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Rh(I)-catalyzed decarbonylative direct C2-olefination of indoles with vinyl carboxylic acids†

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A general and efficient Rh(I)-catalyzed decarbonylative direct C2-olefination of indoles with vinyl carboxylic acids has been developed. The reaction exhibits excellent functional group tolerance, regioselectivity and stereoselectivity, giving a broad range of C2-alkenylated indoles in good to excellent yields.

Indoles are among the most prominent targets in synthetic chemistry because of their biological and pharmaceutical activities.[1] Efficient and economic synthesis of these useful compounds has benefited significantly from the recent substantial advancements of transition-metal catalyzed direct C–H activation/functionalization since no substrate preactivation is required.[2] In this context, the development of direct and regioselective C2 or C3-olefination of indoles with various olefins has attracted much attention,[3–5] but catalysis of C2-olefination remains challenging due to the electrophilic nature of the C2-position. In 2005, Gaunt *et al.* described the Pd-catalyzed oxidative Heck olefination of free (NH) indoles, and the C2/C3 regioselectivity could be controlled by varying the reaction medium and the oxidant.[4a] But low efficiency was observed in the case of C2-olefination. Brown,[4b] Carretero[4d,e] and others[4f–l] found that introducing a suitable *N*-protecting group could change the regioselectivity of C3 to C2 in the olefination of indoles. This strategy also worked well in hydroarylation of alkynes with indoles to give the C2-olefinated indoles.[5a–c] In addition, recent studies indicated that blocking the C3-position with a suitable group could facilitate the C2-olefination of indoles.[4c,5d,e] Despite these impressive advances, there is still much room for improvement, particularly in terms of substrate scope and catalytic efficiency.

Carboxylic acids and their derivatives have been highlighted as advantageous coupling reagents in transition-metal catalyzed decarboxylative or decarbonylative C–C formation reactions over the past decade.[6] In recent years considerable effort has been made to employ vinyl carboxylic acids and their derivatives as olefin sources in transition-metal catalyzed coupling reactions.[7,8] Recently the combination of decarbonylation or decarboxylation of acryloyl compounds with direct activation of C–H bonds has drawn the attention of chemists because of the atom-economical gain and improved reaction efficiency.[9] In particular, Yu and coworkers reported that cinnamoyl chlorides and cinnamic anhydrides could serve as effective vinyl sources in Rh-catalyzed decarbonylative direct olefination of 2-pyridylbenzenes to deliver the olefinated products in high yields.[9a–c] A major drawback of the chemistry was the necessity for prior preparation of acyl chlorides and anhydrides from the corresponding parent carboxylic acids. Obviously, the use of more readily available and inexpensive vinyl carboxylic acids as coupling partners would be more attractive and atom-economic. Along these lines, herein we would like to disclose that the catalytic system consisting of $[Rh(COD)_2]OTf$ and $(t\text{BuCO})_2O$ could efficiently catalyze the decarbonylative direct C2-olefination of *N*-(2-pyrimidyl)indoles with vinyl carboxylic acids under oxidant-free conditions to exclusively produce C2-olefinated indoles, which are important synthetic intermediates for the construction of biologically active natural products and pharmaceuticals.[10]

In consideration of the promoting effect of the *N*-directing group in direct C2-alkenylation of indoles,[4] we started our study by examining the coupling reaction of various *N*-protected indoles with cinnamic acid (**2a**) using $[Rh(CO)_2Cl]_2$ (2.0 mol%) as the catalyst and $(t\text{BuCO})_2O$ as the activator in toluene upon heating at 140 °C (see Table S1, ESI†). To our delight, the reaction of *N*-(2-pyrimidyl)-indole (**1a**) with **2a** exclusively afforded the C2-olefinated product **3aa** in 95% yield (entry 1, Table S1, ESI†). Olefination of *N*-(2-pyridyl)-indole (**1b**) gave the expected product **3ba** with a lower yield of 40% (entry 2, Table S1, ESI†). No reaction was observed when Me, benzyl, Ac, Tos, Boc, Piv, PhCO or Me_2NCO was employed. Using the easily installed and removed *N*-(2-pyrimidyl) directing group,[4k,5a] further screening indicated that $[Rh(COD)_2]OTf$ exhibited the best efficiency as the reaction time could be shortened to 1 h with an excellent yield of 97% (entry 24, Table S1, ESI†). Different solvents were investigated, and toluene turned out to be the best choice

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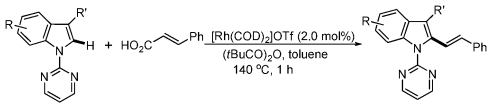
Table 1 Scope of indole derivatives[a]



1 2a 3

Entry	1		Yield[b] (%)
1	R = R′ = H	**1a**	97 (**3aa**)
2	R = 4-Me, R′ = H	**1c**	95 (**3ca**)
3	R = 5-Me, R′ = H	**1d**	96 (**3da**)
4	R = 6-Me, R′ = H	**1e**	93 (**3ea**)
5	R = 7-Me, R′ = H	**1f**	94 (**3fa**)
6	R = 5-OMe, R′ = H	**1g**	91 (**3ga**)
7	R = 5-Cl, R′ = H	**1h**	81 (**3ha**)
8	R = 5-Br, R′ = H	**1i**	85 (**3ia**)
9	R = 5-F, R′ = H	**1j**	83 (**3ja**)
10	R = 5-NO_2, R′ = H	**1k**	85 (**3ka**)
11	R = 5-CO_2Me, R′ = H	**1l**	90 (**3la**)
12[c]	R = H, R′ = Me	**1m**	74 (**3ma**)
13[c]	R = H, R′ = Ph	**1n**	89 (**3na**)
14[c]	R = H, R′ = CN	**1o**	67 (**3oa**)

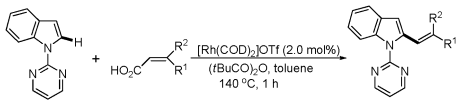
[a] Conditions: **1** (0.5 mmol), **2a** (0.5 mmol), [Rh(COD)$_2$]OTf (2 mol%), (tBuCO)$_2$O (0.5 mmol) in toluene (3.0 mL) at 140 °C for 1 h unless otherwise noted. [b] Isolated yield. [c] 2 h.

(entries 24–30, Table S1, ESI†). Replacing (tBuCO)$_2$O with other activators proved to be less successful (entries 31–35, Table S1, ESI†). Thus the optimal reaction conditions were finally determined as follows: [Rh(COD)$_2$]OTf (2.0 mol%) and (tBuCO)$_2$O (1.0 equiv.) in toluene at 140 °C. It should be stressed that the *E*-isomer was exclusively obtained for **3aa**, and in all cases no C3- or C7-olefination was detected.

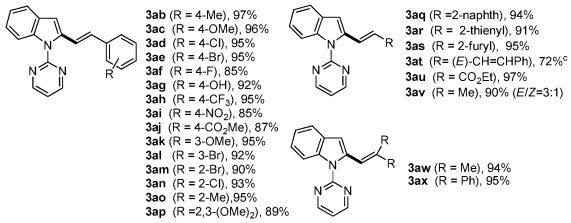
With the optimized reaction conditions in hand, the scope of indoles was explored. As shown in Table 1, a number of functional groups on the benzene ring of the indole moiety were well tolerated regardless of their electronic nature and position, exclusively delivering the C2-olefinated products in good to excellent yields (Table 1, entries 1–11). Notably, the sensitive Br and Cl substituents remained intact over the course of reaction (Table 1, entries 7 and 8), providing the opportunity for further elaboration. The C3-substituted indoles (**1m–o**) also successfully engaged in the coupling reaction to give the expected products in good yields albeit longer reaction times were required (Table 1, entries 12–14). It is worth mentioning that only the *E*-configuration products were obtained in all cases studied.

To further demonstrate the power of our catalytic system, the reaction was extended to other β-substituted acrylic acids (Table 2). Cinnamic acids bearing a variety of substituents on the aromatic rings were observed to afford C2-olefinated indoles (**3ab–3ap**) in good to excellent yields with exclusive *E* stereochemistry, and a range of functional groups were compatible with the reaction conditions. The aryl-substituted acrylic acids **2q–2s** were suitable coupling partners, providing the *E*-configuration products (**3aq–3as**) in excellent yields. (2*E*,4*E*)-5-phenylpenta-2,4-dienoic acid (**2t**) and ethyl hydrogen fumarate (**2u**) was reactive, and gave the products (**3at** and **3au**) in high yields with excellent *E* stereoselectivity. The reaction of crotonic acid (**2v**) with **1a** proceeded readily, producing **3av** as an *E*/*Z* diastereoisomer of 3 : 1. In addition, β,β-disubstituted acrylic acids reacted well to furnish **3aw** and **3ax** in 94% and 95% yields, respectively.

Table 2 Alkenylation of indole **1a** with β-substituted acrylic acids[a,b]

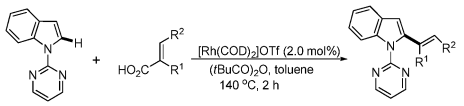


1a 2 3

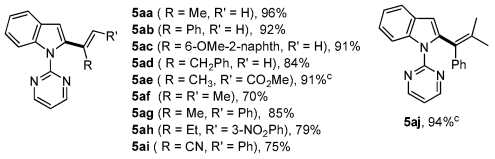


[a] Conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), [Rh(COD)$_2$]OTf (2 mol%), (tBuCO)$_2$O (0.5 mmol) in toluene (3.0 mL) at 140 °C for 1 h unless otherwise noted. [b] Isolated yield. [c] [Rh(COD)$_2$]OTf (4 mol%), 24 h.

Table 3 Alkenylation of indole **1a** with α-substituted acrylic acids[a,b]



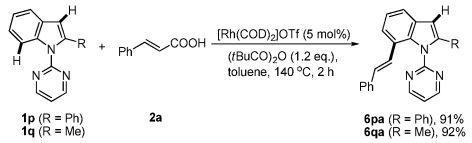
1a 4 5



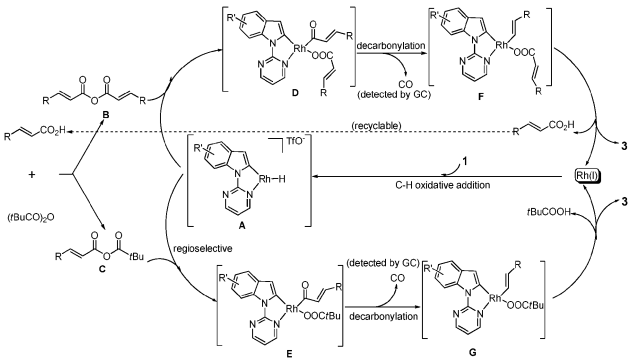
[a] Conditions: **1a** (0.5 mmol), **4** (0.5 mmol), [Rh(COD)$_2$]OTf (2 mol%), (tBuCO)$_2$O (0.5 mmol) in toluene (3.0 mL) at 140 °C for 2 h unless otherwise noted. [b] Isolated yield. [c] [Rh(COD)$_2$]OTf (4 mol%), 24 h.

We next moved our attention to α-substituted acrylic acids, and the results are summarized in Table 3. It was found that the acrylic acids **4a–d** could undergo successful coupling reactions with **1a** to give the desired products (**5aa–5ad**) in high yields. Interestingly, the coupling reaction of monomethyl itaconate (**4e**) led to the formation of a double-bond-isomerised *E*-configuration product **5ae**. The α,β-disubstituted acrylic acids also participated in the coupling effectively to afford the C2-olefinated products (**5af–5ai**) with exclusive *E* stereochemistry. Of particular note is that the challenging tetra-substituted olefin **4j** smoothly provided **5aj** in a yield of 94% albeit requiring a longer reaction time.

As shown in Scheme 1, the current catalytic system was also effective for olefination of C2-substituted indoles (**1p** and **1q**) to exclusively give the C7-olefinated products (**6pa** and **6qa**) in excellent yields, and no C3-olefination was detected. It is worth noting that either C7-alkenylated or C2-alkenylated products could be readily deprotected. For example, treating **3aa**, **5ab** or **6pa** with NaOEt in DMSO at 100 °C could furnish the free indoles **7–9** in high yields (see ESI†).



Scheme 1 Direct C7-olefination of indoles.



Scheme 2 Proposed mechanism for the direct C–H olefination.

The mechanism of this reaction was then studied. Based on the previous reports,[11] it appears that the current reaction may proceed *via* the initial formation of acid anhydrides. The NMR experiments revealed that stirring equimolar amounts of $(t\text{BuCO})_2\text{O}$ and **2a** in toluene at 140 °C for 0.5 h resulted in a mixture of cinnamic pivalic anhydride (**10**), cinnamic anhydride (**11**) and $(t\text{BuCO})_2\text{O}$ in a ratio of 1 : 0.38 : 0.6. The separately synthesized compounds **10** and **11** were found to react smoothly with **1a** to give the product **3aa** in high yields (see ESI†), suggesting that the *in situ* generated anhydrides are indeed involved in the olefination process. The GC-TDC analysis of the gas phase of the reaction mixture confirmed the generation of CO during the reaction, clearly indicating the involvement of a decarbonylation step in this transformation. Therefore, a plausible mechanism is suggested (Scheme 2). First, the reaction of indole **1** with the Rh(I) species produced the cyclorhodium intermediate **A** by the pyrimidyl nitrogen assisted C–H oxidative addition. The anhydrides **B** and **C** arising from the reaction of $\text{RCH}{=}\text{CHCO}_2\text{H}$ and $(t\text{BuCO})_2\text{O}$ reacted with **A** to selectively give the intermediates **D** and **E**,[11] which yielded the intermediates **F** and **G** through decarbonylation. Reductive elimination furnished the desired product **3** and the Rh(I) was regenerated to complete the catalytic cycle.

In conclusion, we have demonstrated an efficient catalytic system for decarbonylative direct C2-olefination of indoles with readily available vinyl carboxylic acids. This catalytic system afforded a range of structurally versatile C2-olefinated indoles in high yields with excellent regioselectivity and stereoselectivity under oxidant-free conditions. This methodology provides a valuable alternative complementary to the existing C2-olefination of indoles known in the literature.

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