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C–C Activation

Divergent Coupling of Benzocyclobutenones with Indoles via C–H and C–C Activations

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Abstract: *Highly selective divergent coupling reactions of benzocyclobutenones and indoles, in which the chemoselectivity is controlled by catalysts, are reported herein. The substrates undergo C2(indole)–C8(benzocyclobutenone) coupling to produce benzylated indoles and benzo[b]carbazoles in the Ni- and Ru-catalyzed reactions. A completely different selectivity pattern C2(indole)–C2(benzocyclobutenone) coupling to form arylated indoles is observed in the Rh-catalyzed reaction. Preliminary mechanistic studies suggest C–H and C–C activations in the reaction pathway. Synthetic utility of this protocol is demonstrated by the selective synthesis of three different types of carbazoles from the representative products.*

Metal-catalyzed C–C bond activation has recently received considerable attention as it provides unique opportunities to develop effective and atom-economical strategies for constructing interesting molecular skeletons.[1] Molecules with highly strained rings, such as benzocyclobutenones are well-recognized entities for C–C bond activation.[2] Although ring-opening, ring expansion and cycloadditions of benzocyclobutenone have been reported,[3] there has been no report on combined C–H and C–C bond activations in the presence of transition metal catalysts using benzocyclobutenone as the coupling partner.

This prospect led us to consider benzocyclobutenone as a substrate for the intermolecular coupling through C–H and C–C bond activations. In contrast to the established metal-catalyzed C–H, C–O, and C–N bond activations, the metal insertion into a C–C bond via oxidative addition forms two reactive M–C bonds. Controlling the selectivity of the two M–C bonds is a primary challenge in the development of coupling reactions via C–C bond activation (Figure 1 A). Figure 1 B shows that C–H activation leads to intermediate **A**, which is capable of undergoing transformation via two distinct pathways for the subsequent C–C activation in benzocyclobutenone **1**. Path A leads to the formation intermediate **B** which undergoes reductive elimination to form C1′(Ar^1)-C8(benzocyclobutenone) coupling products. Path B leads to the formation of C1′(Ar^1)-C1(benzocyclobutenone) or C1′(Ar^1)-C2(benzocyclobutenone) coupling products through intermediate **C**. This scenario highlights an inherent challenge in C–C activation chemistry-controlling the selectivity when both sides of the C–C bond to be cleaved are susceptible to reaction.[4] It is also well established that acyl metal complexes can undergo reversible CO de-insertion reactions. Therefore, the competition between decarbonylation and no-decarbonylation is another challenge for developing this process.[5]

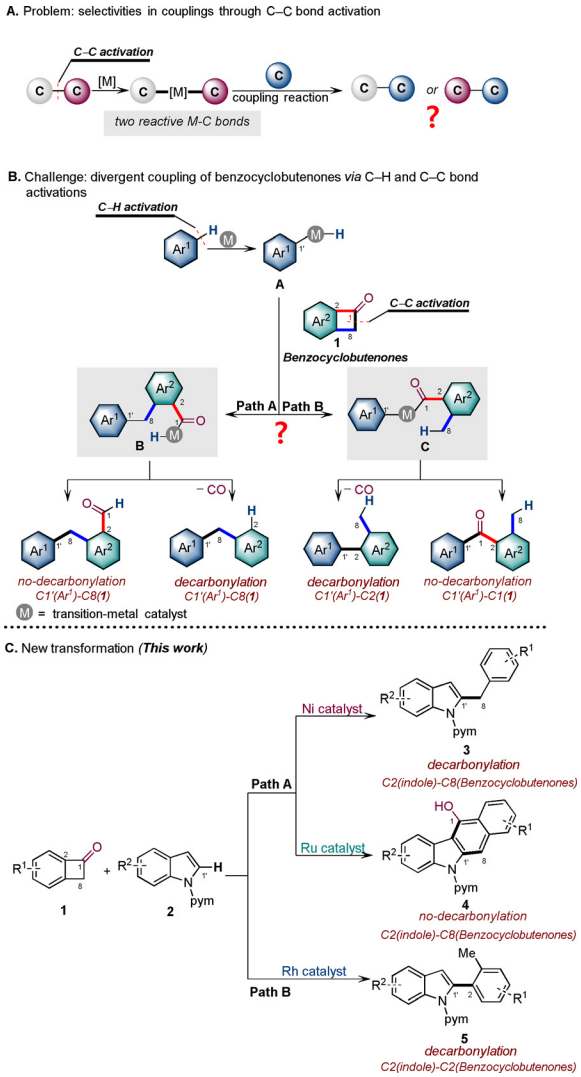

Figure 1. Divergent coupling of benzocyclobutenone.

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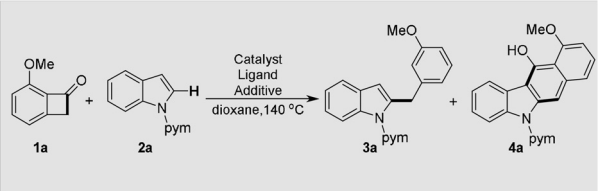
Developing tunable reactions that allow to achieve the desirable chemoselectivity under controlled experimental conditions is one of the ultimate goals in organic synthesis. Among the different strategies in this field, catalyst-controlled methods have been found to be effective for achieving this goal.[6] Therefore, we expect that the intricate selectivity in this divergent system can be tuned by a careful choice of the metal catalyst. If successful, these reactions might not only be novel examples of intermolecular C–H/C–C bond coupling, but also be an important additional reaction for the transformation of benzocyclobutenone, thus enabling benzocyclobutenone to act as a versatile synthon for coupling reactions. Herein, we report the selective coupling of benzocyclobutenones and indoles by switching the coupling mode using different metal catalysts (Figure 1 C). In particular, the three types of compounds synthesized, namely, benzylated indoles,[7] benzo[*b*]carbazoles,[8] and arylated indoles,[9] are known to exhibit biological activities (Figure 2).

Our initial investigation focused on optimizing the reaction conditions for the coupling of **1a** with *N*-(2-pyrimidyl)indole **2a**. Decarbonylative coupling in the presence of $Ni(cod)_2$ and PCy_3 in 1,4-dioxane, gave benzylated indole **3a** in 68% yield (Table 1, entry 1), as confirmed by X-ray crystallography (**3k**). Formation of **3a** suggested the existence of intermediate **B** (Figure 1) and the feasibility of Path A. This excellent selectivity encouraged us to optimize the conditions further.[10] A series of phosphine ligands were examined (Table 1, entries 2–4). To our delight, desired product **3a** was obtained with excellent selectivity with all the ligands; dppp was found to be the most efficient ligand (Table 1, entry 3). Screening of various solvents suggested that 1,4-dioxane was better than the other solvents (Table 1, entries 5–6).

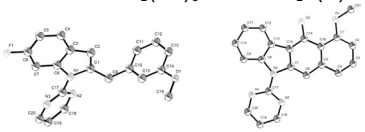
When the Ni catalyst was replaced with $Ru_3(CO)_{12}$, benzo[*b*]carbazole **4a** was formed. The molecular structure of this compound suggested that it is formed through Path A (Figure 1); it is also consistent with C1-C8 bond cleavage of benzocyclobutenone. The selectivity of **4a** was further confirmed by single-crystal X-ray analysis. Since this unexpected reactivity provided a new synthetic route to benzo[*b*]carbazole, we screened various readily available ligands to improve the yield of **4a** (Table 1, entries 8–11). Use of $Ph_2P(O)H$ gave even better results.[11] In addition, $ZnCl_2$ was compatible with this reaction, and a high yield was obtained (Table 1, entry 12). It was interesting to find that cobalt complexes, such as $Co_2(CO)_8$, also afforded the desired product **4a**, albeit in a low yield (entry 13).

With the optimized conditions for the synthesis of **3a** and **4a** in hand, other metal salts were screened in an attempt to obtain the products through Path B. However, no reactivity was observed using Ag, Cu or Pd salts.[10] To our delight, we found that Rh-catalysts could switch the selectivity between the two coupling pathways. $Rh(PPh_3)_3Cl$ and dppb was found to be the best (Table 2, entry 1). Next, we screened various readily available phosphine ligands to improve the efficiency of **5a** formation, and dppb still proved to the best (Table 2, entries 2–4). Addition of AgTFA further improved the yield of **5a** (Table 2, entries 5–7).[12] Further optimization revealed that the temperature has an obvious influence on the yield, but no impact on the selectivity, as the same with the observation in Ni and Ru catalyzed conditions.[10]

Table 1: Optimization of C2(indole)–C8(benzocyclobutenone) coupling[a]



Entry	Catalyst	Ligand	Yield[b] [%] 3a	4a
1	$Ni(cod)_2$	PCy_3	68	<5
2	$Ni(cod)_2$	PPh_3	72	–
3	$Ni(cod)_2$	dppp	80	–
4	$Ni(cod)_2$	dppb	67	<5
5[c]	$Ni(cod)_2$	dppp	72	–
6[d]	$Ni(cod)_2$	dppp	30	<5
7	$Ru_3(CO)_{12}$	PPh_3	–	32
8	$Ru_3(CO)_{12}$	dppp	–	–
9	$Ru_3(CO)_{12}$	$Ph_2P(O)H$	–	54
10	$Ru_3(CO)_{12}$	$Me_2P(O)H$	–	–
11	$Ru_3(CO)_{12}$	$(2\text{-naphyl})_2P(O)H$	–	48
12[e]	$Ru_3(CO)_{12}$	$Ph_2P(O)H$	–	78
13	$Co_2(CO)_8$	$Ph_2P(O)H$	–	12



X ray structure of **3k** X ray structure of **4a**

[a] Conditions: With [Ni], **1a** (0.2 mmol), **2a** (0.1 mmol), $Ni(cod)_2$ (0.01 mmol), ligand (0.02 mmol) in dioxane at 140 °C. With [Ru], **1a** (0.2 mmol), **2a** (0.1 mmol), $Ru_3(CO)_{12}$ (0.003 mmol), ligand (0.006 mmol) in dioxane at 140 °C. [b] Yield of isolated products. [c] Toluene was used as solvent. [d] PhCl was used as solvent. [e] $ZnCl_2$ (0.02 mmol) was added.

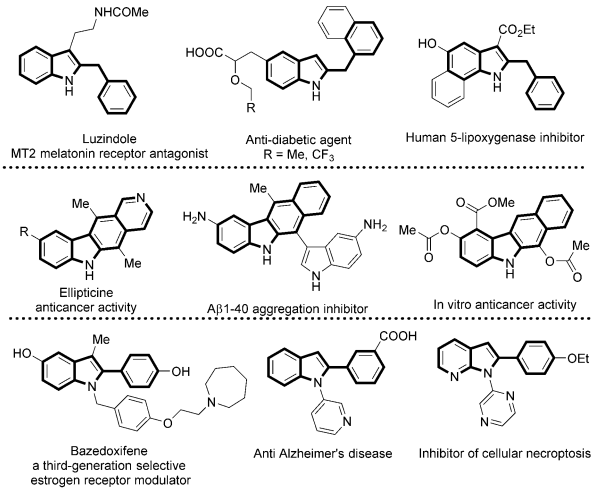
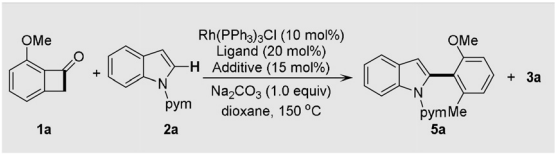


Figure 2. Biologically active benzylated indoles, benzo[*b*]carbazoles and arylated indoles.

Table 2: Optimization of C2(indole)–C2(benzocyclobutenone) coupling.[a]



Entry	Ligand	Additive	Yield[b] [%]	
			5a	**3a**
1	dppb	–	54	–
2	dppp	–	<5	–
3	dppf	–	27	–
4	dppe	–	<5	–
5	dppb	AgTFA	85	–
6	dppb	$AgSbF_6$	34	–
7	dppb	$AgPF_6$	50	8

[a] Conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), Na_2CO_3 (0.1 mmol), $Rh(PPh_3)_3Cl$ (0.01 mmol), ligand (0.02 mmol), additive (0.015 mmol) in dioxane at 150°C. [b] Yield of isolated products.

Next, the substrate scope of Ni catalysis was examined. Table 3 shows that reactants with electron donating and electron withdrawing substituents at the 3-, 4-, 5-, and 6-positions of indole were compatible (**3b**–**3k**) in this reaction. Although Ni catalysts facilitate the decarbonylation of aldehydes and esters,[13] under our conditions, aldehydes (**3c** and **3h**) and esters (**3i**, **3l**, **3m** and **3n**) did not compete with the decarbonylation. Various benzocyclobutenone substrates with different steric properties gave good to moderate yields (**3l**–**3o**). Notably, no benzo[*b*]carbazoles **4** and arylated indoles **5** were observed in all cases.

Substrate scope of the Ru-catalyzed coupling is summarized in Table 3. A unique selectivity was also observed under Ru-catalyzed conditions, giving benzo[*b*]carbazoles **4** as the only product. Substrates bearing various groups at 4-, 5-, and 6-positions were well tolerated and gave the corresponding benzo[*b*]carbazoles in good to moderate yields (**4b**–**4h**), indicating a broad substrate scope. Benzocyclobutenone bearing various substituents were also examined; the electronic nature and position of the substituents seemed to have no obvious influence on this reaction (**4i**–**4k**). The reaction could also be extended to a pyrrole substrate, and **4l** was generated as the sole product.

Scope of the Rh-catalyzed synthesis was also evaluated. Recently, C–H arylation has received significant attention as an effective synthetic route to arylated indoles.[14,15] However, there are very few methods for the synthesis of di-*ortho*, *ortho"* substituted arylated indoles by C–H arylation. Table 3 shows that the optimized conditions can be applied to the synthesis of a range of sterically hindered arylated indoles. The electronic nature and position of the substituents on indole did not have any remarkable effect on the efficiency of the reaction (**5a**–**5i**). Common functional groups, such as ether (**5c**), fluoride (**5d**), chloride (**5e**), cyanide (**5f**), and ester (**5g**), remained intact under the reaction conditions, highlighting the versatility of the transformation. The substrate derived from pyrrole was also compatible (**5n**). Compared to the unique selectivity of Ni- and Ru-catalyzed conditions, hindered benzocyclobutenone gave the product **5k** with small amount of benzylated indole in 8% yield.

To gain insights into the reaction mechanism, we synthesized deuterated substrate *d*-**2a** and subjected it to the standard conditions (Scheme 1A). Initially, substrate *d*-**2a** was reacted under the standard conditions for Ni catalysis, leading to deuterium incorporation on the phenyl group of *d*-**3a**. On the other hand, complete deuterium transfer from the C2-position of indole to the methyl group of *d*-**5a** was observed in the Rh-catalyzed reaction. However, no deuterium incorporation was detected in the product formed in the Ru-catalyzed reaction. These results are consistent with our proposed reaction pathways.

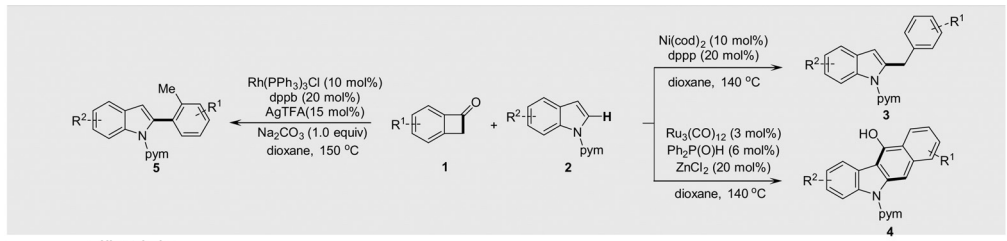
Furthermore, the reaction of **2a** with stoichiometric $Rh(PPh_3)_3Cl$ was investigated (Scheme 1B). C–H bond cleavage occurred smoothly to generate complex **M1**, which was characterized by X-ray analysis. As a catalyst precursor, **M1** could successfully catalyze the coupling to afford product **5a** in 68% yield. Mixing of $Ru_3(CO)_{12}$, $Ph_2P(O)H$ and **2a** generated complex **M2**. The structure of **M2** was also confirmed by X-ray analysis. This complex was also found to be catalytically active for the coupling of benzocyclobutenone, giving yields comparable to those obtained using $Ru_3(CO)_{12}$. We also attempted but failed to isolate a nickel-cycle intermediate **M3**. Fortunately, this Ni^{II} hydride species was detected by ESI-TOF, indicating that C–H activation was likely to follow.

Next, a set of control experiments were performed to investigate the mechanism (Scheme 1C). It was found that no decarbonylation occurred using aldehyde **6a** as the substrate in the Ni-catalyzed reaction. However, a spontaneous cyclization of aldehyde **6a** was observed at room temperature, yielding benzo[*b*]carbazole **8** as product. These observations rule out the possibility of aldehydes being the precursor of decarbonylation in the Ni-catalyzed reaction, although the aldehyde is likely a reactive species in the Ru-catalyzed reaction. Next, ketone **9** was examined in the Rh-catalyzed reaction. No-decarbonylation occurred, suggesting that a ketone is not the reactive intermediate, and intermediate **C** (Figure 1) is a more probable precursor of decarbonylation.

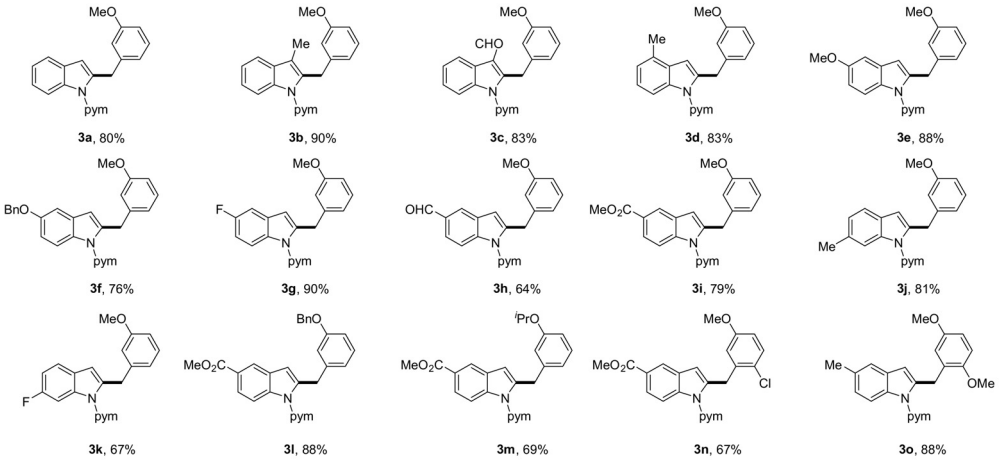
Often, useful information about reaction intermediates can be obtained from the analysis of byproducts. Decarbonylative coupling in the presence of $[Rh(cod)OH]_2$ and BINAP in toluene, a byproduct, ketone **9**, was isolated and characterized. The presence of this ketone is consistent with C1-C8 bond cleavage of benzocyclobutenone, with **C** being the possible intermediate (Scheme 1D). In addition, intermolecular kinetic isotope effects of $k_H/k_D = 1.05$, 1.12 and 1.11 between **2a** and *d*-**2a** in parallel reactions in the Ni- Ru-, and Rh- catalyzed reactions were observed, respectively, suggesting that C–H cleavage might not be the rate-limiting step (Scheme 1E).

Based on our mechanistic studies, we propose a plausible mechanism (Scheme 2). Initially, coordination of the directing group in **2a** to the metal catalysts precedes the C–H activation, generating five-membered metal cycle species **1-INT1** and **2-INT1**. After this step, the mechanism of C–C bond activation may diverge depending on the selectivity of the catalysts. Ni and Ru catalysts lead to intermediate **1-INT2.**

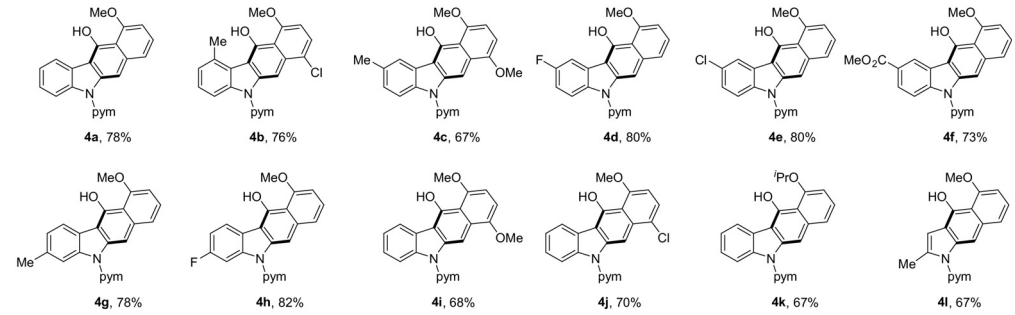
Table 3: Substrate scope.[a,b]



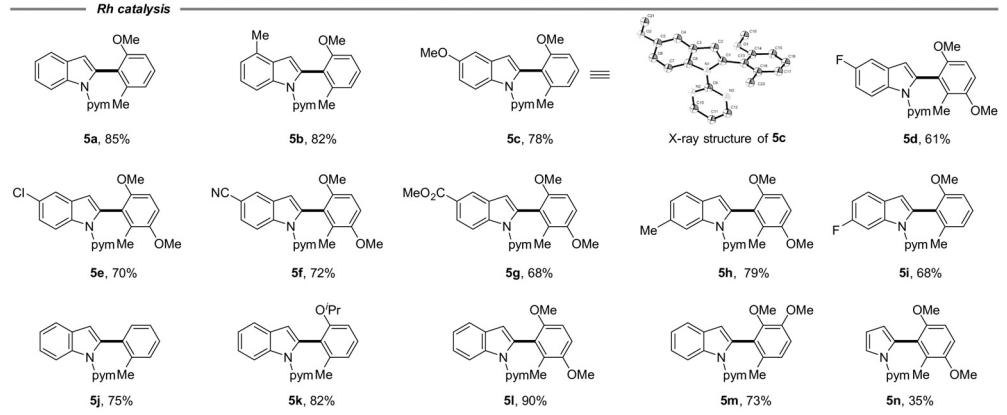
Ni catalysis



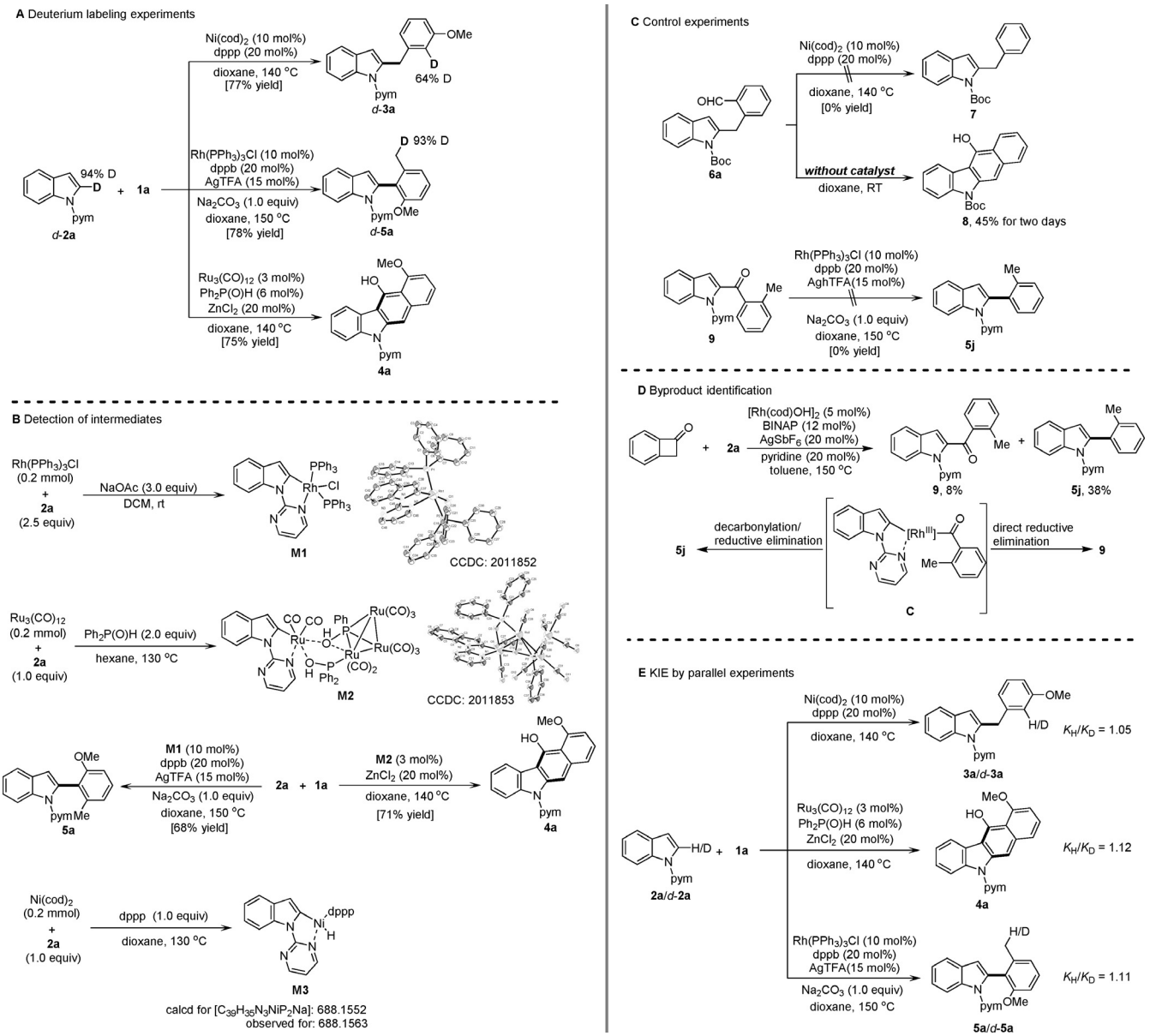
Ru catalysis



Rh catalysis



[a] Conditions: With [Ni], **1** (0.2 mmol), **2** (0.1 mmol), $Ni(cod)_2$ (0.01 mmol), dppp (0.02 mmol,) in dioxane at 140 °C. With [Ru], **1** (0.2 mmol), **2** (0.1 mmol), $Ru_3(CO)_{12}$ (0.003 mmol), $PPh_2P(O)H$ (0.006 mmol), $ZnCl_2$ (0.02 mmol) in dioxane at 140 °C. With [Rh], **1** (0.2 mmol), **2** (0.1 mmol), $Rh(PPh_3)_3Cl$ (0.01 mmol), dppb (0.02 mmol), AgTFA (0.015 mmol), Na_2CO_3 (0.1 mmol) in dioxane at 150 °C. [b] Yield of isolated products.

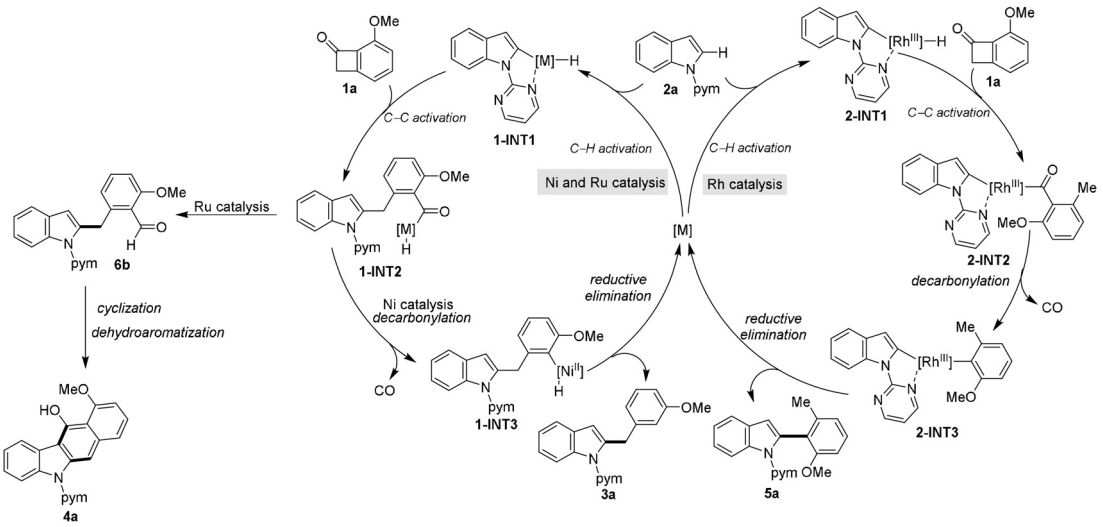


Scheme 1. Mechanistic studies.

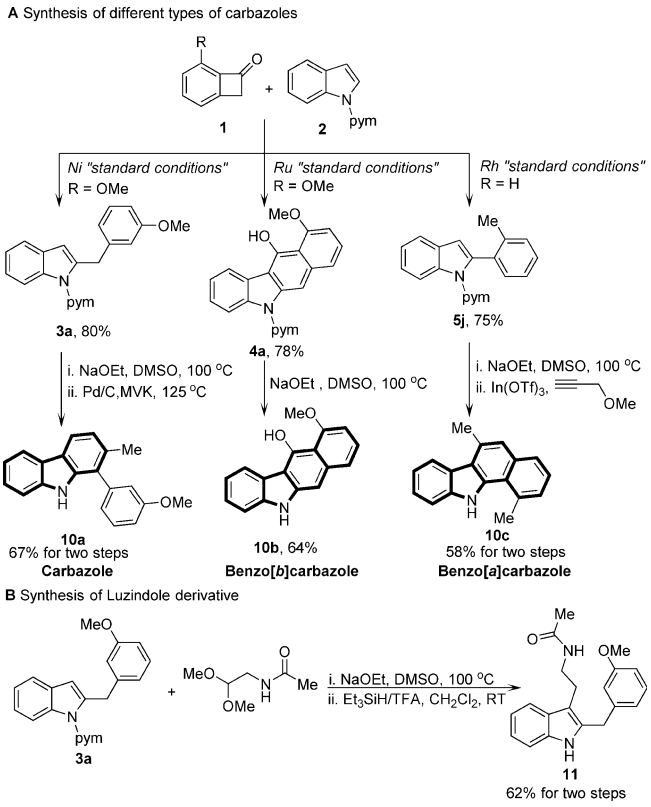
The Ni catalyst promotes decarbonylation and reductive elimination, generating the product **3a**. The Ru catalyst promotes the reductive elimination from **1-INT2**, generating aldehyde **6b**. The final cyclization produces benzo[*b*]carbazole **4a**. Alternatively, Rh catalysis may generate intermediate **2-INT2**, whose subsequent decarbonylation and reductive elimination furnishes product **5a**.

Carbazoles are an important class of *N*-fused polyaromatic compounds, and such moieties found in many bioactive molecules.[16] To highlight the synthetic utility of our strategy, three different types of carbazoles were selectively synthesized by derivatization of the representative products (Scheme 3). Carbazole derivative **10a** was obtained in a high yield through annulation with **3a**.[17] Treatment of **4a** with NaOEt gave N-H benzo[*b*]carbazole **10b**, and an In-catalyzed annulation afforded benzo[*a*]carbazole **10c** from **5j**.[18] Additionally, Luzindole derivatives could be synthesized from **3a**, which further demonstrated the synthetic utility of our strategy.[7b]

In conclusion, we have developed a catalyst-enabled divergent coupling of benzocyclobutenones with indoles via C–H/C–C activations. The divergent reactivity of benzocyclobutenone allows the facile synthesis of three types of valuable indole derivatives. We believe that this unique divergent coupling will not only aid in understanding the behaviors of different metal catalysts in C–C bond cleavage but also open pathways for the preparation of novel C–C activation systems for the rapid construction of useful products. In future, efforts will be made to understand the origin of these unexpected selectivities and expand the reaction scope to unstrained ketones.



Scheme 2. Proposed mechanism.



Scheme 3. Synthesis applications.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: benzocyclobutenone · carbazole · catalyst-control · C—C activation · divergent synthesis

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