic acids and molecular hydrogen†

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The direct CH-alkylation of indoles using carboxylic acids is presented for the first time. The catalytic system based on the combination of $\text{Co}(\text{acac})_3$ and 1,1,1-tris(diphenylphosphinomethyl)-ethane (Triphos, **L1**), in the presence of $\text{Al}(\text{OTf})_3$ as co-catalyst, is able to perform the reductive alkylation of 2-methyl-1*H*-indole with a wide range of carboxylic acids. The utility of the protocol was further demonstrated through the C3 alkylation of several substituted indole derivatives using acetic, phenylacetic or diphenylacetic acids. In addition, a careful selection of the reaction conditions allowed to perform the selective C3 alkenylation of some indole derivatives. Moreover, the alkenylation of C2 position of 3-methyl-1*H*-indole was also possible. Control experiments indicate that the aldehyde, *in situ* formed from the carboxylic acid hydrogenation, plays a central role in the overall process. This new protocol enables the direct functionalization of indoles with readily available and stable carboxylic acids using a non-precious metal based catalyst and hydrogen as reductant.

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Introduction

Indoles are privileged scaffolds, acting as building blocks in multiple natural products.¹ In fact, the essential amino acid tryptophan and the neurotransmitter serotonin contain the indole moiety in their structure. Inspired by nature, chemists have designed a myriad of indole based compounds with biological activities for its use as drugs or agrochemicals.² For example, indometacin, sumatriptan or fluvastatin are currently marketed as drugs for the treatment of inflammation, migraine or hipercholesterolemia, respectively (Fig. 1). Hence, the development of new methodologies for the derivatization of this class of heterocycles continues to be an important topic in organic synthesis and catalysis.

Traditionally, the cyclisation of pre-functionalized benzoid precursors is the method of choice for the synthesis of substituted indoles.³ Since the development of the useful Fisher indole synthesis in the 19th century,⁴ many other catalytic and non-catalytic cyclisation protocols have been described along the years.⁵ In contrast, the direct functionalization of indole has emerged more recently as a preferred methodology as it is more practical and step economical.⁶ Among the several approaches to the direct substitution of indoles, transition metal catalysed

CH activations are attractive.^{5a,7} While positions C2 and C3 are the most activated ones, direct C3 alkylations are still limited. Therefore, allylic alkylations,⁸ Baylis–Hillman⁹ and more frequently Friedel–Crafts type reactions¹⁰ have been especially useful to achieve this transformation. Intimately related with Friedel–Crafts functionalizations are reductive alkylations. Thus, reactions at indole C3 position have been successfully performed employing aldehydes or ketones¹¹ in the presence of silanes,¹² hydrogen¹³ or other reductants.¹⁴ Despite being a practical transformation, the use of carbonyl compounds limits its applicability as they are sometimes not easily available or undergo unwanted side-reactions, *e.g.*, aldol condensations. Hence, the use of more stable carboxylic acids can be more convenient. However, to the best of our knowledge, this strategy has not been explored and only an example of a related indole methylation using CO_2 was described by our group in 2014.¹⁵

Selective hydrogenation of carboxylic acids is a challenging transformation of interest for organic synthesis and catalysis. The first homogeneously catalysed examples of this reaction

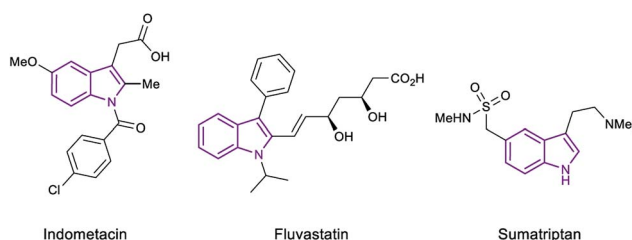


Fig. 1 Examples of indole-based marketed drugs.

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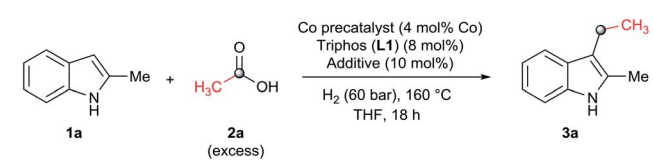


employed a ruthenium¹⁶ or an iridium¹⁷ based complex. Nowadays, the substitution of precious metals by earth abundant non-noble metals, less toxic and expensive, is an exciting goal in catalysis.¹⁸ In this direction, many examples of homogeneous hydrogenation catalysts based on cobalt have been reported recently.^{19,20} In 2015, the groups of de Bruin and Elsevier described the first base metal catalyst able to hydrogenate carboxylic acids using a system composed by $[\text{Co}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}/\text{Triphos} (\mathbf{L1})]$.²¹ Later on, our group reported the CO_2 hydrogenation to methanol using a modified related catalyst $[\text{Co}(\text{acac})_3/\text{Triphos} (\mathbf{L1})/\text{HNTf}_2]$.²² Inspired by these precedents, we envisaged the development of a methodology for the alkylation of indole directly using carboxylic acids with a cobalt based catalytic system. Here we describe the first general reductive alkylation of indole C3 position with a variety of carboxylic acids).

Results and discussion

As a starting point of this project, we selected the reductive C–H alkylation of 2-methyl-1H-indole **1a** with acetic acid **2a** (4 eq. respect to **1a**) as benchmark reaction (Table 1). Notably,

Table 1 Cobalt-catalysed reductive C–H alkylation of 2-methyl-1H-indole (**1a**) with acetic acid (**2a**) and molecular hydrogen: initial screening of the reaction conditions



Entry ^a	2a (eq.)	[Co]	Additive	Conv. ^b (%)	3a ^b (%)
1	4	$\text{Co}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$	—	15	—
2	4	$\text{Co}(\text{acac})_3$	—	—	—
3	4	$\text{Co}(\text{acac})_3$	HNTf ₂	89	42
4	4	$\text{Co}(\text{acac})_3$	Al(OTf) ₃	>99	52
5	2	$\text{Co}(\text{acac})_3$	Al(OTf) ₃	>99	69
6 ^c	2	$\text{Co}(\text{acac})_3$	Al(OTf) ₃	74	53
7	1.5	$\text{Co}(\text{acac})_3$	Al(OTf) ₃	89	62
8 ^d	4	$\text{Co}(\text{acac})_3$	Al(OTf) ₃	>99	44
9 ^d	3	$\text{Co}(\text{acac})_3$	Al(OTf) ₃	91	48
10 ^e	2	$\text{Co}(\text{acac})_3$	Al(OTf) ₃	>99	68
11 ^e	1.75	$\text{Co}(\text{acac})_3$	Al(OTf) ₃	>99	68
12 ^e	1.5	$\text{Co}(\text{acac})_3$	Al(OTf) ₃	94	67
13 ^f	1.75	Co(acac)₃	Al(OTf)₃	>99	70
14 ^f	1.5	$\text{Co}(\text{acac})_3$	Al(OTf) ₃	90	63
15 ^g	1.75	$\text{Co}(\text{acac})_3$	Al(OTf) ₃	94	67
16 ^h	1.75	$\text{Co}(\text{acac})_3$	Al(OTf) ₃	35	—

^a Standard reaction conditions: 2-methyl-1H-indole **1a** (67.0 mg, 0.5 mmol), Co precatalyst (0.02 mmol, 4 mol%), Triphos **L1** (25.0 mg, 0.04 mmol, 8 mol%, 2 eq. to Co), additive (0.05 mmol, 10 mol%, 2.5 eq. to Co), THF (2 mL), acetic acid **2a** (0.75–1.25 mmol, 1.5–2.5 eq.) and H₂ (60 bar) at 160 °C. ^b Conversions of **1a** and yields of product **3a** were calculated by GC using hexadecane as internal standard. ^c Run with 2 mol% of $\text{Co}(\text{acac})_3$, 4 mol% of ligand **L1** (2 eq. to Co) and 5 mol% of Al(OTf)₃ (2.5 eq. to Co). ^d Run at 140 °C. ^e Run at 40 bar of H₂. ^f Run at 30 bar of H₂. ^g Run at 15 bar of H₂. ^h Run without ligand **L1**.

functionalization of 2-substituted indoles is an interesting task for medicinal chemistry due to increased metabolic stability of the resulting products. Inspired by the previously known catalytic systems *vide supra*, $\text{Co}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ and $\text{Co}(\text{acac})_3$ (4 mol%) in combination with 1,1,1-tris(diphenylphosphinomethyl)-ethane, so-called Triphos (ligand **L1**, 2 eq. to Co), were tested under 60 bar of H₂, at 160 °C, using THF as solvent during 18 h (Table 1, entries 1 and 2). Unfortunately, no activity was observed. Previous works involving carboxylic acid derivatives hydrogenation catalysed by a Ru/Triphos system showed the crucial effect of an acid additive for the catalytic activity.^{16a,23} Usually this additive provides a weakly coordinating counter anion, able to stabilize the active complex, as well as the optimal reaction medium pK_a for the hydrogenation events to take place. Recently, we showed a similar effect in the Co/Triphos catalysed CO₂ hydrogenation to methanol, where the presence of HNTf₂ is required to form the catalytic active species.²² Hence, we decided to explore the reductive alkylation of indole **1a** with the Co/Triphos system in the presence of an external acid additive.

Gratifyingly, moderate yields of 3-ethyl-2-methyl-1H-indole **3a** were detected when catalytic amounts of HNTf₂ or Al(OTf)₃ (10 mol%, 2.5 eq. to Co) were added to the $[\text{Co}(\text{acac})_3/\text{Triphos} (\mathbf{L1})]$ mixture (42–52%, Table 1, entries 3 and 4, respectively). Surprisingly, no traces of N-alkylated products or bis(indole) derivatives were observed in the reaction mixtures by GC analysis.

Next, a more detailed investigation regarding the effect of alkylating agent **2a** amount, catalyst loading, pressure and temperature on the catalytic activity was carried out (Table 1, entries 5–15). In general, high conversions of **1a** were detected, although only moderate yields of the desired C3-alkylated product **3a** were obtained, indicating some degradation of the indoles. Nevertheless, the yield of the desired C3-alkylated indole derivative **3a** could be improved to 70% using 1.75 eq. of acetic acid **2a** under 30 bar of hydrogen and 160 °C (Table 1, entry 13). Milder reaction temperatures or lower catalysts loadings and hydrogen pressures did not afford better yields of **3a** (Table 1, entries 6, 8, 9 and 15). In the absence of ligand **L1**, no desired product was detected and only some degradation of **1a** was observed (Table 1, entry 16).

At this point we became interested in studying the influence of the acid co-catalyst. Fig. 2 (up) shows that, among the different Brønsted and Lewis acid additives tested for the CH-alkylation of the indole **1a**, aluminium(III) trifluoromethanesulfonate [Al(OTf)₃] afforded the best yield of **3a** (70%). Other Lewis acid additives such as In(OTf)₃, Ga(OTf)₃ or Sn(OTf)₂ also promoted the desired transformation and gave yields of alkylated product **3a** above 60%. In order to improve the model reaction further on, we varied the relative Al(OTf)₃ amount (with respect to the cobalt precatalyst). As shown in Fig. 2 (bottom) 10 mol% of Al(OTf)₃ (2.5 eq. to Co) gave the optimal yield (70% of **3a**).

Next, the influence of the solvent was investigated in detail (see ESI, Table S1†). The presence of water (10% v/v respect to THF) was detrimental for the activity of the catalytic system, affording very poor yields of product **3a** (7%, Table S1,† entry 2). In general, other ether-type solvents gave similar results compared to THF (Table S1,† entries 2–8), being methyl



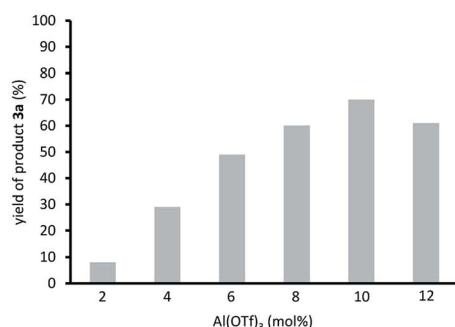
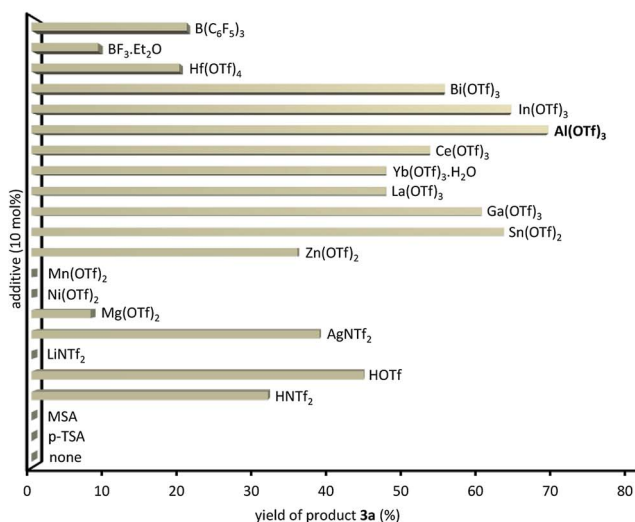
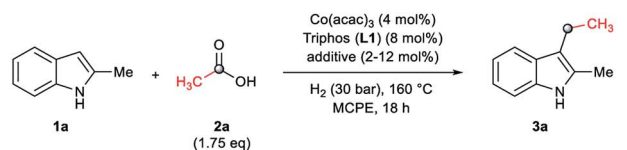


Fig. 2 Up: Testing of additives in the cobalt-catalysed reductive C–H alkylation of 2-methyl-1H-indole **1a** with acetic acid **2a** and molecular hydrogen. Bottom: Influence of the $\text{Al}(\text{OTf})_3$ loading in the formation of product **3a** from **1a** and **2a**. Standard reaction conditions: 2-methyl-1H-indole **1a** (67.0 mg, 0.5 mmol), $\text{Co}(\text{acac})_3$ (7.2 mg, 0.02 mmol, 4 mol%), Triphos **L1** (25.0 mg, 0.04 mmol, 8 mol%, 2 eq. to Co), additive (2–12 mol%, 0.5–3 eq. to Co), THF (2 mL), acetic acid **2a** (50.3 μL , 0.875 mmol, 1.75 eq.) and H_2 (30 bar) at 160 °C. The yields of product **3a** were calculated by GC using hexadecane as internal standard.

cyclopentyl ether (MCPE) the one that gave the best result (Table S1,† entry 6, 83% yield **3a**). Also in toluene a good yield of the desired indole **3a** was obtained (76%, Table S1,† entry 9). In contrast, the catalyst was totally inactive when DMF was used (Table S1,† entry 10).

To our delight, the employment of MCPE allowed to use a lower catalyst loading (2 mol% of cobalt) with excellent results (Table 2, entry 5, 89% yield of **3a**). Blank experiments revealed that the presence of all the three components of the catalytic system, $[\text{Co}(\text{acac})_3/\text{Triphos}(\text{L1})/\text{Al}(\text{OTf})_3]$, are required for the reductive alkylation of indole (Table 2, entries 6–10). In addition, these experiments showed that the partial degradation of **1a** can be attributed mainly to the presence of the acid additive (Table 2, entries 7 and 10).

Table 2 Cobalt-catalysed reductive C–H alkylation of 2-methyl-1H-indole (**1a**) with acetic acid (**2a**) and molecular hydrogen: optimization of the reaction conditions using MCPE as solvent

Entry ^a	T (°C)	H ₂ (bar)	2a (eq.)	[Co] (mol%)	Conv. ^b (%)	3a ^b (%)
1	160	30	1.75	4	>99	83
2	160	30	1.5	4	>99	79
3	160	30	1.25	4	86	62
4	160	30	2.5	2	>99	85
5	160	30	1.75	2	>99	89
6 ^c	160	30	1.75	2	24	—
7 ^d	160	30	1.75	2	57	—
8 ^e	160	30	1.75	2	14	—
9 ^e	160	30	1.75	—	12	—
10 ^d	160	30	1.75	—	54	—
11 ^f	160	30	1.75	2	64	42
12 ^g	160	30	1.75	2	47	—
13	160	30	1.5	2	87	76
14 ^c	160	30	2.5	1	47	31
15 ^d	160	30	1.75	1	40	23
16	160	15	1.75	2	56	27
17 ^h	160	—	1.75	2	15	—
18	140	30	1.75	4	96	68
19	140	30	2.5	4	96	70
20	140	60	1.75	2	69	41
21	140	60	2.5	2	83	49
22 ⁱ	160	30	1.75	2	70	64

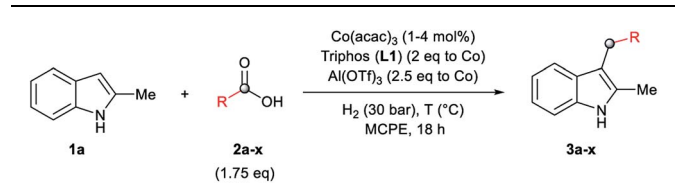
^a Standard reaction conditions: 2-methyl-1H-indole **1a** (67.0 mg, 0.5 mmol), $\text{Co}(\text{acac})_3$ (1–4 mol%), Triphos **L1** (2–8 mol%, 2 eq. to Co), $\text{Al}(\text{OTf})_3$ (2.5–10 mol%, 2.5 eq. to Co), MCPE (2 mL), acetic acid **2a** (0.75–1.25 mmol, 1.5–2.5 eq.) and H_2 (15–60 bar) at 140–160 °C. ^b Conversion of **1a** and yield of product **3a** were calculated by GC using hexadecane as internal standard. ^c Run without ligand **L1** and $\text{Al}(\text{OTf})_3$. ^d Run without ligand **L1**. ^e Run without $\text{Al}(\text{OTf})_3$. ^f Run with 3 mol% of ligand **L1** (1.5 eq. to Co). ^g Run with 2 mol% of ligand **L1** (1 eq. to Co). ^h Run with 30 bar of N_2 . ⁱ Run at 6 h.

Notably, the relative amounts of ligand **L1** with respect to the cobalt precursor had a significant influence on the product yield. When the reaction was conducted using 1.5 and 1 equivalents of ligand, moderate yields (42%) of **3a** or no product were detected, respectively (Table 2, entries 11 and 12), showing that 2 eq. of Triphos (**L1**) are the minimum required to perform the reaction efficiently.

Next, the catalytic activity of different metal pre-catalysts was evaluated under the optimized reaction conditions (30 bar of H_2 , 160 °C, 1.75 eq. of **2a**, 2 mol% of cobalt and 18 h; see Table 1 and ESI, Fig. S1†). Among the different $\text{Co}(\text{III})$, $\text{Co}(\text{II})$, $\text{Ru}(\text{III})$, $\text{Mn}(\text{III})$, $\text{Fe}(\text{III})$ and $\text{Cu}(\text{II})$ acetylacetonate complexes tested, $\text{Co}(\text{acac})_3$ was the one that gave the best yields of the desired alkylated indole **3a** (89%, see ESI, Fig. S1†). In addition, $\text{Co}(\text{acac})_3 \cdot \text{H}_2\text{O}$ afforded a slightly lower yield (78% yield of **3a**, Fig. S1†), while other related metal salts were not active. These results indicate that cobalt is unique for this reaction.

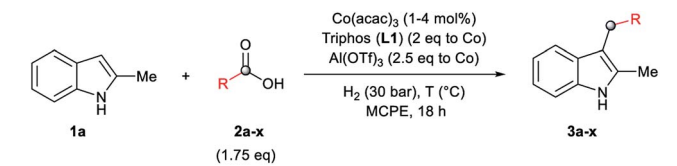


Table 3 [Co/Triphos (L1)]-catalysed reductive C(3)-H alkylation of 2-methyl-1*H*-indole (**1a**) using different carboxylic acids and molecular hydrogen



Entry ^a	T (°C)	[Co] (mol%)	Product 3	Yield ^b (%)
1	160	2		[80]
2	140	2		[80]
3	160	2		[67]
4	160	2		[74]
5 ^c	140	2		[59]
6	160	2		[74]
7 ^c	160	2		[70]
8	140	4		[75]
9 ^c	160	4		[64]
10	140	2		[49]

Table 3 (Contd.)



Entry ^a	T (°C)	[Co] (mol%)	Product 3	Yield ^b (%)
11 ^c	160	3		[46]
12	160	3		[68]
13 ^d	140	2		[47]
14	140	1		[35]
15	140	2		[73]
16	140	2		[78]
17	160	3		[70]



Table 3 (Contd.)

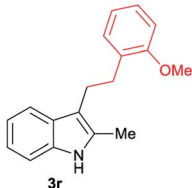
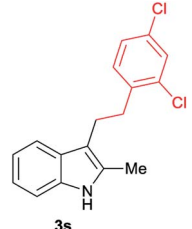
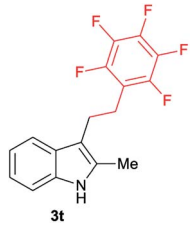
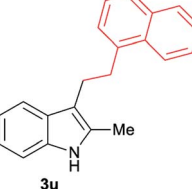
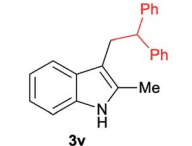
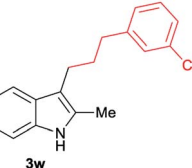
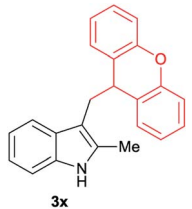
Entry ^a	T (°C)	[Co] (mol%)	Product 3	Yield ^b (%)
18	140	2		[55]
19	160	3		[72]
20	160	2		[42]
21	140	2		[64]
22	140	2		[70]
23	140	2		[72]

Table 3 (Contd.)

Entry ^a	T (°C)	[Co] (mol%)	Product 3	Yield ^b (%)
24	140	2		[55]

^a Standard reaction conditions: 2-methyl-1H-indole **1a** (67.0 mg, 0.5 mmol), Co(acac)₃ (1–4 mol%), Triphos **L1** (2–8 mol%, 2 eq. to Co), Al(OTf)₃ (2.5–10 mol%, 2.5 eq. to Co), MCPE (2 mL), carboxylic acid (0.875 mmol, 1.75 eq.) and H₂ (30 bar) at 140–160 °C. The selectivity to the desired product was >95% in all cases. In some examples degradation problems were observed. ^b Yield of isolated product after column chromatography on silica. ^c Run with (1.75 mmol, 2.5 eq.) of carboxylic acid. ^d Run at 5 h.

Among the different cobalt-based precatalysts containing counteranions such as [BF₄⁻], [ClO₄⁻], [OAc⁻], [F⁻], [NO₃⁻] and [SO₄²⁻] (see ESI, Fig. S1†) tested for the alkylation of indole **1a**, only Co(BF₄)₂·6H₂O and Co(SO₄)·7H₂O promoted the formation of the product **3a**, albeit in lower yields (21% and 8% yield of **3a**, respectively, Fig. S1†).

With regard to the ligand, we compared the activity of Triphos **L1** with several multidentate (**L2**–**L11**) and one monodentate ligands (**L11**) (see ESI, Scheme S1†). All the other tested ligands showed lower activities than Triphos (**L1**), and only the tridentate ligands **L2** and **L3** or the tetradentate **L5** afforded 3-ethyl-2-methyl-1H-indole **3a**, though in low yields (18%, 17% and 3%, respectively, Scheme S1†).

At this point, we decided to explore the general applicability of the cobalt-based system in the C3-alkylation of 2-methyl-1H-indole **1a** using a wide range of carboxylic acids (Table 3). In some cases, higher catalyst loadings (up to 4 mol%) or excess of the alkylating agent (up to 2.5 eq.) were needed in order to achieve a total conversion of indole **1a**.

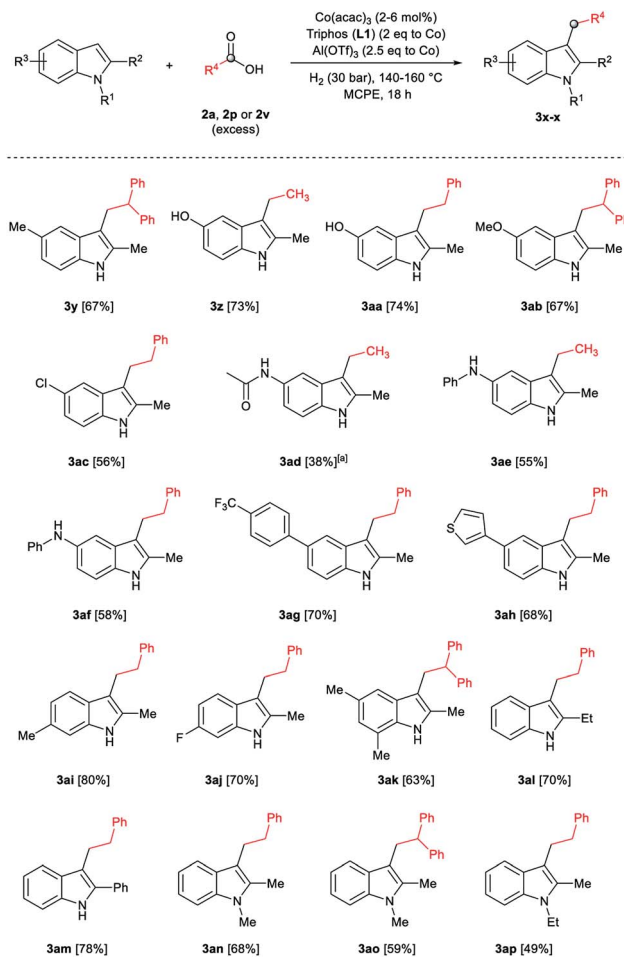
Aliphatic carboxylic acids **2a**–**g**, including examples containing heteroatoms such as oxygen-(**2e**) or fluorine-(**2f** and **2g**), afforded the corresponding C3-alkylated indoles **3a**–**g** in good to very good isolated yields (59–80%, Table 3, entries 1–7). Moreover, benzoic acid **2h** and different *o*-, *m*- and *p*-substituted benzoic acids containing chloro (**2i**), trifluoromethyl (**2j**) or methoxy groups (**2k**–**m**), could also be used as alkylating agents giving good isolated yields of the C3-benzylated indole derivatives **3h**–**m** (46–75%, Table 3, entries 8–13). Gratifyingly, perfluorinated benzoic acid **2n** and naphthoic acid **2o** also gave the desired functionalized indole derivatives **3n** and **3o** in moderate



to good yields after isolation (36 and 73%, Table 3, entry 14 and 15, respectively). In addition, more sensitive phenylacetic acid **2p**, naphthaleneacetic acid **2u** as well as 2-hydroxy-(**2q**), 2-methoxy-(**2r**), 2,4-dichloro-(**2s**) and perfluoro-(**2t**) substituted phenylacetic acids were successfully employed as alkylating agents of indole **1a** (42–78%, Table 3, entries 16–21). In general, no clearly correlation between the reactivity and the electronic character of the substituent attached to the benzene ring of the carboxylic acid could be observed. Finally, diphenylacetic acid **2v**, 3-(3-(trifluoromethyl)phenyl)propanoic acid **2w** and 9-xanthene carboxylic acid **2x**, as an example of (hetero)aromatic acid, exhibited good activity (55–70%, Table 3, entries 22–24). These examples illustrate the potential of the base metal catalysed methodology as a practical tool for introducing molecular diversity in the indole core using readily available carboxylic acids as alkylating agents.

After showing the reductive alkylation using different carboxylic acids, we investigated the reaction of several substituted indole derivatives (Scheme 1). Using the optimized conditions, a variety of indoles were reacted with acetic acid **2a**, phenylacetic acid **2p** or diphenylacetic acid **2v**. In general, for the same indole, **2p** was the most reactive carboxylic acid followed by **2v** and **2a**, as the less reactive one. As shown in Scheme 1, several 5-substituted 2-methyl-1*H*-indole derivatives – some of them previously synthesized by us (see ESI† for experimental details) – containing methyl, hydroxy, methoxy, chloro, amino, phenylamino, trifluoromethyl and thiophenyl groups were well tolerated. The desired C3-alkylated products **3y–ah** were obtained in moderate to good yields after isolation (38–74%, Scheme 1). Interestingly, in the case of 5-amino-2-methyl-1*H*-indole reacting with acetic acid, the main product was the one corresponding to the simultaneous C3 alkylation and amidation, being possible to isolate the amide **3ad** in moderate yields (38%, Scheme 1). This result indicates that the [Co(acac)₃/Triphos (L1)/Al(OTf)₃] catalysts exhibits selectivity towards the hydrogenation of a carboxylic acid in the presence of an amide. Moreover, 6-substituted as well as 5,7-substituted indole substrates were also successfully alkylated giving products **3ai–ak** in 63–80% isolated yields. At this point it was interesting to explore the tolerance of our protocol towards different alkyl and aryl substituents in the C2 position as well as in the nitrogen atom of the indole. To our delight, the reductive alkylation of this indoles class was successfully achieved under different reaction conditions using phenylacetic acid **2p** and diphenylacetic acid **2v** as alkylating agents. Thus, the desired C3-alkylated products **3al–ap** could be isolated in 49–70% yields (Scheme 1).

As expected, in case of 2,3-dimethyl-1*H*-indole **S1** (Scheme S2,† eqn (A)), no products were detected after its reaction with acetic acid **2a**, discarding a possible *N*-alkylation catalysed by our system. In agreement with this observation, for 3-methyl-1*H*-indole **1b** where the C3 position is blocked, only very low amounts of C2-ethylated product **S3** (<2%) were detected (Scheme S2,† eqn (B)), confirming the lower nucleophilicity of C2 position in comparison with C3. Finally, when simple indole **1c** or *N*-methyl derivative **1d** were used, low conversions (<20%) and poor yields of the desired C3-ethylated products **S3** and **S5** were observed (10 and 8%, respectively, Scheme S2,† eqn (C)



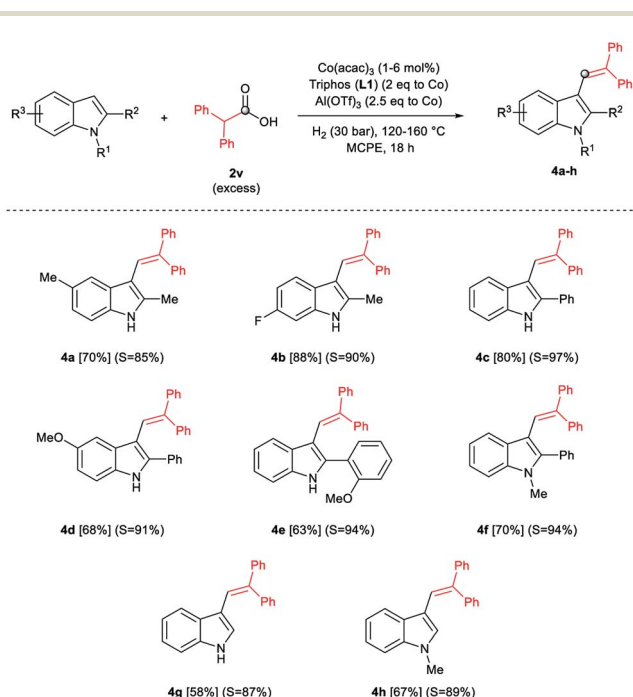
Scheme 1 Standard reaction conditions: indole (0.5 mmol), Co(acac)₃ (1–4 mol%), Triphos L1 (2–8 mol%, 2 eq. to Co), Al(OTf)₃ (2.5–10 mol%, 2.5 eq. to Co), MCPE (2 mL), carboxylic acid (0.875–1.75 mmol, 1.75–3.5 eq.) and H₂ (30 bar) at 140–160 °C during 18–60 h. Yield of isolated product after column chromatography on silica are given. The selectivity to the desired product, calculated by GC-MS, was >90% in all cases. In some examples degradation problems were observed. Specific reaction conditions for substrate **3y** and **3ak**: Co(acac)₃ (4 mol%), carboxylic acid (0.875 mmol, 1.75 eq.), 160 °C, 18 h; for substrate **3z**: Co(acac)₃ (2 mol%), carboxylic acid (0.875 mmol, 1.75 eq.), 160 °C, 18 h; for substrates **3aa** and **3ai**: Co(acac)₃ (2 mol%), carboxylic acid (0.875 mmol, 1.75 eq.), 140 °C, 18 h; for substrate **3ab**: Co(acac)₃ (3 mol%), carboxylic acid (0.875 mmol, 1.75 eq.), 160 °C, 48 h; for substrate **3ac**: Co(acac)₃ (6 mol%), carboxylic acid (1.5 mmol, 3.5 eq.), 160 °C, 18 h; for substrates **3ad–ae**: Co(acac)₃ (4 mol%), carboxylic acid (1.5 mmol, 3 eq.), 160 °C, 18 h; for substrate **3af**: Co(acac)₃ (3 mol%), carboxylic acid (0.875 mmol, 1.75 eq.), 160 °C, 18 h; for substrates **3ag–ah** and **3aj**: Co(acac)₃ (5 mol%), carboxylic acid (1.25 mmol, 2.5 eq.), 160 °C, 18 h; for substrate **3al**: Co(acac)₃ (2 mol%), carboxylic acid (1.25 mmol, 2.5 eq.), 160 °C, 18 h; for substrate **3am**: Co(acac)₃ (6 mol%), carboxylic acid (1.25 mmol, 2.5 eq.), 160 °C, 18 h; for substrate **3an**: Co(acac)₃ (3 mol%), carboxylic acid (1.25 mmol, 2.5 eq.), 160 °C, 18 h; for substrate **3ao**: Co(acac)₃ (6 mol%), carboxylic acid (0.875 mmol, 1.75 eq.), H₂ (60 bar), 160 °C, 60 h; for substrate **3ap**: Co(acac)₃ (6 mol%), carboxylic acid (1.25 mmol, 2.5 eq.), 160 °C, 18 h. [a] 2-Methyl-1*H*-indol-5-amine was used as starting material.

and (D)). Interestingly, in these two cases small amounts of bis(indole) compounds **S4** and **S6** (<2 and <5%, respectively, Scheme S2,† eqn (C) and (D)) were detected.



During the development of the alkylation reactions of different indoles using diphenylacetic acid **2v** (see Scheme 1), we observed alkenylation of selected substrates as a side reaction.²⁴ A fine control of the reaction parameters (temperature, pressure of hydrogen, catalyst loading, amount of alkylating agent and reaction time) allowed us to selectively stop the reaction at the alkene stage (Scheme 2). For example, 5-methyl- and 6-fluoro-2-methyl-1*H*-indole derivatives were selectively alkenylated (selectivity alkene vs. alkane >85%) affording the desired tri-substituted alkenes **4a** and **4b** in very good isolated yields (70 and 88%, respectively, Scheme 2). To the best of our knowledge such alkenylations using carboxylic acids have not described, yet.

In addition, different C2-phenyl and/or nitrogen-alkyl substituted indole derivatives gave the corresponding alkene products **4c–f** with high selectivities towards alkene vs. alkane (>94%) and good isolated yields (63–80%, Scheme 2). Notably, the simple indole **1c** and the *N*-methyl substituted **1d**,



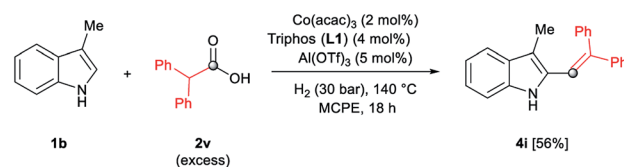
Scheme 2 Cobalt-catalysed reductive selective C(3)-H diphenylvinylation of different indoles using diphenylacetic acid **2v** and molecular hydrogen. Standard reaction conditions: indole (0.5 mmol), Co(acac)₃ (1–6 mol%), Triphos **L1** (2–12 mol%, 2 eq. to Co), Al(OTf)₃ (2.5–15 mol%, 2.5 eq. to Co), MCPE (2 mL), diphenylacetic acid **2v** (1.25–1.75 mmol, 2.5–3.5 eq.) and H₂ (30 bar) at 120–160 °C over 18 h. Yield of isolated products after column chromatography on silica are given between brackets. Between parentheses is shown the selectivity to the desired alkene vs. alkane by-product, calculated by GC-MS. In some examples degradation problems were observed. Specific reaction conditions for substrate **4a**: Co(acac)₃ (2 mol%), carboxylic acid (1.75 mmol, 3.5 eq.), 120 °C; for substrate **4b**: Co(acac)₃ (2 mol%), carboxylic acid (1.75 mmol, 3.5 eq.), 130 °C; for substrates **4c–e**: Co(acac)₃ (4 mol%), carboxylic acid (1.25 mmol, 2.5 eq.), 160 °C; for substrate **4f**: Co(acac)₃ (6 mol%), carboxylic acid (1.75 mmol, 3.5 eq.), 160 °C; for substrate **4g**: Co(acac)₃ (1 mol%), carboxylic acid (2.25 mmol, 4.5 eq.), 140 °C; for substrate **4h**: Co(acac)₃ (4 mol%), carboxylic acid (1.75 mmol, 3.5 eq.), 120 °C.

unreactive towards alkylation when acetic acid was used (*vide supra*), were also successfully vinylylated in C3 position using diphenylacetic acid **2v**. In these cases only traces of C2-alkenylated products were detected (<2%), observing a full selectivity to C3 vs. C2-position. In fact, C3-alkenylated products **4g** and **4h** were isolated in moderate to good yields (58 and 67%, respectively, Scheme 2) with selectivities alkene vs. alkane between 87–89%. Finally, despite the lower nucleophilicity of the indole C2 position, it was possible to perform the cobalt catalysed C2 alkenylation of 3-methyl-1*H*-indole **1b** by using an excess of diphenylacetic acid **2v** as alkylating source. The desired C2-alkenylated product **4i** could be isolated in 56% (Scheme 3). Hence, this novel non-precious metal based methodology opens the way to the development of further transformations for the C2 and C3-functionalization of indoles.

To gain insight into the mechanism of the cobalt-catalysed reductive alkylation of indoles, some kinetic studies (see Fig. 3 and 4) and control experiments were performed (see Schemes 4–6). Fig. 3 and 4 show the concentration/time profiles for the reductive alkylation of 2-methyl-1*H*-indole **1a** with acetic acid **2a** and phenylacetic acid **2p**, respectively (optimized reaction conditions for each acid). It should be noted that no induction periods were observed in any of the experiments, indicating that the active catalytic species is easily formed. Interestingly, in the case of the reaction with phenylacetic acid **2p** it is possible to detect low amounts of the intermediate (*E*)-alkene **3p'**, observed in slightly higher concentrations at initial reaction times (see Fig. 4). This observation indicates that the hydrogenation of the alkene **3p'** is not the rate determining step of the process.

Next, we carried out the reaction under the optimized conditions for phenylacetic acid **2p** but in the absence of any indole (Scheme 4A). This experiment revealed that our catalytic system is able to hydrogenate the carboxylic acid to the corresponding alcohol in moderate yields (14% of 2-phenylethanol **5** and 17% of 2-phenethyl phenylacetate **8** were detected, Scheme 4A). The experiment at shorter reaction times and using phenylacetaldehyde **9** as starting material, afforded 2-phenylethanol **5** in good yields (76%, Scheme 4B).

At this point it was interesting to compare the reactivity of several possible alkylating agents, all of them being related derivatives of phenylacetic acid **2p**. Thus, reactions of indole **1a**



Scheme 3 Cobalt-catalysed reductive C(2)-H diphenylvinylation of 3-methyl-1*H*-indole **1b** using diphenylacetic acid **2v** and molecular hydrogen. Standard reaction conditions: 3-methyl-1*H*-indole **1b** (67.0 mg, 0.5 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol, 2 mol%), Triphos **L1** (12.5 mg, 0.02 mmol, 4 mol%, 2 eq. to Co), Al(OTf)₃ (11.9 mg, 0.025 mmol, 5 mol%, 2.5 eq. to Co), MCPE (2 mL), diphenylacetic acid **2v** (486.0 mg, 2.25 mmol, 4.5 eq.) and H₂ (30 bar) at 140 °C over 18 h. Yield of isolated product after column chromatography on silica is given. The selectivity to the alkene product **4i** was 97%.



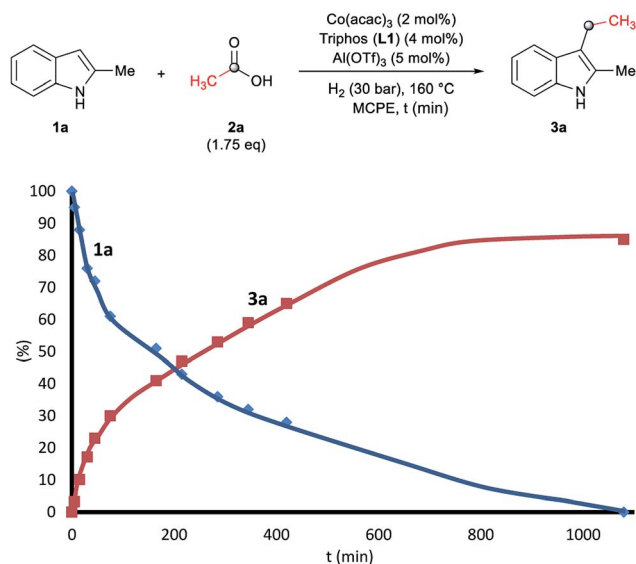


Fig. 3 Concentration/time profile for 2-methyl-1H-indole **1a** (blue line) and 3-ethyl-2-methyl-1H-indole **3a** (red line) in the reductive C–H alkylation of **1a** with acetic acid **2a** at 160 °C and 30 bar of molecular hydrogen. Standard reaction conditions: 2-methyl-1H-indole **1a** (3.0 mmol, 402.0 mg), $\text{Co}(\text{acac})_3$ (21.6 mg, 0.06 mmol, 2 mol%), Triphos **L1** (75.0 mg, 0.12 mmol, 4 mol%, 2 eq. to Co), $\text{Al}(\text{OTf})_3$ (71.4 mg, 0.15 mmol, 5 mol%, 2.5 eq. to Co), MCPE (12.0 mL), acetic acid **2a** (301.8 μL , 5.25 mmol, 1.75 eq.) and H_2 (30 bar) at 160 °C. Percentages of **1a** and **3a** were calculated by GC using hexadecane as internal standard.

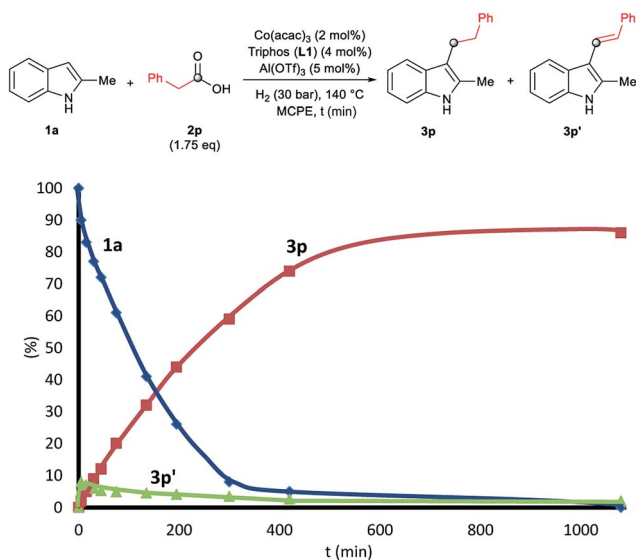


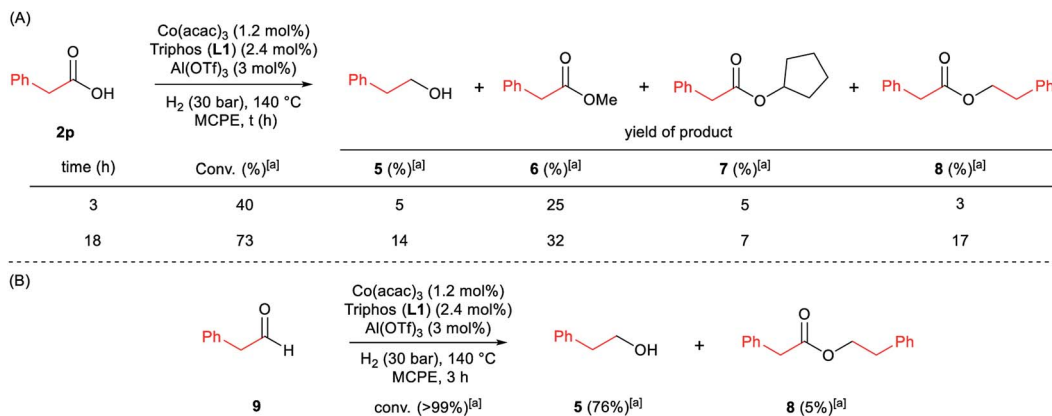
Fig. 4 Concentration/time profile for 2-methyl-1H-indole **1a** (blue line), 2-methyl-3-phenethyl-1H-indole **3p** (red line) and (*E*)-2-methyl-3-styryl-1H-indole **3p'** (green line) in the reductive C–H alkylation of **1a** with phenylacetic acid **2p** at 140 °C and 30 bar of molecular hydrogen. Standard reaction conditions: 2-methyl-1H-indole **1a** (3.0 mmol, 402.0 mg), $\text{Co}(\text{acac})_3$ (21.6 mg, 0.06 mmol, 2 mol%), Triphos **L1** (75.0 mg, 0.12 mmol, 4 mol%, 2 eq. to Co), $\text{Al}(\text{OTf})_3$ (71.4 mg, 0.15 mmol, 5 mol%, 2.5 eq. to Co), MCPE (12.0 mL), phenylacetic acid **2p** (720.0 mg, 5.25 mmol, 1.75 eq.) and H_2 (30 bar) at 140 °C. Percentages of **1a**, **3p** and **3p'** were calculated by GC using hexadecane as internal standard.

were performed in the presence of the $[\text{Co}(\text{acac})_3/\text{Triphos} (\mathbf{L1})/\text{Al}(\text{OTf})_3]$ system at 140 °C and 30 bar of H_2 , using phenylacetic acid **2p**, phenylacetaldehyde **9**, phenethyl alcohol **5** and methyl phenylacetate **6** (usually formed from phenylacetic acid and methanol coming from MCPE cleavage) (Scheme 5A–D). Under these conditions, the best alkylating agent was the acid derivative (Scheme 5A), while the ester **6** and the alcohol **5** only afforded only traces of the alkylated product **3p** (Scheme 5C and D, respectively). The aldehyde **9** gave the alkylated indole **3p** in low yield (21%) together with traces of the alkenylated product **3p'** (Scheme 5B). This latter result is especially surprising considering the general use and high reactivity of aldehydes as alkylating agents. At milder reaction temperatures of 100 and 60 °C, a decrease in the catalytic activity was observed for phenylacetic acid **2p**, while phenethyl alcohol **5** and methyl phenylacetate **6** were totally unreactive (Scheme 5A, C and D, respectively). Interestingly, the reaction with phenylacetaldehyde **9** at 100 and 60 °C gave moderate and good yields of the alkenylated product **3p'**, respectively (Scheme 5B). This observation suggests that the aldehyde could be an important reaction intermediate that, when formed slowly from the carboxylic acid at the optimized conditions, is able to afford the alkylated product in good yields. The low yields of **3p** obtained when the reaction was performed starting from the aldehyde at 140 °C, are partially explained by the aldehyde fast hydrogenation to the corresponding alcohol (Scheme 4B) and/or its degradation at this temperature. Notably, when the reaction was performed at low hydrogen pressure or in its total absence, low yields of the alkylated and alkenylated products were observed with phenethyl alcohol **5** and phenylacetaldehyde **9** as alkylating agents (Scheme 5B and C, respectively). This indicates that dehydrogenation pathways could also be partially contributing to the formation of the alkylated product, either by forming the aldehyde from the alcohol or by abstracting hydrogen from water or alcohols in the reaction media.

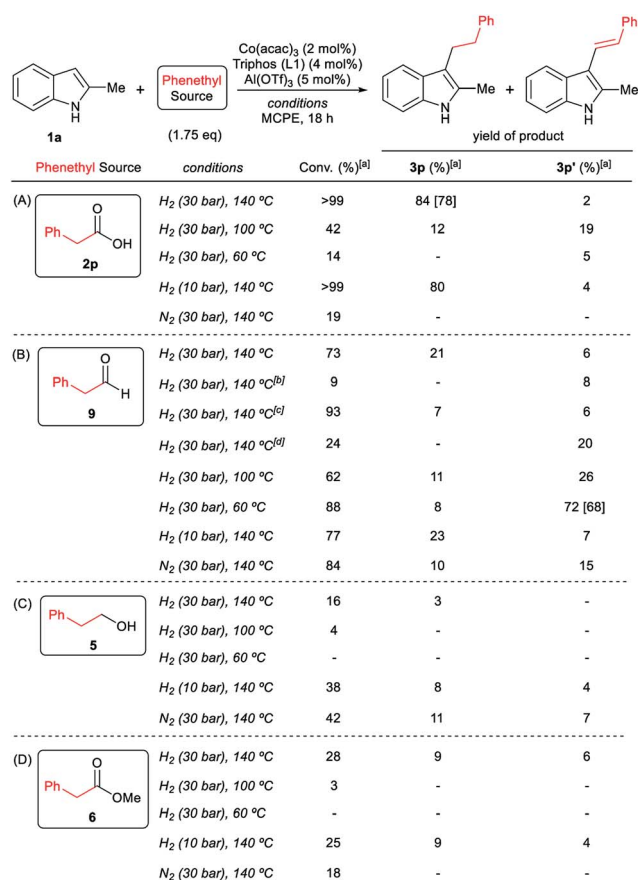
In addition, it was demonstrated that the presence of the three components of the catalytic system, $[\text{Co}(\text{acac})_3/\text{Triphos} (\mathbf{L1})/\text{Al}(\text{OTf})_3]$, was required for the hydrogenation of the (*E*)-styryl indole **3p'** to the alkylated product **3p** (Scheme 6A). Surprisingly, when **3p'** was submitted to the optimized reaction conditions, 2-methyl-1H-indole **1a** was formed in 68% yield. In the presence of 0.75 eq. of phenylacetic acid **2p**, lower amounts of indole **1a** were detected (Scheme 6B).

Finally, to obtain some information about the catalytic system, the resting state of the reaction mixture after standard conditions was studied by ^{31}P NMR (Fig. S2a†). In addition, the same experiment was repeated for several mixtures to see the effect of indole **1a**, acetic acid **2a** and $\text{Al}(\text{OTf})_3$ in the nature of resting state (Fig. S2b–d†). In all these experiments it was possible to detect signals between 18–32 ppm, corresponding to phosphine ligands coordinated to cobalt,²⁵ and similar to the spectra obtained for the $[\text{Co}(\text{acac})_3/\text{Triphos} (\mathbf{L1})/\text{HNTf}_2]$ system.²² Interestingly, when the $[\text{Co}(\text{acac})_3/\text{Triphos} (\mathbf{L1})/\text{Al}(\text{OTf})_3]$ system was employed, signals in the ranges of 18.7–20.2 ppm and 28.7–31.5 ppm were detected (Fig. S2a–c†). However, in the absence of $\text{Al}(\text{OTf})_3$ (Fig. S2d†), only signals





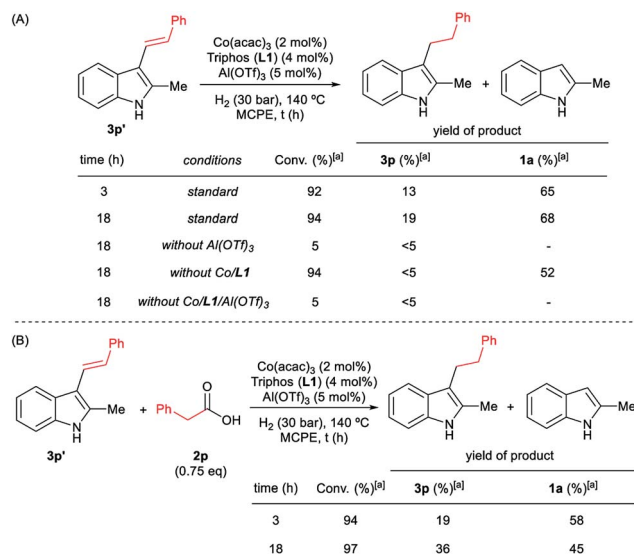
Scheme 4 Control experiments in the hydrogenation of phenylacetic acid **2p** (A) or phenylacetaldehyde **9** (B) in the absence of 2-methyl-1*H*-indole **1a**. Standard reaction conditions: phenylacetic acid **2p** or phenylacetaldehyde **9** (0.875 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol, 1.2 mol%), Triphos **L1** (12.5 mg, 0.02 mmol, 2.4 mol%, 2 eq. to Co), Al(OTf)₃ (11.9 mg, 0.025 mmol, 3 mol%, 2.5 eq. to Co), MCPE (2 mL) at 140 °C during 3–18 h. [a] Conversion of **2p** and **9** and yield of products **5**, **6**, **7** and **8** were calculated by GC using hexadecane as internal standard.



Scheme 5 Control experiments in the C–H phenethylation of 2-methyl-1*H*-indole **1a** using phenylacetic acid **2p** (A), phenylacetaldehyde **9** (B), phenethyl alcohol **5** (C) and methyl phenylacetate **6** (D) as alkylating agent. Standard reaction conditions: 2-methyl-1*H*-indole **1a** (67.0 mg, 0.5 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol, 2 mol%), Triphos **L1** (12.5 mg, 0.02 mmol, 4 mol%, 2 eq. to Co), Al(OTf)₃ (11.9 mg, 0.025 mmol, 5 mol%, 2.5 eq. to Co), MCPE (2 mL), alkylating agent (0.875 mmol, 1.75 eq.) and H₂ (10–30 bar) or N₂ (30 bar) at 60–140 °C during 18 h. [a] Conversion of **1a** and yield of products **3p** and **3p'** were calculated by GC using hexadecane as internal standard. Between brackets is shown the isolated yield of the product after column chromatography on silica. [b] Run without Al(OTf)₃. [c] Run without Co(acac)₃ and Triphos **L1**. [d] Run without Co(acac)₃, Triphos **L1** and Al(OTf)₃.

around 30 ppm were observed, clearly indicating a main role of the additive in the formation of some of the active complexes.

With all these observations in hand, a plausible mechanism can be proposed for the cobalt catalysed reductive alkylation of indoles (Fig. 5). The major pathway involves in first place the hydrogenation of the carboxylic acid **2** to the corresponding aldehyde **A** or hemiacetal, which would react at the C3 nucleophilic position of indole **1** to afford the alkylated indole **B**. Subsequent dehydration leads to the captured alkene intermediate **D**, that finally gets hydrogenated to afford the alkylated indole. Minor pathways would involve the formation of an ester



Scheme 6 Control experiments in the hydrogenation of (*E*)-2-methyl-3-styryl-1*H*-indole **3p'** in the absence (A) or in the presence (B) of phenylacetic acid **2p**. Standard reaction conditions: (*E*)-2-methyl-3-styryl-1*H*-indole **3p'** (116.7 mg, 0.5 mmol), phenylacetic acid **2p** or not (25.7 mg, 0.375 mmol, 0.75 eq.), Co(acac)₃ (3.6 mg, 0.01 mmol, 2 mol%), Triphos **L1** (12.5 mg, 0.02 mmol, 4 mol%, 2 eq. to Co), Al(OTf)₃ (11.9 mg, 0.025 mmol, 5 mol%, 2.5 eq. to Co), MCPE (2 mL) at 140 °C during 3–18 h. [a] Conversion of **3p'** and yield of products **3p** and **1a** were calculated by GC using hexadecane as internal standard.



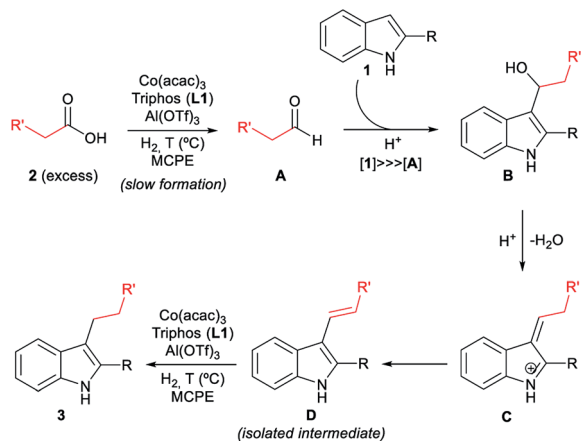


Fig. 5 Possible reaction mechanism for the [Co/L1/Al(OTf)₃]-catalysed reductive alkylation of indoles with carboxylic acids (simplified version). The extended version of the overall mechanism containing additional possible minor pathways and secondary transformations is depicted in Scheme S6 (see ESI[†]).

that can be also hydrogenated to the aldehyde, as well as a dehydrogenation mechanism from the formed alcohol. Scheme S6 (see ESI[†]) shows the extended version of the reaction mechanism containing additional possible minor pathways and secondary transformations involved in the overall process.

Conclusions

For the first time, a general reductive C–H alkylation of indoles using carboxylic acids as alkylating agents is presented. This cobalt-catalysed methodology allows functionalization of different indoles at C3 in a straightforward manner. Using the [Co(acac)₃/Triphos (L1)] system in combination with Al(OTf)₃ as acid co-catalyst a wide range of carboxylic acids can be employed as alkylating agents in the presence of molecular hydrogen. In addition to alkylations, selective alkenylations of some substrates have been successfully performed. Control experiments revealed that the major reaction pathway involves the *in situ* formation of the corresponding aldehyde from the hydrogenation of the carboxylic acid, able to react with the indole. This novel protocol complements previously described reductive alkylations of indoles, mainly employing carbonyl compounds as alkylating agents. Advantageously, the use of carboxylic acids enlarges the potential molecular diversity introduced in the indole scaffold, due to the availability and stability of this class of compounds. Furthermore, the use of a catalyst based on a non-precious metal increases the interest of this transformation.

Experimental details

General experimental procedure for the reductive C–H alkylation of 2-methyl-1H-indole (1a) with acetic acid (2a)

A 8 mL glass vial containing a stirring bar was sequentially charged with 2-methyl-1H-indole **1a** (67.0 mg, 0.5 mmol),

Co(acac)₃ (3.6 mg, 0.01 mmol, 2 mol%), Triphos **L1** (12.5 mg, 0.02 mmol, 4 mol%, 2 eq. to Co), Al(OTf)₃ (11.9 mg, 0.025 mmol, 5 mol%, 2.5 eq. to Co), *n*-hexadecane (50.0 mg) as an internal standard, MCPE (2.0 mL) as solvent and acetic acid **2a** (50.3 μL, 0.875 mmol, 1.75 eq.). Afterwards, the reaction vial was capped with a septum equipped with a syringe and set in the alloy plate, which was then placed into a 300 mL autoclave. Once sealed, the autoclave was purged three times with 30 bar of hydrogen, then pressurized to 30 bar and placed into an aluminium block, which was preheated at 160 °C. After 18 h, the autoclave was cooled in an ice bath, and the remaining gas was carefully released. Finally, the reaction mixture was diluted with ethyl acetate and analysed by GC.

General experimental procedure for the reductive C–H alkylation of indoles with carboxylic acids

A 8 mL glass vial containing a stirring bar was sequentially charged with the indole substrate (0.5 mmol), Co(acac)₃ (2–6 mol%), Triphos **L1** (4–12 mol%, 2 eq. to Co), Al(OTf)₃ (5–15 mol%, 2.5 eq. to Co), MCPE (2.0 mL) as solvent and the carboxylic acid (0.875–1.75 mmol, 1.75–3.5 eq.). Afterwards, the reaction vial was capped with a septum equipped with a syringe and set in the alloy plate, which was then placed into a 300 mL autoclave. Once sealed, the autoclave was purged three times with 30–60 bar of hydrogen, then pressurized to 30 bar and placed into an aluminium block, which was preheated at 120–160 °C. After 18–48 h, the autoclave was cooled in an ice bath, and the remaining gas was carefully released. Finally, the reaction mixture was diluted with ethyl acetate and purified by silica gel column chromatography (*n*-heptane/ethyl acetate mixtures) obtaining the desired C3-substituted indole derivatives.

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Notes and references

- (a) G. W. Gribble, in *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees, E. F. V. Scriven and C. W. Bird, Pergamon Press, Oxford (UK), 1996, vol. 2, p. 207; (b) R. J. Sundberg, in *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees, E. F. V. Scriven and C. W. Bird, Pergamon Press, Oxford (UK), 1996, vol. 2, p. 119; (c) M. Somei and F. Yamada, *Nat. Prod. Rep.*, 2005, **22**, 73–103; (d) S. R. Walker, E. J. Carter, B. C. Huff and J. C. Morris, *Chem. Rev.*, 2009, **109**, 3080–3098; (e) R. J. Melander, M. J. Minvielle and C. Melander, *Tetrahedron*, 2014, **70**, 6363–6372; (f) N. Netz and T. Opatz, *Mar. Drugs*, 2015, **13**, 4814–4914; (g) E. Stempel and T. Gaich, *Acc. Chem. Res.*, 2016, **49**, 2390–2402.
- (a) J. Poojitha, K. N. Mounika, G. N. Raju and R. R. Nadendla, *World J. Pharm. Res.*, 2015, **4**, 656–666; (b) M.-Z. Zhang, Q. Chen and G.-F. Yang, *Eur. J. Med. Chem.*, 2015, **89**, 421–



- 441; (c) T. Saini, S. Kumar and B. Narasimhan, *Cent. Nerv. Syst. Agents Med. Chem.*, 2016, **16**, 19–28; (d) T. V. Sravanthi and S. L. Manju, *Eur. J. Pharm. Sci.*, 2016, **91**, 1–10; (e) D. Sunil and P. R. Kamath, *Curr. Top. Med. Chem.*, 2017, **17**, 959–985.
- 3 D. F. Taber and P. K. Tirunahari, *Tetrahedron*, 2011, **67**, 7195–7210.
- 4 (a) E. Fischer and F. Jourdan, *Ber. Dtsch. Chem. Ges.*, 1883, **16**, 2241–2245; (b) B. Robinson, *Chem. Rev.*, 1963, **63**, 373–401.
- 5 For some reviews dealing with the synthesis of indoles by cyclization protocols:(a) G. W. Gribble, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1045–1075; (b) G. Zeni and R. C. Larock, *Chem. Rev.*, 2004, **104**, 2285–2310; (c) G. R. Humphrey and J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875–2911; (d) S. Cacchi, G. Fabrizi and A. Goggiamani, *Org. Biomol. Chem.*, 2011, **9**, 641–652; (e) S. A. Patil, R. Patil and D. D. Miller, *Curr. Med. Chem.*, 2011, **18**, 615–637; (f) M. Platon, R. Amardeil, L. Djakovitch and J.-C. Hierso, *Chem. Soc. Rev.*, 2012, **41**, 3929–3968; (g) M. Inman and C. J. Moody, *Chem. Sci.*, 2013, **4**, 29–41; (h) N. Yoshikai and Y. Wei, *Asian J. Org. Chem.*, 2013, **2**, 466–478; (i) T. Guo, F. Huang, L. Yu and Z. Yu, *Tetrahedron Lett.*, 2015, **56**, 296–302; (j) L. L. Anderson, M. A. Kroc, T. W. Reidl and J. Son, *J. Org. Chem.*, 2016, **81**, 9521–9529; (k) G. Chelucci, *Coord. Chem. Rev.*, 2017, **331**, 37–53; (l) R. B. Susick, L. A. Morrill, E. Picazo and N. K. Garg, *Synlett*, 2017, **28**, 1–11; (m) J. J. Song, J. T. Reeves, D. R. Fandrick, Z. Tan, N. K. Yee and C. H. Senanayake, *ARKIVOC*, 2010, 390–449; (n) S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2011, **111**, PR215–PR283.
- 6 For some reviews dealing with the direct functionalization of indole:(a) M. Bandini and A. Eichholzer, *Angew. Chem., Int. Ed.*, 2009, **48**, 9608–9644; (b) G. Bartoli, G. Bencivenni and R. Dalpozzo, *Chem. Soc. Rev.*, 2010, **39**, 4449–4465; (c) C. C. J. Loh and D. Enders, *Angew. Chem., Int. Ed.*, 2012, **51**, 46–48; (d) R. Dalpozzo, *Chem. Soc. Rev.*, 2015, **44**, 742–778.
- 7 For some reviews dealing with functionalization of indoles by CH activation:(a) G. Brogini, E. M. Beccalli, A. Fasana and S. Gazzola, *Beilstein J. Org. Chem.*, 2012, **8**, 1730–1746; (b) L. Ackermann, *J. Org. Chem.*, 2014, **79**, 8948–8954; (c) A. H. Sandtorv, *Adv. Synth. Catal.*, 2015, **357**, 2403–2435; (d) N. Della Ca, M. Fontana, E. Motti and M. Catellani, *Acc. Chem. Res.*, 2016, **49**, 1389–1400.
- 8 For selected examples of allylic alkylation of indole C3 position:(a) M. Bandini, A. Melloni and A. Umani-Ronchi, *Org. Lett.*, 2004, **6**, 3199–3202; (b) B. M. Trost and J. Quancard, *J. Am. Chem. Soc.*, 2006, **128**, 6314–6315; (c) Q.-F. Wu, H. He, W.-B. Liu and S.-L. You, *J. Am. Chem. Soc.*, 2010, **132**, 11418–11419; (d) L. Du, P. Cao, J. Xing, Y. Lou, L. Jiang, L. Li and J. Liao, *Angew. Chem., Int. Ed.*, 2013, **52**, 4207–4211; (e) Y. Liu and H. Du, *Org. Lett.*, 2013, **15**, 740–743; (f) Q.-L. Xu, L.-X. Dai and S.-L. You, *Chem. Sci.*, 2013, **4**, 97–102; (g) X. Zhang, W.-B. Liu, H.-F. Tu and S.-L. You, *Chem. Sci.*, 2015, **6**, 4525–4529; (h) R.-D. Gao, Q.-L. Xu, L.-X. Dai and S.-L. You, *Org. Biomol. Chem.*, 2016, **14**, 8044–8046.
- 9 For selected examples of C3 alkylation of indole using Baylis–Hillman reaction:(a) J. S. Yadav, B. V. S. Reddy, A. K. Basak, A. V. Narsaiah, A. Prabhakar and B. Jagadeesh, *Tetrahedron Lett.*, 2005, **46**, 639–641; (b) Z. Shafiq, L. Liu, Z. Liu, D. Wang and Y.-J. Chen, *Org. Lett.*, 2007, **9**, 2525–2528; (c) C. Ramesh, V. Kavala, B. R. Raju, C.-W. Kuo and C.-F. Yao, *Tetrahedron Lett.*, 2009, **50**, 4037–4041; (d) C. Ramesh, P.-M. Lei, D. Janreddy, V. Kavala, C.-W. Kuo and C.-F. Yao, *J. Org. Chem.*, 2012, **77**, 8451–8464; (e) P. Goswami, A. J. Borah and P. Phukan, *J. Org. Chem.*, 2015, **80**, 438–446.
- 10 For selected examples of C3 alkylation of indole by Friedel–Crafts reaction:(a) J. F. Austin and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2002, **124**, 1172–1173; (b) C. Liu, X. Han, X. Wang and R. A. Widenhoefer, *J. Am. Chem. Soc.*, 2004, **126**, 3700–3701; (c) H. D. King, Z. Meng, D. Denhart, R. Mattson, R. Kimura, D. Wu, Q. Gao and J. E. Macor, *Org. Lett.*, 2005, **7**, 3437–3440; (d) J. Itoh, K. Fuchibe and T. Akiyama, *Angew. Chem., Int. Ed.*, 2008, **47**, 4016–4018; (e) G. Blay, I. Fernandez, A. Monleon, M. C. Munoz, J. R. Pedro and C. Vila, *Adv. Synth. Catal.*, 2009, **351**, 2433–2440; (f) M. Veguillas, M. Ribagorda and M. C. Carreno, *Org. Lett.*, 2011, **13**, 656–659; (g) X. Liang, S. Li and W. Su, *Tetrahedron Lett.*, 2012, **53**, 289–291; (h) F. de Nanteuil, J. Loup and J. Waser, *Org. Lett.*, 2013, **15**, 3738–3741; (i) H.-M. Ko, K. K.-Y. Kung, J.-F. Cui and M.-K. Wong, *Chem. Commun.*, 2013, **49**, 8869–8871; (j) C. García-García, L. Ortiz-Rojano, S. Álvarez, R. Álvarez, M. Ribagorda and M. C. Carreño, *Org. Lett.*, 2016, **18**, 2224–2227; (k) X.-W. Wang, Y.-Z. Hua and M.-C. Wang, *J. Org. Chem.*, 2016, **81**, 9227–9234; (l) P. C. Rao and S. Mandal, *ChemCatChem*, 2017, **9**, 1172–1176.
- 11 Reductive alkylation employing alcohols and alkynes has also been described:(a) T. Tsuchimoto and M. Kanbara, *Org. Lett.*, 2011, **13**, 912–915; (b) X. Han and J. Wu, *Angew. Chem., Int. Ed.*, 2013, **52**, 4637–4640.
- 12 (a) J. E. Appleton, K. N. Dack, A. D. Green and J. Steele, *Tetrahedron Lett.*, 1993, **34**, 1529–1532; (b) A. Mahadevan, H. Sard, M. Gonzalez and J. C. McKew, *Tetrahedron Lett.*, 2003, **44**, 4589–4591; (c) J. A. Campbell, V. Bordunov, C. A. Broka, J. Dankwardt, R. T. Hendricks, J. M. Kress, K. A. M. Walker and J.-H. Wang, *Tetrahedron Lett.*, 2004, **45**, 3793–3796; (d) J. R. Rizzo, C. A. Alt and T. Y. Zhang, *Tetrahedron Lett.*, 2008, **49**, 6749–6751; (e) S. Chandrasekhar, S. Khatun, G. Rajesh and C. Raji Reddy, *Tetrahedron Lett.*, 2009, **50**, 6693–6697; (f) N. D. Shashikumar, G. N. Krishnamurthy, S. R. Rao, K. K. Shridhara, H. S. B. Naik and K. Nagarajan, *Org. Process Res. Dev.*, 2010, **14**, 918–920; (g) S. Nomiyama, T. Hondo and T. Tsuchimoto, *Adv. Synth. Catal.*, 2016, **358**, 1136–1149.
- 13 (a) A. P. Gray, *J. Org. Chem.*, 1958, **23**, 1453–1454; (b) L.-L. Cao, D.-S. Wang, G.-F. Jiang and Y.-G. Zhou, *Tetrahedron Lett.*, 2011, **52**, 2837–2839; (c) Y. Duan, M.-W. Chen, Z.-S. Ye, D.-S. Wang, Q.-A. Chen and Y.-G. Zhou, *Chem.–Eur. J.*, 2011, **17**, 7193–7197.
- 14 (a) A. T. Gillmore, M. Badland, C. L. Crook, N. M. Castro, D. J. Critcher, S. J. Fussell, K. J. Jones, M. C. Jones, E. Kougioulos, J. S. Mathew, L. McMillan, J. E. Pearce,



- F. L. Rawlinson, A. E. Sherlock and R. Walton, *Org. Process Res. Dev.*, 2012, **16**, 1897–1904; (b) A. Taheri, B. Lai, C. Cheng and Y. Gu, *Green Chem.*, 2015, **17**, 812–816.
- 15 Y. Li, T. Yan, K. Junge and M. Beller, *Angew. Chem., Int. Ed.*, 2014, **53**, 10476–10480.
- 16 (a) F. M. A. Geilen, B. Engendahl, M. Hölscher, J. Klankermayer and W. Leitner, *J. Am. Chem. Soc.*, 2011, **133**, 14349–14358; (b) T. vom Stein, M. Meuresch, D. Limper, M. Schmitz, M. Hölscher, J. Coetzee, D. J. Cole-Hamilton, J. Klankermayer and W. Leitner, *J. Am. Chem. Soc.*, 2014, **136**, 13217–13225; (c) X. Cui, Y. Li, C. Topf, K. Junge and M. Beller, *Angew. Chem., Int. Ed.*, 2015, **54**, 10596–10599.
- 17 T. P. Brewster, A. J. M. Miller, D. M. Heinekey and K. I. Goldberg, *J. Am. Chem. Soc.*, 2013, **135**, 16022–16025.
- 18 R. M. Bullock, *Science*, 2013, **342**, 1054.
- 19 For examples involving homogeneous cobalt catalysed hydrogenation of alkenes, alkynes, carbonyl compounds, nitriles, carboxylic acid derivatives, CO₂ and *N*-heteroarenes:(a) C. Federsel, C. Ziebart, R. Jackstell, W. Baumann and M. Beller, *Chem.–Eur. J.*, 2012, **18**, 72–75; (b) S. Monfette, Z. R. Turner, S. P. Semproni and P. J. Chirik, *J. Am. Chem. Soc.*, 2012, **134**, 4561–4564; (c) G. Zhang, B. L. Scott and S. K. Hanson, *Angew. Chem., Int. Ed.*, 2012, **51**, 12102–12106; (d) M. Amezcua-Valencia and A. Cabrera, *J. Mol. Catal. A: Chem.*, 2013, **366**, 17–21; (e) M. R. Friedfeld, M. Shevlin, J. M. Hoyt, S. W. Krska, M. T. Tudge and P. J. Chirik, *Science*, 2013, **342**, 1076–1080; (f) D. Gärtner, A. Welther, B. R. Rad, R. Wolf and A. Jacobi von Wangelin, *Angew. Chem., Int. Ed.*, 2014, **53**, 3722–3726; (g) T.-P. Lin and J. C. Peters, *J. Am. Chem. Soc.*, 2014, **136**, 13672–13683; (h) A. Mukherjee, D. Srimani, S. Chakraborty, Y. Ben-David and D. Milstein, *J. Am. Chem. Soc.*, 2015, **137**, 8888–8891; (i) S. Rösler, J. Obenauf and R. Kempe, *J. Am. Chem. Soc.*, 2015, **137**, 7998–8001; (j) D. Srimani, A. Mukherjee, A. F. G. Goldberg, G. Leitner, Y. Diskin-Posner, L. J. W. Shimon, Y. Ben David and D. Milstein, *Angew. Chem., Int. Ed.*, 2015, **54**, 12357–12360; (k) R. Xu, S. Chakraborty, H. Yuan and W. D. Jones, *ACS Catal.*, 2015, **5**, 6350–6354; (l) A. Z. Spentzos, C. L. Barnes and W. H. Bernskoetter, *Inorg. Chem.*, 2016, **55**, 8225–8233; (m) K. Tokmic and A. R. Fout, *J. Am. Chem. Soc.*, 2016, **138**, 13700–13705; (n) D. Zhang, E.-Z. Zhu, Z.-W. Lin, Z.-B. Wei, Y.-Y. Li and J.-X. Gao, *Asian J. Org. Chem.*, 2016, **5**, 1323–1326; (o) R. Adam, C. B. Bheeter, J. R. Cabrero-Antonino, K. Junge, R. Jackstell and M. Beller, *ChemSusChem*, 2017, **10**, 842–846; (p) R. Adam, J. R. Cabrero-Antonino, A. Spannenberg, K. Junge, R. Jackstell and M. Beller, *Angew. Chem., Int. Ed.*, 2017, **56**, 3216–3220; (q) J. Guo, X. Shen and Z. Lu, *Angew. Chem., Int. Ed.*, 2017, **56**, 615–618.
- 20 For reviews dealing with cobalt catalysed hydrogenation:(a) P. J. Chirik, *Acc. Chem. Res.*, 2015, **48**, 1687–1695; (b) J.-L. Renaud and S. Gaillard, *Synthesis*, 2016, **48**, 3659–3683.
- 21 T. J. Korstanje, J. Ivar van der Vlugt, C. J. Elsevier and B. de Bruin, *Science*, 2015, **350**, 298.
- 22 J. Schneidewind, R. Adam, W. Baumann, R. Jackstell and M. Beller, *Angew. Chem., Int. Ed.*, 2017, **56**, 1890–1893.
- 23 For examples of hydrogenation of carboxylic acids employing the [Ru/Triphos/acid additive] catalytic system:(a) A. A. Núñez Magro, G. R. Eastham and D. J. Cole-Hamilton, *Chem. Commun.*, 2007, 3154–3156; (b) D. L. Dodds, J. Coetzee, J. Klankermayer, S. Brosinski, W. Leitner and D. J. Cole-Hamilton, *Chem. Commun.*, 2012, **48**, 12249–12262; (c) K. Beydoun, T. vom Stein, J. Klankermayer and W. Leitner, *Angew. Chem., Int. Ed.*, 2013, **52**, 9554–9557; (d) J. Coetzee, D. L. Dodds, J. Klankermayer, S. Brosinski, W. Leitner, A. M. Z. Slawin and D. J. Cole-Hamilton, *Chem.–Eur. J.*, 2013, **19**, 11039–11050; (e) Y. Li, I. Sorribes, T. Yan, K. Junge and M. Beller, *Angew. Chem., Int. Ed.*, 2013, **52**, 12156–12160; (f) K. Beydoun, G. Ghattas, K. Thenert, J. Klankermayer and W. Leitner, *Angew. Chem., Int. Ed.*, 2014, **53**, 11010–11014; (g) S. Savourey, G. Lefevre, J.-C. Berthet and T. Cantat, *Chem. Commun.*, 2014, **50**, 14033–14036; (h) T. vom Stein, M. Meuresch, D. Limper, M. Schmitz, M. Hoelscher, J. Coetzee, D. J. Cole-Hamilton, J. Klankermayer and W. Leitner, *J. Am. Chem. Soc.*, 2014, **136**, 13217–13225; (i) X. Cui, Y. Li, C. Topf, K. Junge and M. Beller, *Angew. Chem., Int. Ed.*, 2015, **54**, 10596–10599; (j) E. J. Derrah, M. Hanauer, P. N. Plessow, M. Schelwies, M. K. da Silva and T. Schaub, *Organometallics*, 2015, **34**, 1872–1881; (k) Y. Li, C. Topf, X. Cui, K. Junge and M. Beller, *Angew. Chem., Int. Ed.*, 2015, **54**, 5196–5200; (l) I. Sorribes, J. R. Cabrero-Antonino, C. Vicent, K. Junge and M. Beller, *J. Am. Chem. Soc.*, 2015, **137**, 13580–13587; (m) S. Wesselbaum, V. Moha, M. Meuresch, S. Brosinski, K. M. Thenert, J. Kothe, T. v. Stein, U. Englert, M. Holscher, J. Klankermayer and W. Leitner, *Chem. Sci.*, 2015, **6**, 693–704; (n) R. Adam, J. R. Cabrero-Antonino, K. Junge, R. Jackstell and M. Beller, *Angew. Chem., Int. Ed.*, 2016, **55**, 11049–11053; (o) K. Beydoun, K. Thenert, E. S. Streng, S. Brosinski, W. Leitner and J. Klankermayer, *ChemCatChem*, 2016, **8**, 135–138; (p) J. R. Cabrero-Antonino, R. Adam, K. Junge and M. Beller, *Catal. Sci. Technol.*, 2016, **6**, 7956–7966; (q) J. R. Cabrero-Antonino, E. Alberico, K. Junge, H. Junge and M. Beller, *Chem. Sci.*, 2016, **7**, 3432–3442; (r) J. R. Cabrero-Antonino, I. Sorribes, K. Junge and M. Beller, *Angew. Chem., Int. Ed.*, 2016, **55**, 387–391; (s) M. L. Yuan, J. H. Xie and Q. L. Zhou, *ChemCatChem*, 2016, **8**, 3036–3040.
- 24 Alkenylation of indole C3 position has been reported using carbonyl compounds:(a) G. Fridkin, N. Boutard and W. D. Lubell, *J. Org. Chem.*, 2009, **74**, 5603–5606; (b) A. Taheri, C. Liu, B. Lai, C. Cheng, X. Pan and Y. Gu, *Green Chem.*, 2014, **16**, 3715–3719.
- 25 B. Capelle, A. L. Beauchamp, M. Dartiguenave, Y. Dartiguenave and H. F. Klein, *J. Am. Chem. Soc.*, 1982, **104**, 3891–3897.

