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Ring-Strain Enabled Transannulation of *N*-Aryl Bicyclo[1.1.0]butane Carboxamides via Rhodium(II)Carbene Intermediate

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Abstract

The C–C bond cleavage is a fascinating area in synthetic organic chemistry, driven by ring-strain-enabled transformations. Here, we report the reactivity of the rhodium(II)-catalyzed, ring-strain-enabled *N*-aryl bicyclo[1.1.0]butane carboxamide in a transannulation reaction. The efficiency of this methodology demonstrates significant advances in metallocarbene chemistry, generating a novel class of acceptor type allyl carboxamide Rh(II)-carbene intermediate, notably without the need for coordinating groups or external ligands. The reactivity was systematically investigated using various substituted *N*-aryl bicyclo[1.1.0]butane-1-carboxamides, leading to impressively efficient synthesis of 3-allyl oxindoles via transannulation. [1,2]-*H* Migration is also shown via an in situ-generated Rh(II)-carbene intermediate. Furthermore, the broad synthetic utility of this method is a promising development, enabling the diversification of key functional groups and the access to structurally relevant intermediates and biologically active molecule precursors, including the CB2 agonist and Horsfiline. Control experiments and DFT calculations showed that the transformation proceeds via a Rh(II)-carbene intermediate.

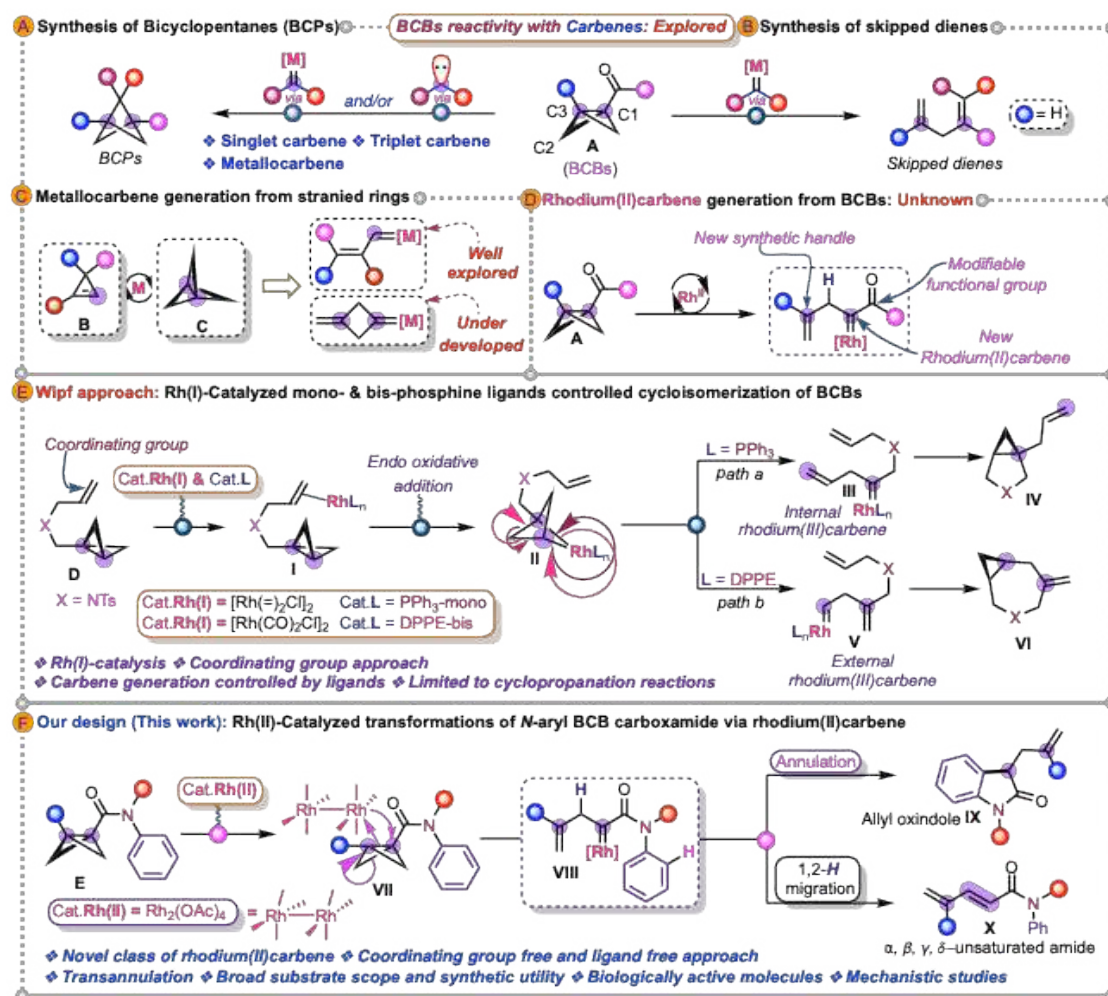
Keywords: Bicyclobutanes, Rhodium catalysis, Carbenes, Oxindoles, Transannulation.

Introduction

Metallocarbenes are highly reactive, transient intermediates that have emerged as versatile tools in modern organic synthesis.¹⁻² These intermediates are typically generated through the reaction of diazo compounds and related precursors in the presence of suitable metal catalysts.³⁻⁷ However, it is challenging to handle due to its instability and uncontrolled nature, as well as the stabilizing groups, which, depending on their needs, are difficult to modify.³⁻¹¹ Developing a novel class of metallocarbene precursors containing modifiable functional groups on both sides of the metallocarbene carbon is highly desirable.

Recent advances in C–C bond cleavage are a fascinating area in organic chemistry, driven by ring-strain-enabled transformations that have increased the complexity, particularly in the cleavage of the smallest alicyclic compounds, such as three- and four-membered rings, through strain-release energy as the major driving force.¹²⁻¹⁵ Among them, bicyclo[1.1.0]butanes (BCBs) **A** (Scheme 1A) showcase a unique butterfly-

like geometry, with a bond angle of approximately 122° between two cyclopropane rings, and a C1 and C3 inverted umbrella-like geometry.¹⁶⁻¹⁷ BCBs have high ring-strain energy of around ~ 65 kcal/mol, a property attributed to their central C-C σ -bond behaving like an olefin, and the C1-C3 σ -bond connects to two cyclopropane rings, which undergo various reactions.¹⁸⁻²³ This unique feature allows BCBs to participate in a variety of transformations, e.g., radical reactivity via 1,3-diradical intermediates, reactions with electrophiles and nucleophiles via polar intermediates, and metal-catalyzed C-H activation strategies.¹⁸⁻³⁵ The extensive study of BCBs, including their reaction with free carbenes via single atom insertion of singlet, triplet carbenes which are derived from halocarbene precursors, acceptor-substituted carbene precursors, and others through the skeletal editing of BCBs to access the bicyclo[1.1.1] pentanes (BCPs), is well studied (Scheme 1A).³⁶⁻⁴⁷ Recently, the metalcarbene reaction has shown reactivity that differs from that of free carbenes. In the case of Rh and Cu-carbenes, which gave the skipped dienes (Scheme 1B),⁴⁸⁻⁵⁰ and in the case of Rh-carbene derived from *N*-sulfonylhydrazone, gave the substituted BCPs.⁵¹



Scheme-1: Reactivity of bicyclo[1.1.0]butanes [BCBs]

The generation of metallocarbenes (Scheme 1C) via the C–C bond cleavage of cyclopropenes **B**,⁵²⁻⁵⁷ and bicyclic systems, such as [1.1.1]propellanes **C**, is studied.⁵⁸⁻⁶³ We are fascinated by ring-strain-enabled generation of metallocarbenes from cyclopropene and [1.1.1]propellanes via metal complexation followed by C–C σ -bond cleavage, and their reactivity has been well-explored.⁵²⁻⁶⁷ The curiosity arises: can we generate metallocarbenes, such as acceptor rhodium(II)-carbene, from BCBs (Scheme 1D) in the presence of a Rh(II)-catalyst via a ring-strain-enabled strategy? Here, we are interested in developing the generation of a novel class of acceptor Rh(II)-carbene, such as allyl carboxamide Rh(II)-carbene from the BCBs, which has a novel class of synthetic handle and modifiable functional groups (Scheme 1D) via a ring-strain-enabled fashion in the presence of Rh(II)-catalyst.

The generation of metallocarbene from BCBs is underdeveloped and has been reported in only a few reports.⁶⁸⁻⁷⁷ In 1970, the Gassman group observed the generation of metallocarbene from BCBs in the presence of Rh(I)-catalyst.⁶⁸ In 2008, the Wipf group studied the Rh(I)-catalyzed cycloisomerization (Scheme 1E)⁷³ of *N*-allyl tethered BCBs **C** for the synthesis of cyclopropane fused pyrrolidine **IV**, and azepines **VI** as a mixture of regio-isomers. The mono- and bis-phosphine ligands control the regioselectivity in the presence of a highly reactive rhodium(I)-catalyst. The reaction proceeds through the initial coordination of the tethered olefin moiety of BCBs **D** with Rh(I)-catalyst in the presence of phosphine ligands to form the active Rh(I)-complex **I**, which then undergoes endo oxidative addition to form the Rh(III)-complex **II**. The phosphine ligands dictate the formation of internal rhodium(III)carbene **III** in *path a* and external **V** rhodium(III)carbene in *path b*.⁷⁴ To generate the internal and external rhodium(III)-carbenes, one must use the mono- and bis-phosphine ligands and coordinating olefin functionality, which acts as a directing group. As discussed above, to address the mentioned problem. Here, we propose a more general approach for the generation of a novel class of metallocarbene, i.e., Rh(II)-carbene **VIII** (Scheme 1F), derived from the *N*-aryl tethered BCB (NAr BCB) carboxamide, which has a novel class of synthetic handle, such as an allyl moiety and amide functionality, which are easily modifiable functional groups. The hypothesis involves the rhodium-metal acts as a π -acid^{55, 64-67} and which then coordinate through the central σ -bond of C1–C3 (which behaves like a olefin) of BCB **E** to form the Rh(II)-complex **VII** followed by cleavage of σ -bond of C1–C3 and C1–C2 through ring-opening to generate the Rh(II)-carbene **VIII** (Scheme 1G), which then undergoes intramolecular annulation to form the 3-allyl oxindole **IX** and [1,2]-*H* migration to form the corresponding α , β , γ , δ -unsaturated amide **X**.

Results

Reaction optimization

Table 1: Optimization table

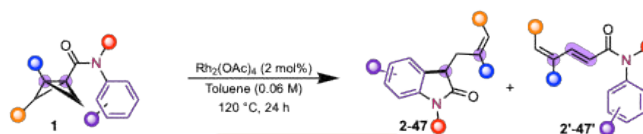
Entry	Deviation from standard	Yield of 2 (%) ^b	Yield of 2' (%) ^b

1	None	66 (63)^c	24 (18)^c
2	Rh ₂ (esp) ₂ in lieu of Rh ₂ (OAc) ₄	28	24
3	Rh ₂ (Oct) ₄ in lieu of Rh ₂ (OAc) ₄	38	32
4	Rh ₂ (TFA) ₄ in lieu of Rh ₂ (OAc) ₄	12	8
5	Cu(OTf) ₂ in lieu of Rh ₂ (OAc) ₄	14	12
6	[Rh(CO) ₂ Cl] ₂ , DPPE (4 mol%) in lieu of Rh ₂ (OAc) ₄	ND	ND
7	Without Rh ₂ (OAc) ₄	ND	ND
8	110 °C in lieu of 120 °C	60	24
9	150 °C in lieu of 120 °C	54	22
10	40, 60 and 80 °C in lieu of 120 °C	NR	NR

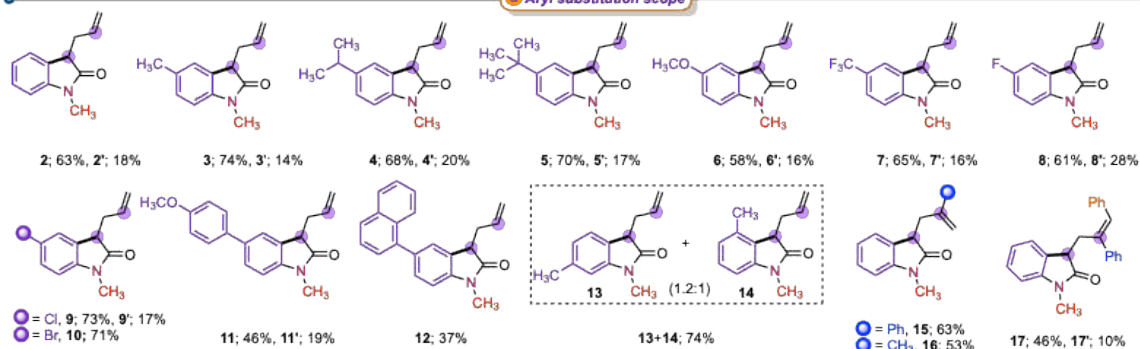
^aReaction conditions: **1** (0.1 mmol), Rh₂(OAc)₄ (2 mol%), Toluene (0.06 M), 120 °C, 24 h. ^bYield determined by ¹H NMR using CH₂Br₂ as an internal standard. ^cIsolated yield for 0.2 mmol. ND = not detected. NR = no reaction. DPPE = 1,2-Bis(diphenylphosphino)ethane.

The oxindoles are interesting motifs in synthetic organic chemistry, and these scaffolds are found in several alkaloids, natural products, antitumor agents, and pharmaceutically important compounds.⁷⁸⁻⁸¹ We are interested in the functionalization of carbenes via the non-diazo approach.⁸²⁻⁸⁴ Here, we have synthesized oxindole through the Rh(II)-carbene via a diazo-free approach of NAr BCB carboxamide in the presence of Rh(II)-catalyst. We began our investigation for the synthesis of 3-allyl oxindole via in situ generation of a rhodium(II)-carbene from *N*-methyl-*N*-phenyl bicyclo[1.1.0]butane-1-carboxamide **1** and the Rh₂(OAc)₄ catalyst, using a ring-strain-enabled transannulation strategy. After screening various reaction parameters such as catalysts, solvents, concentration, temperature (for detail optimization see SI) we found the best optimized conditions are *N*-Me, *N*-Ph BCB carboxamide **1** underwent intramolecular transannulation in the presence of Rh₂(OAc)₄ (2 mol%) at 120 °C in toluene (0.06 M) afford the 3-allyl oxindole **2** in 63% isolated yield, along with [1,2]-*H* migration product to give the α , β , γ , δ -unsaturated amide in detectable amount **2'** (entry 1, Table 1). We also checked other Rh(II)-catalysts, such as Rh₂(esp)₂, Rh₂(Oct)₄, and Rh₂(TFA)₄ (entries 2-4, Table 1), and observed that product **2** was obtained in lower yield. The Cu(OTf)₂ catalyst also gave the corresponding product, but only in a detectable amount (entries 5, Table 1). However, a Rh(I)-catalyst such as [Rh(CO)₂Cl]₂ in the presence of DPPE (1,2-Bis(diphenylphosphino)ethane) ligand failed to give the corresponding products **2** and **2'** (entry 6, Table 1), which are used for cycloisomerization of BCBs.⁷³ Importantly, without the Rh₂(OAc)₄ catalyst, no product was observed (entry 7, Table 1), which confirms the role of the Rh(II)-catalyst for the generation of Rh(II)-carbene. A change in temperature, either decreasing or increasing, resulted in no yield improvement being observed (entries 8-9, Table 1). When we performed the reaction at 40, 60, and 80 °C, starting material **1** remained unreacted, demonstrating that reaction temperature influences the in situ formation of Rh(II)-carbene via a ring-strain-enabled strategy.

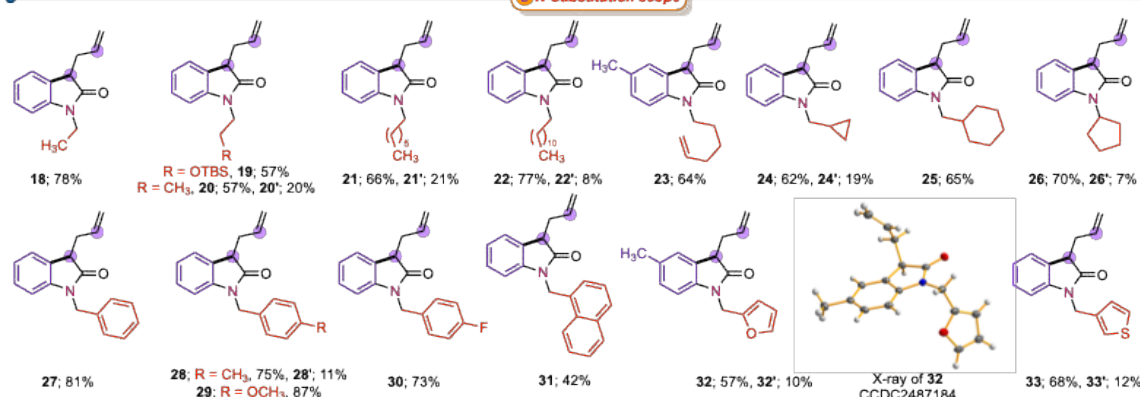
Substrate scope



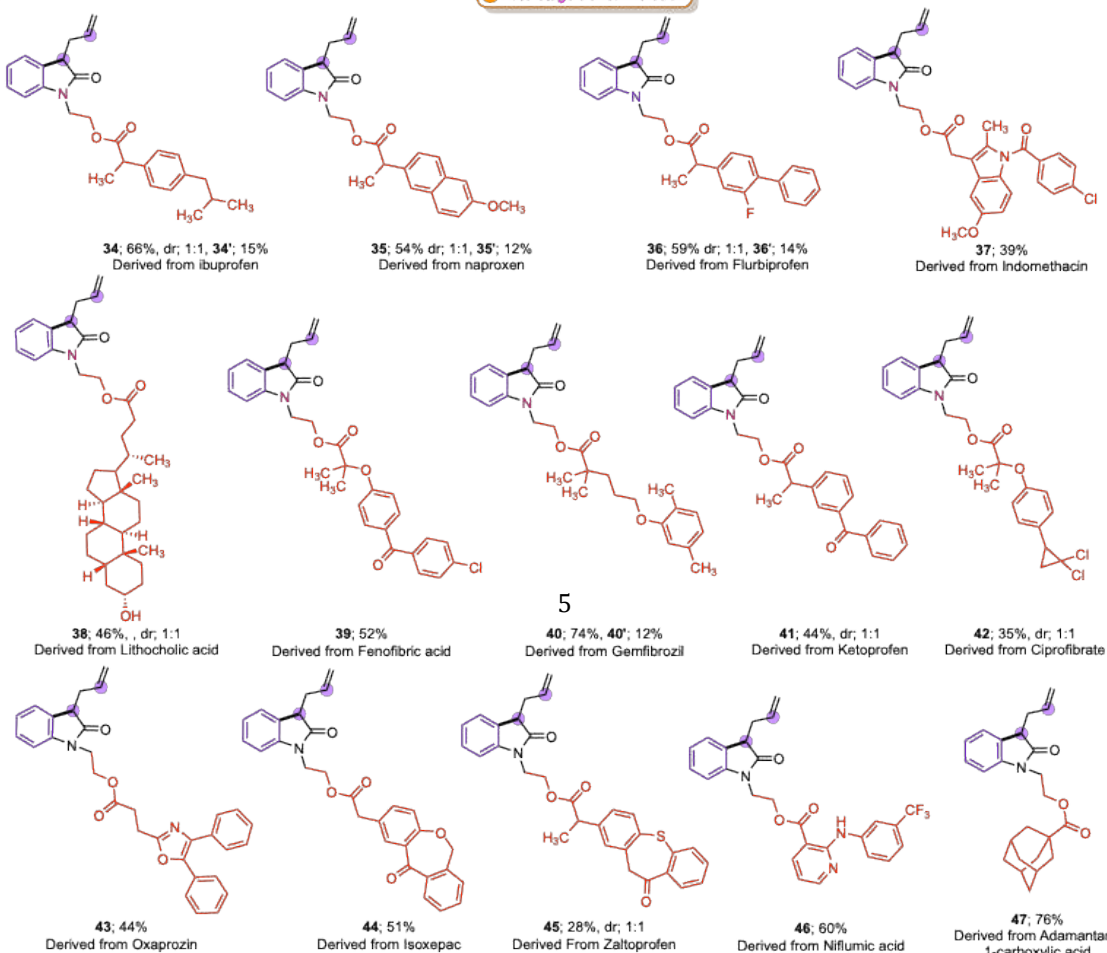
Aryl substitution scope



N-Substitution scope



Late-stage transannulation



Reaction Conditions: 1 (0.2 mmol, 1.0 equiv.), $\text{Rh}_2(\text{OAc})_4$ (2 mol%), Toluene (3.0 mL, 0.06 M), 120 °C, 24 h

Scheme-2: Substrate scope

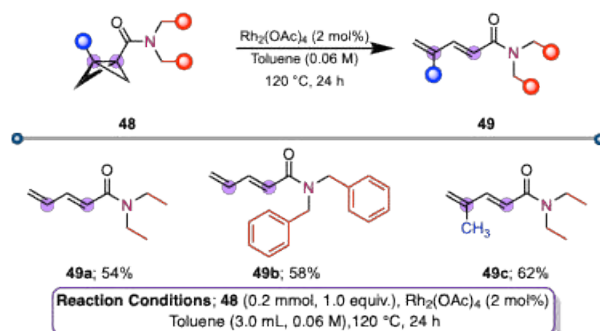
After finding the optimized conditions, we checked the scope of this transformation, demonstrating its broad applicability. It was a significant discovery that several NAr BCB carboxamides reacted efficiently for the Rh(II)-catalyzed transannulation reaction, yielding the corresponding 3-allyl-oxindoles with good yields and [1,2]-*H* migration product, such as α , β , γ , δ -unsaturated amides, with detectable amounts of yields were reported (Scheme 2). The various *para*-substitutions on NAr BCB carboxamide, such as electron-donating groups including methyl, isopropyl, tertiary butyl, and methoxy, were explored well to give corresponding 3-allyl oxindole **3-6** and [1,2]-*H* migration product **3'-6'**. Electron-withdrawing groups, e.g., trifluoromethyl (**7**), and halogen-substituted groups, e.g., fluorine (**8**), chlorine (**9**), and bromine (**10**), could be incorporated onto the 3-allyl oxindole moieties with up to 73% yield, which are potential synthetic modifications for downstream cross-coupling reactions. Similarly, *p*-methoxyphenyl- and 1-naphthyl-substituted NAr BCB carboxamides also participated in the reaction to give the corresponding 3-allyl oxindoles with acceptable yields **11-12**. In the case of *meta*-substitution, the *m*-methyl phenyl substrate gave a mixture of regioisomers (**13** and **14**) in good yield. Under optimized conditions, the 1,3-disubstituted BCB carboxamide also underwent intramolecular transannulation to yield phenyl- and methyl-substituted 3-allyl oxindoles **15** and **16** in good yields, thereby demonstrating the adaptability of the methodology to diverse substrates. Interestingly, the reactivity of NAr BCB carboxamide bearing bridged substituents was also tested, yielding the corresponding 3-allyl oxindole **17** in moderate yield.

The reactivity of *N*-substitution of NAr BCB carboxamides was also tested (Scheme 2b). We explored a wide range of substrates, incorporated the ranging from those with linearly increasing alkyl chain lengths 3-allyl oxindole products such as ethyl (**18**), ethyl silyl ether (**19**) propyl (**20**), heptyl (**21**), dodecyl (**22**), hexenyl (**23**), cyclopropyl methyl (**24**), and cyclohexyl methyl (**25**), to cyclic substrates like the cyclopentyl substrate (**26**), and even electronically diverse substituted *N*-benzyl substrates (**27-31**) derived from the corresponding benzaldehydes, naphthaldehydes. Heteroaromatics such as 2-furfural and 3-thiophene carboxaldehyde yielded the corresponding 3-allyl oxindoles **32** and **33** in good yields. The successful formation of 3-allyl oxindole **32** was confirmed by single-crystal X-ray analysis.⁸⁵

The ring-strain-enabled Rh(II)-catalyzed transannulation strategy, a novel approach that enables late-stage transannulation, has been successfully applied to many drug molecules via Rh(II)-carbene intermediate. NPh BCB carboxamide, derived from drug molecules such as *ibuprofen*, *naproxen*, *flurbiprofen*, *indomethacin*, *lithocholic acid*, *fenofibric acid*, *gemfibrozil*, *ketoprofen*, *ciprofibrate*, *oxaprozin*, *isoxepac*, *zaltoprofen*, *niflumic acid*, and adamantane 1-carboxylic acid, all smoothly underwent intramolecular transannulation to give the corresponding biologically active molecule containing 3-allyl oxindoles **34-47** with good to moderate yield and along with [1,2]-*H* migration product was observed (Scheme 2c). This transannulation approach offers a novel synthesis of a new class of drug-like molecules. It holds great promise in drug discovery and organic synthesis.

During the optimization studies, we observed detectable [1,2]-*H* migration product from the in situ-generated Rh(II)-carbene intermediate. We checked the generality of this [1,2]-*H* migration reaction, for that we have designed the substrate instead of *N*-aryl tethered BCB carboxamide, e.g., *N*, *N*-dialkyl BCB carboxamide **48**, observed the [1,2]-*H* migration product, such as α , β , γ , δ -unsaturated amide **49a** and **49b** in 54% and 58% yield respectively (Scheme 3). Interestingly, 1,3-disubstituted *N*, *N*-diethyl BCBC **48c**

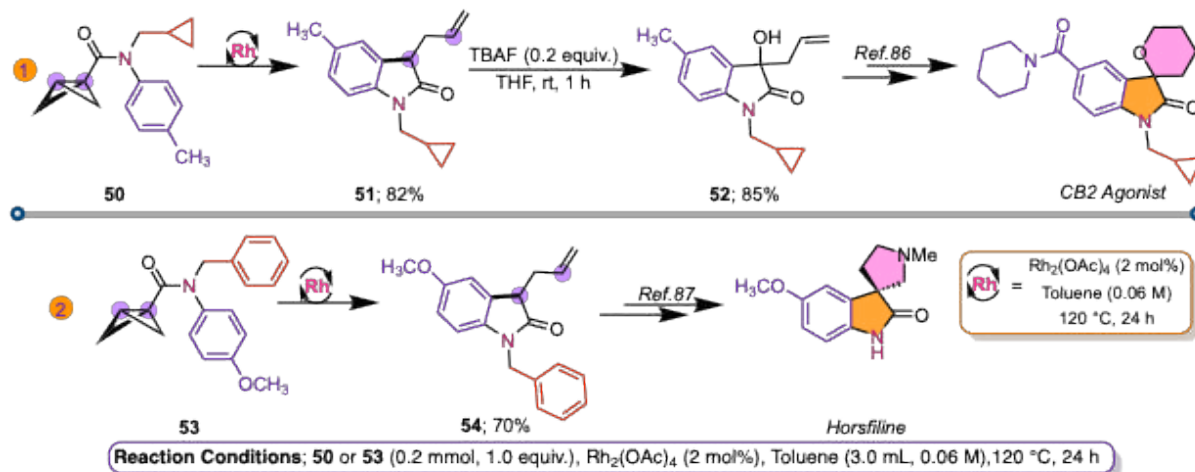
also underwent [1,2]-*H* migration to give the corresponding α , β , γ , δ -unsaturated amide **49c** with 62% yield. These experiments confirm the in situ generation of Rh(II)-carbene from BCB carboxamide, which does not require a tethered *N*-aryl group.



Scheme-3: Synthesis of α , β , γ , δ -unsaturated amides via [1,2]-*H* migration

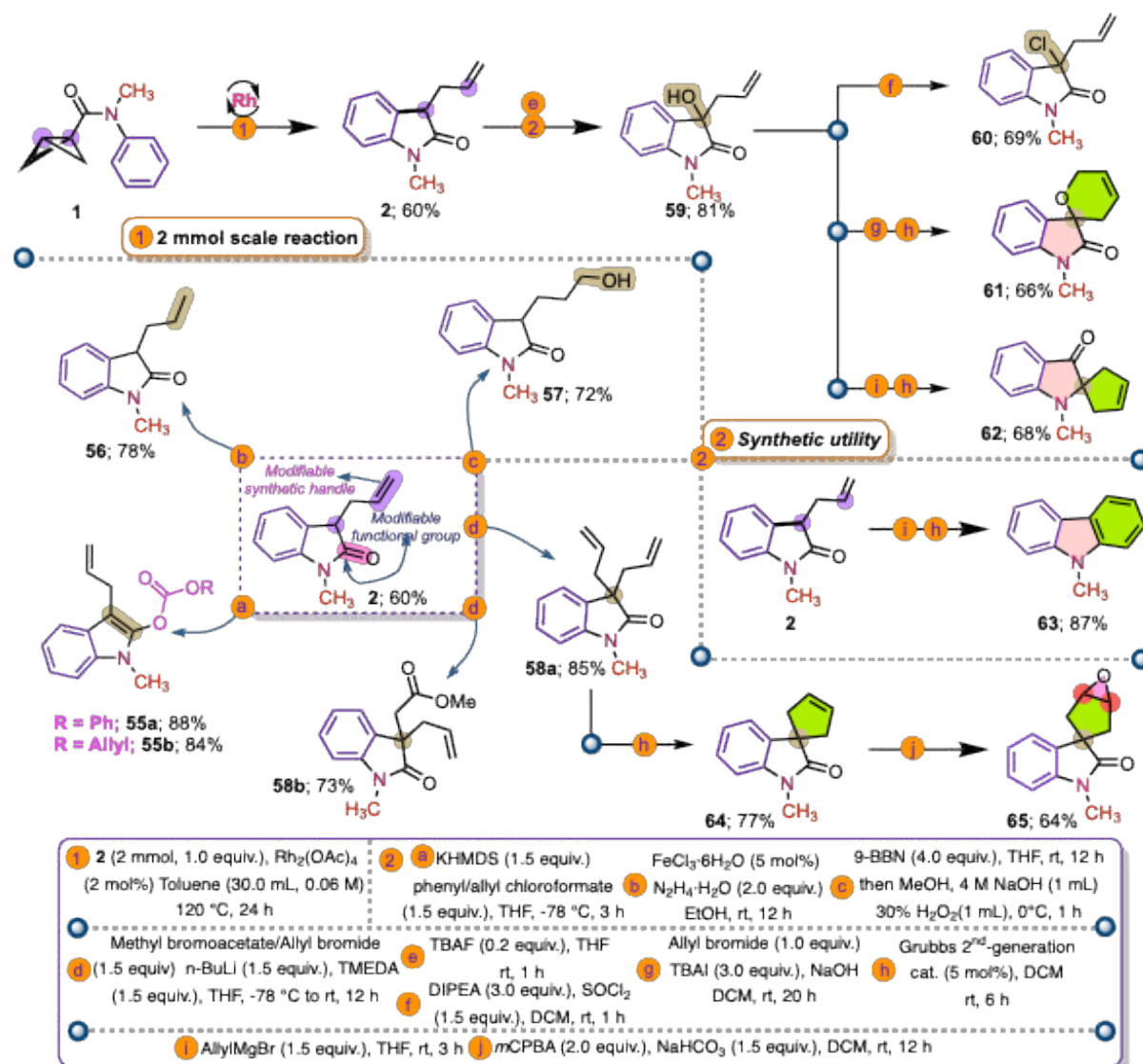
Application

Next, we have successfully synthesized precursors of biologically active molecules such as CB2 Agonist (Scheme 4, eq.1) and Horsfiline (Scheme 4, eq.2). The synthesis of CB2 Agonist precursor **52** was achieved, under optimized conditions, from the corresponding starting material **50** in the presence of $\text{Rh}_2(\text{OAc})_4$ catalyst to give the corresponding 3-allyl oxindole **51** with 82% yield, and then treated with TBAF, underwent aerial oxidation to form the quaternary carbon-containing homoallyl alcohol **52** in 85% yield, which is the precursor for the CB2 Agonist compound.⁸⁶ Similarly, the Horsfiline precursor is also synthesized via a Rh(II)-catalyzed transannulation of **53**, yielding **54** in 70% yield, which is en route to the synthesis of spirooxindole alkaloid horsfiline.⁸⁷



Scheme-4: Synthesis of bioactive molecule precursors

To demonstrate the robustness of this methodology, we scaled up the reaction to 2 mmol without modification under optimized conditions and observed the desired product (Scheme 5, eq.1) with 60% yield. Next, we have demonstrated the synthetic utility of 3-allyl oxindole **2**, a modifiable synthetic handle and functional group for downstream transformations (Scheme 5). At first, we successfully converted oxindole to indoles **55a** & **55b** with good yield by treating **2** with phenyl chloroformate and allyl chloroformate in the presence of KHMDS at -78 °C. Next, we focused on the synthetic handle allyl moiety of oxindole **2** to introduce various functionalities on the oxindole core, converting the alkene functionality to alkane **56** in 78% yield. Alkene functionality was further converted to terminal alcohol **57** in 72% yield via hydroboration followed by oxidation.



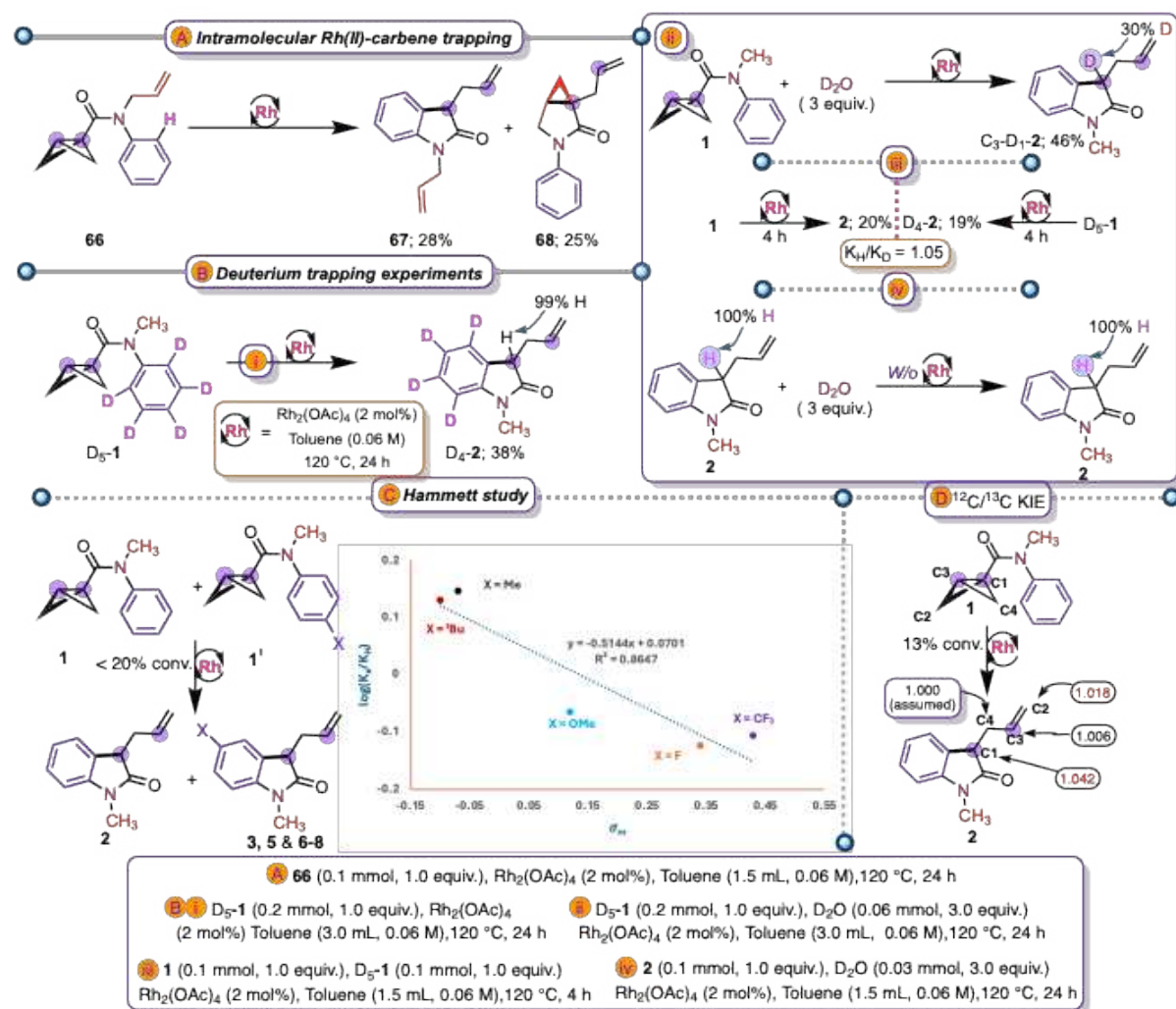
Scheme-5: Synthetic application

Furthermore, we have converted the C3-position of the 3°-carbon of oxindole into a quaternary carbon by introducing various functionalities, such as allylation **58a** and alkylation **58b** with methyl bromoacetate and allyl bromide under basic conditions, yielding **73%** and **85%**, respectively (Scheme 5). Introduce the hydroxy (OH) and chlorine (Cl) functionality through TBAF-catalyzed areal oxidation of 3-allyl oxindole **2** to give the homoallyl alcohol containing oxindole **59** in 81% yield, which was then treated with thionyl chloride in the presence of DIPEA to introduce the chlorine functionality, such as homoallyl chloride **60**, in 69% yield. These functionalities serve as intermediates for subsequent transformations, demonstrating the efficiency of our methodology. The synthesis of spirooxindole is also achieved using the 2nd-generation Grubbs catalyst via RCM (ring-closing metathesis). The homoallyl alcohol of oxindole **59** was treated with allyl bromide to give C3-allyl and C3'-O-allyl containing compounds in situ, subjected to RCM reaction to synthesize the spiro dihydropyran oxindole **61**, 66% yield. Similarly, cyclopentene-containing indolin-3-one **62** is obtained in 68% yield via RCM from **59**, demonstrating the effectiveness of our approach. We synthesized N-methyl carbazole **63** (87% yield) and spirocyclopentene containing 3-oxindole **64** (77% yield) from compounds **2** and **58a**, respectively, via a two-step process involving allyl magnesium bromide addition followed by RCM. In addition, we have converted the spirocyclopentene containing 3-oxindole **64** to an oxirane-containing tetracyclic compound **65** with 64% yield via epoxidation using *m*CPBA (*m*-chloroperbenzoic acid).

Mechanistic Investigations

To elucidate the reaction mechanism to prove the Rh(II)-carbene generation from the NAr BCB carboxamide. We designed the substrate *N*-allyl and *N*-phenyl tethered BCB carboxamide **66** to provide concrete evidence for in situ generation of electrophilic Rh(II)-carbene intermediate, and the synthesized corresponding starting material was treated under optimized conditions. The result was an almost 1:1 ratio (Scheme 6A) of transannulation product **67** and intramolecular cyclopropanation product, such as fused-cyclopropane γ -lactam **68**, which unequivocally proves that the reaction proceeds through the Rh(II)-carbene intermediate. We then synthesized D5-*N*-aryl BCB **1**, treated it under optimized conditions, and observed the D4-containing 3-allyl oxindole **2** in 38% yield (Scheme 6B, eq i). However, we did not observe the deuterium incorporation at the C3-position, which confirms the reaction does not proceed through the C(sp²)-H insertion reaction. Interestingly, when we use D₂O (3 equiv.) and observed 30% incorporation of D at the C3-position of oxindole (Scheme 6B, eq ii), which confirms that the reaction proceeds through the nucleophilic attack of arene to electrophilic Rh(II)-carbene and then [1,2]-*H* shuffle through a stepwise mechanism.⁸⁸ Moreover, we have performed the reactions H5-*N*-aryl BCB-**2** and D5-*N*-aryl BCB-**2** in individual reactions only 4 h to measure the initial rates, and observed a *K_H*/*K_D* of 1.05 (Scheme 6B, eq iii), which proves that the C-H functionalization is not the rate-determining step. These results suggest that the reaction proceeds via electrophilic addition of the Rh(II)-carbene, followed by a [1,2]-*H* shuffle to form the corresponding product. Moreover, to prove deuterium incorporation at the C3-position of oxindole (Scheme 6, eq ii), to check whether it proceeds through enolization followed by trapping with D/H under reaction conditions. We have taken 3-allyl oxindole **2** and treated it under optimized conditions with and without Rh(II)-catalyst reaction with D₂O (3 equiv.); no deuterium incorporated product was observed (Scheme 6, eq. iv), which again confirms that deuterium is observed only through the [1,2]-*H* shuffle, not through the enolization of the corresponding oxindole. Hammett's analysis also suggested an electrophilic addition reaction mechanism (Scheme 6c), as evidenced by sensitivity to electronic effects ($\rho = -0.51$) and nucleophilic attack of the tethered arene on the electrophilic Rh(II)-carbene intermediate.⁸⁹ We have also checked ¹²C/¹³C KIE for the rate-determining step,⁹⁰ which confirms that the generation of Rh(II)-carbene

via ring-stained enabled cleavage of the C1–C3 σ -bond of NAr BCB carboxamide **1**, based on the computed reaction energy profile (**TS1** (please see Figure 1), $\Delta G^\ddagger = 26.2$ kcal/mol), is the rate-determining step, which is consistent with the experimental ^{13}C KIE values (Scheme 6D).



Scheme-6: Mechanistic insights

To gain mechanistic insight into the reaction mechanism, density functional theory (DFT) calculations were performed using the Gaussian 16 program (Figure 1). The process initiates with the coordination of the strained bicyclobutane substrate **69** to Rh₂(OAc)₄ ([Rh]), affording a loosely bound intermediate **70**, which is 6.7 kcal/mol uphill in energy. Subsequent cleavage of the σ -bond of the C1–C3 bond of the BCB occurs *via* transition state **TS1** with an activation barrier of 26.2 kcal/mol, generating the internal Rh(II)-carbene intermediate **71**. The results indicate that the rate-determining step is the opening of the BCB ring, with a transition-state barrier of 26.2 kcal/mol. This transformation is mediated *via* a concerted transition state, where C1–C3 σ -bond cleavage and formation of internal Rh(II)-carbene **71** occur simultaneously. Furthermore, from Rh(II)-carbene intermediate **71**, two competing pathways are possible: (i)

intramolecular electrophilic attack (path a) to give the transannulation product **73** and (ii) a 1,2-hydride shift (path b) to give **75**. The transannulation product may form either directly or with the assistance of water. The annulation pathway, **71** proceeds via intramolecular electrophilic attack to generate **72** through **TS2** with a free-energy barrier of 21.9 kcal/mol is kinetically favored by 5.2 kcal/mol over the direct 1,2-hydride migration to form **75** via transition state **TS3** (27.1 kcal/mol) through the Rh-complex **74** followed by the regeneration of the catalyst to give the $\alpha, \beta, \gamma, \delta$ -unsaturated amide **75**. From intermediate **72**, two possible hydrogen-transfer processes were examined to furnish the transannulation product. In the first case, a direct 1,2-hydride shift occurs via **TS4**, with a barrier of 16.2 kcal/mol, without a water assistant, to form the product complex with [Rh]-complex **76**. On the other hand, a proton-shuttling mechanism is feasible in the presence of water, which abstracts a hydrogen atom from the arenium ion intermediate **72** and transfers it to the oxygen atom via a hydrogen-bonded relay, producing a significantly stabilized intermediate **72_1** in a nearly barrierless manner. Finally, the subsequent keto-enol tautomerization of **72_1** furnished the desired product **73** along with regeneration of the active Rh(II) catalyst. Alternatively, generation of the external Rh(II)-carbene intermediate **71'** (path c) via **TS1'** from the corresponding intermediate **70** is unfavorable by 5.9 kcal/mol relative to the internal Rh(II)-carbene complex **71**, which

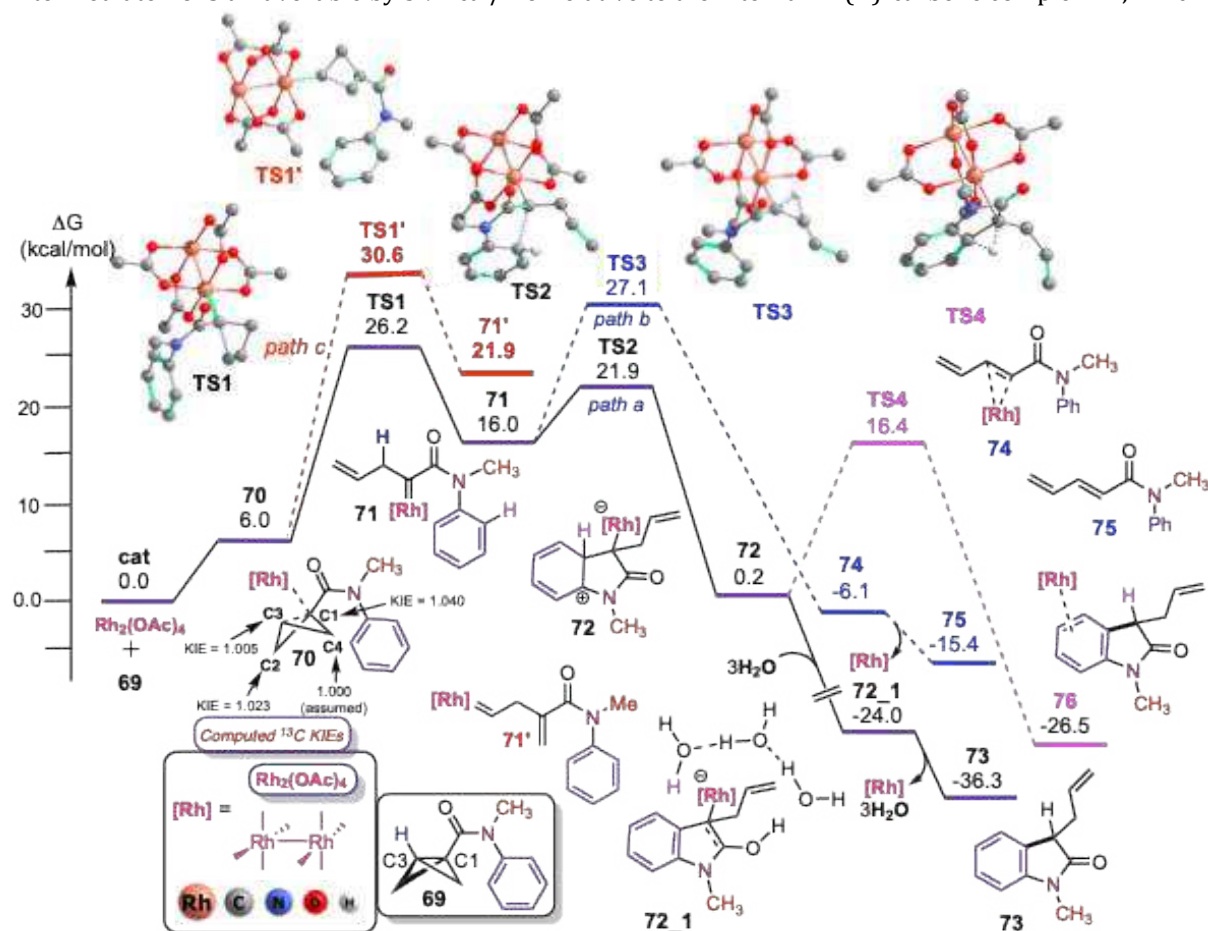
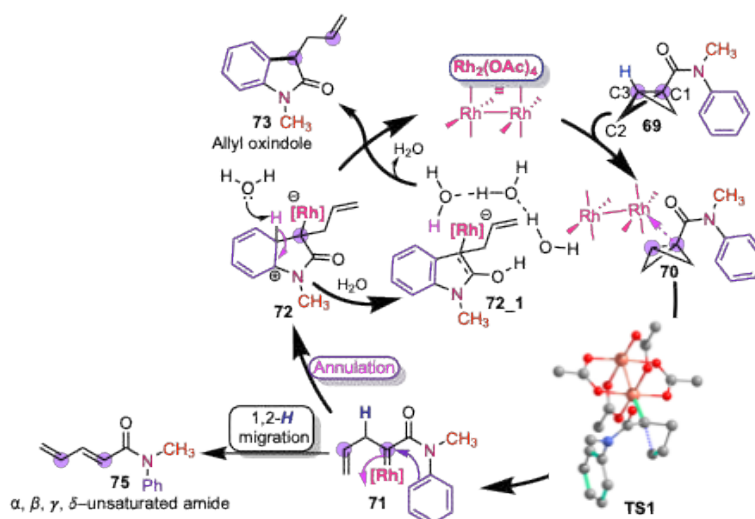


Figure-1: Free energy profile diagram of rhodium-catalyzed $[\text{Rh}_2(\text{OAc})_4]$ with **69** using DFT calculations. (Method: M06/SDD/def2TZVP//B3LYP-D3(BJ)/SDD/def2SVP). Non-essential hydrogen atoms are omitted for clarity.

has a barrier of 30.6 kcal/mol, ruling out the formation of external Rh(II)-carbene intermediate in the present study.

We have proposed the following mechanism based on the control experiments and DFT studies. The high ring-strain energy of BCBs **69** leads to their central C1–C3 σ -bond behaving like an olefin, and the coordination of this C1–C3 σ -bond with the π -acid^{55, 64–67} of Rh₂(OAc)₄ to form the Rh-complex **70** (Scheme 7). The formation of the allyl carboxamide electrophilic Rh(II)-carbene intermediate **71** via **TS1** can be explained by the formation of intermediate **70**, which then triggers cleavage of the C1–C3 σ -bond of *N*-aryl BCB carboxamide **69**. The nucleophilic attack of the arene of *N*-aryl tethered BCB carboxamide to electrophilic Rh(II)-carbene **71** to form the intermediate **72** and then subsequent [1,2]-*H* shuffle with the aid of moisture via intermediate **72_1** to form the corresponding 3-allyl oxindole **73** and then regeneration of the Rh(II)-catalyst. We were unable to locate a transition state for H-shuffle via moisture, even after several attempts to form **72_1** from **72** (see more details in SI). The formation of α , β , γ , δ -unsaturated amide **75** is explained by [1,2]-*H* migration of the in situ-generated allyl Rh(II)-carbene intermediate **71**. To gain deeper insight into the α C–H insertion step for *N*, *N*-dialkyl substituted BCB substrates **48** (Scheme 3), additional DFT calculations were performed using substrate **48a**, as shown in Figure 2. Under our reaction conditions, [1,2]-*H* migration via **TS6** is energetically more favorable than the α -C–H insertion through **TS6'**, both via in situ generated internal Rh(II)-carbene intermediate **78**. The calculations reveal that the α -C–H insertion step lies higher in energy than [1,2]-*H* migration by 8.1 kcal/mol (Figure 2). The formation of terminal Rh(II)-carbene intermediate **78'** uphill task (Figure 2) compared to the internal Rh(II)-carbene intermediate **78**.



Scheme-7: Plausible mechanism

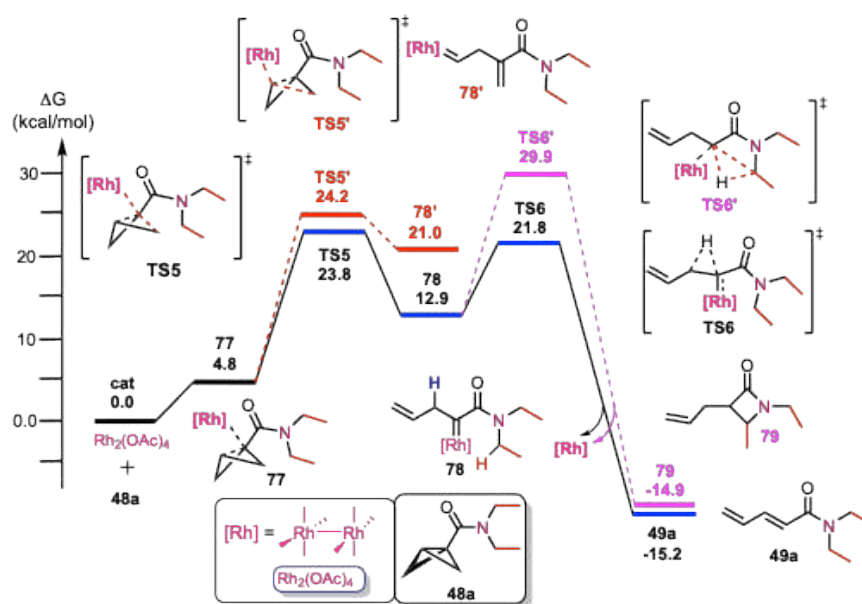


Figure-2: Free energy profiles for the $[\text{Rh}_2(\text{OAc})_4]$ with **48a**. (Method: M06/SDD/def2TZVP//B3LYP-D3(BJ)/SDD/def2SVP).

In conclusion, we have demonstrated Rh(II)-catalyzed transannulation of *N*-aryl bicyclo[1.1.0]butane carboxamides via ring-strain enabled Rh(II)-carbene intermediate. We have shown the in situ generation of a novel class of acceptor carbene precursor, such as allyl carboxamide Rh(II)-carbene from BCB carboxamide, which was explored for the intramolecular transannulation reaction for the efficient synthesis of 3-allyl oxindoles with broad substrate scope, excellent functional group tolerance, and late-stage transannulation of biologically active molecules, yielding up to 87%. We have demonstrated the application of the methodology to the synthesis of biologically active molecules, the synthetic utility of synthetic intermediates for the synthesis of oxindole motifs, and diverse heterocyclic scaffolds. We have also shown the [1,2]-*H* migration to access the α , β , γ , δ -unsaturated amides. In addition, we have demonstrated the formation of a Rh(II)-carbene intermediate via [1,2]-*H* migration, an intramolecular cyclopropanation reaction, and a deuterium-shuffle reaction, providing comprehensive evidence for the proposed mechanism, which is further supported by DFT calculations. This novel allyl carboxamide Rh(II)-carbene precursor will find broad application in synthetic organic chemistry and the synthesis of biologically relevant molecules.

Methods

General procedure for the synthesis of oxindoles.

To an oven dried reaction tube (10 mL) equipped with magnetic stir bar, bicyclobutane-1-carboxamide **1** (0.2 mmol, 1.0 equiv.) and $\text{Rh}_2(\text{OAc})_4$ (1.8 mg, 0.004 mmol, 0.02 equiv.) were added in glove box (argon atmosphere) followed by addition of toluene (0.06 M, 3 mL) under nitrogen atmosphere outside the glove

box and closed the reaction tube with stopper. The reaction mixture was stirred at 120 °C (using an oil bath) for 24 h. The residue was diluted with ethyl acetate (10 mL) and filtered using celite. The solvent was removed under reduced pressure using a rotary evaporator, and the residue was purified by column chromatography on silica gel using ethyl acetate and hexane as eluents.

Data Availability

The X-ray crystallographic data for compounds have been deposited in the Cambridge Crystallographic Data Center (CCDC) under deposition numbers CCDC2487184 (**32**). Characterization data for materials and products, general methods, optimization studies, experimental procedures, mechanistic studies, including DFT calculations, and characterization of new compounds and NMR spectra are available in the Supplementary Information. All data are also available from the corresponding author upon request.

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Author contributions

D.Y. conceived the project. M.S and D.Y. designed the experiments, and M.S. and A.K. performed the experiments. D.Y. and M. V. M. designed the DFT calculations; M. V. M. performed the calculations. All authors contributed to the analysis and interpretation of data. D.Y. wrote the manuscript based on the feedback from the M.S. All the authors approved the final version of the manuscript.

Conflict of interest.

The authors declare no competing interests.

Figure Legends/Captions (For Main Text Figures)

Scheme-1. Reactivity of bicyclo[1.1.0]butanes [BCBs]. (A) Synthesis of bicyclopentanes (BCPs). (B) Synthesis of skipped dienes. (C) Metallocarbene generation via C-C bond cleavage. (D) Rhodium (II)carbene generation from BCBs. (E) Rh(I)-Catalyzed mono- & bis-phosphine ligands controlled cycloisomerization of BCBs. (F) Rh (II)-Catalyzed transformations of N-aryl BCB carboxamide via rhodium (II)carbene.

Table-1. Optimization Table. ^aReaction conditions: **1a** (0.1 mmol), Rh₂(OAc)₄ (2 mol%), Toluene (0.06 M), 120 °C, 24 h. ^bYield determined by ¹H NMR using CH₂Br₂ as an internal standard. ^cIsolated yield for 0.2 mmol. ND = not detected. NR = no reaction.

Scheme-2. Substrate Scope. (a) aryl substitution scope. (b) *N*- substitution scope. (c) Late-stage transannulation. Reaction Condition; **1** (0.2 mmol, 1.0 equiv.), Rh₂(OAc)₄ (2 mol%), Toluene (3.0 mL, 0.06 M), 120 °C, 24 h.

Scheme-3. Synthesis of α , β , γ , δ -unsaturated amides via [1,2]-*H* migration. Reaction Condition; **48** (0.2 mmol, 1.0 equiv.), Rh₂(OAc)₄ (2 mol%), Toluene (3.0 mL, 0.06 M), 120 °C, 24 h.

Scheme-4. Biologically active molecule synthesis. Reaction Condition; **50** or **53** (0.2 mmol, 1.0 equiv.), Rh₂(OAc)₄ (2 mol%), Toluene (3.0 mL, 0.06 M), 120 °C, 24 h.

Scheme-5. Synthetic application. Reaction conditions; (1) **1** (2 mmol, 1.0 equiv.), Rh₂(OAc)₄ (2 mol%), Toluene (30 mL, 0.06 M), 120 °C, 24 h. (2) (a) KHMDS (1.5 equiv.), phenyl/ allyl chloroformate (1.5 equiv.), THF, -78 °C, 3 h. (b) FeCl₃·6H₂O (5 mol%), N₂H₄·H₂O (2.0 equiv.), EtOH, rt, 12 h. (c) 9-BBN (4.0 equiv.), THF, rt, 12 h then MeOH, 4 M NaOH (1 mL) 30% H₂O₂ (1 mL), 0 °C, 1 h (d) Methyl bromoacetate/allyl bromide (1.5 equiv.) *n*-BuLi (1.5 equiv.), TMEDA (1.5 equiv.), THF, -78 °C to rt, 12 h. (e) TBAF (0.2 equiv.), THF, rt, 1 h. (f) DIPEA (3.0 equiv.), Thionyl chloride (1.5 equiv.), DCM, rt, 1 h. (g) Allyl bromide (1.0 equiv.), TBAI (3.0 equiv.), NaOH, DCM, rt, 20 h. (h) Grubbs 2nd generation cat. (5 mol%), DCM, rt, 6 h. (i) AllylMgBr (1.5 equiv.), THF, rt, 3 h. (j) *m*CPBA (2.0 equiv.), NaHCO₃ (1.5 equiv.), DCM, rt, 12 h.

Scheme-6. Mechanistic insights. Reaction conditions; (A) **66** (0.1 mmol, 1.0 equiv.), Rh₂(OAc)₄ (2 mol%), Toluene (1.5 mL, 0.06 M), 120 °C, 24 h. (B) (i) D₅-**1** (0.2 mmol, 1.0 equiv.), Rh₂(OAc)₄ (2 mol%), Toluene (3.0 mL, 0.06 M), 120 °C, 24 h. (ii) D₅-**1** (0.2 mmol, 1.0 equiv.), D₂O (0.06 mmol, 3.0 equiv.), Rh₂(OAc)₄ (2 mol%), Toluene (3.0 mL, 0.06 M), 120 °C, 24 h. (iii) **1** (0.1 mmol, 1.0 equiv.), D₅-**1** (0.1 mmol, 1.0 equiv.), Rh₂(OAc)₄ (2 mol%), Toluene (1.5 mL, 0.06 M), 120 °C, 4 h. (iv) **2** (0.1 mmol, 1.0 equiv.), D₂O (0.03 mmol, 3.0 equiv.), Rh₂(OAc)₄ (2 mol%), Toluene (1.5 mL, 0.06 M), 120 °C, 24 h. (C) Hammett study. (D) ¹²C/¹³C KIE

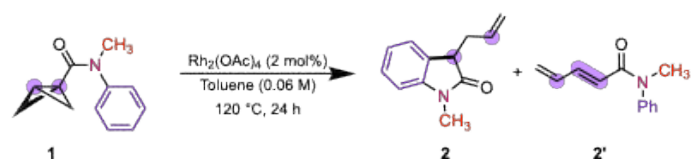
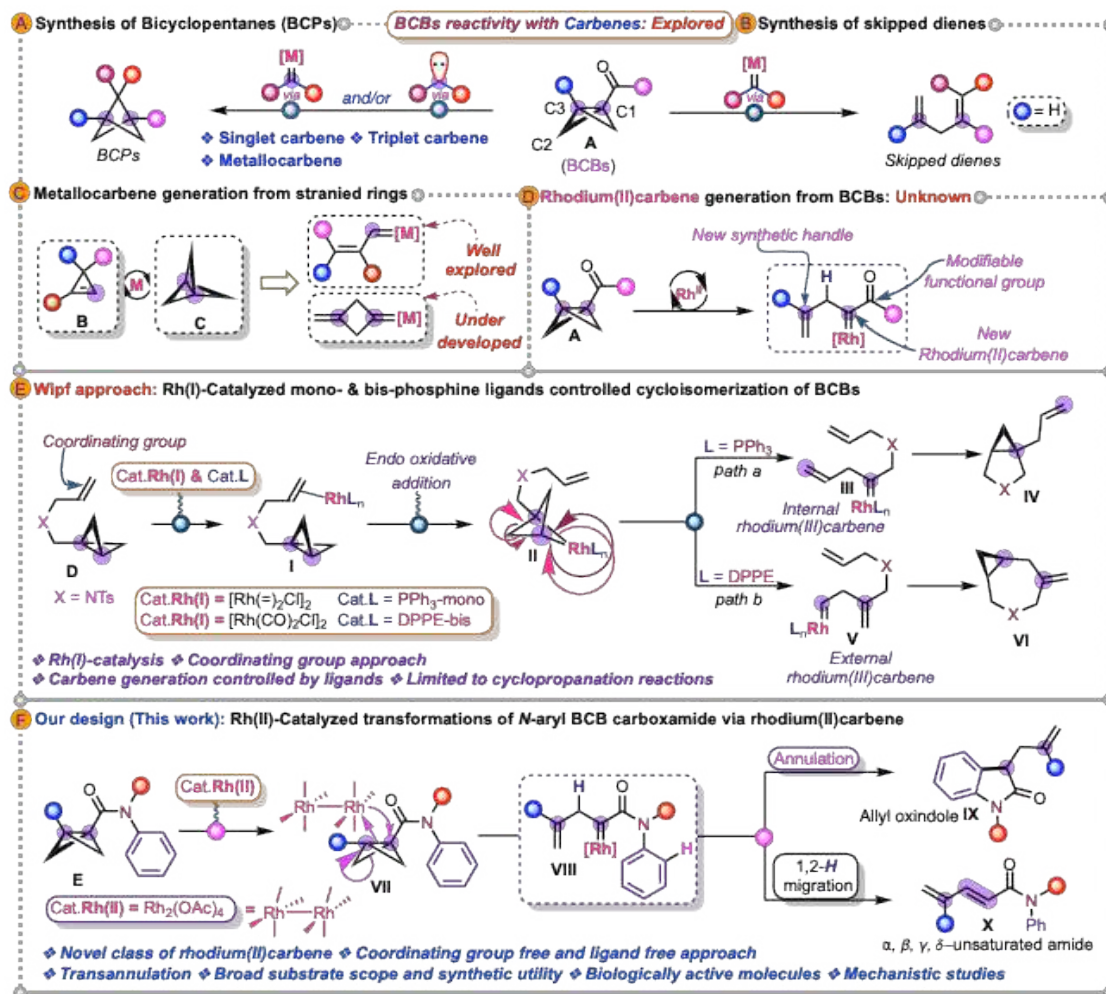
Figure-1: Free energy profile diagram of rhodium-catalyzed [Rh₂(OAc)₄] reaction using DFT calculations. (Method: M06/SDD/def2TZVP//B3LYP-D3(BJ)/SDD/def2SVP). Non-essential hydrogen atoms are omitted for clarity.

Scheme-7. Plausible mechanism.

Figure-2: Free energy profiles for the [Rh₂(OAc)₄] with **48a**. (Method: M06/SDD/def2TZVP//B3LYP-D3(BJ)/SDD/def2SVP).

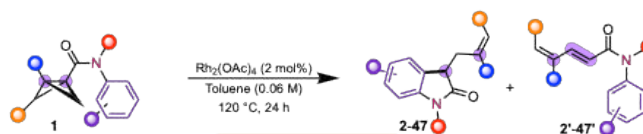
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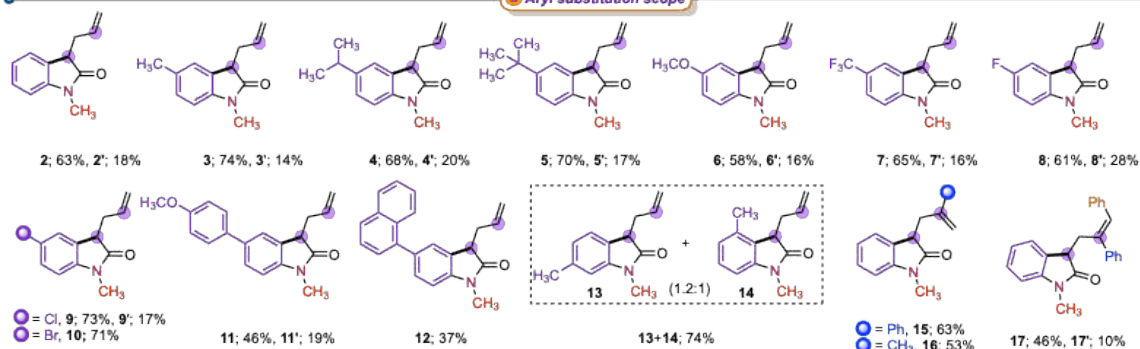


Entry	Deviation from standard	Yield of 2 (%) ^b	Yield of 2' (%) ^b
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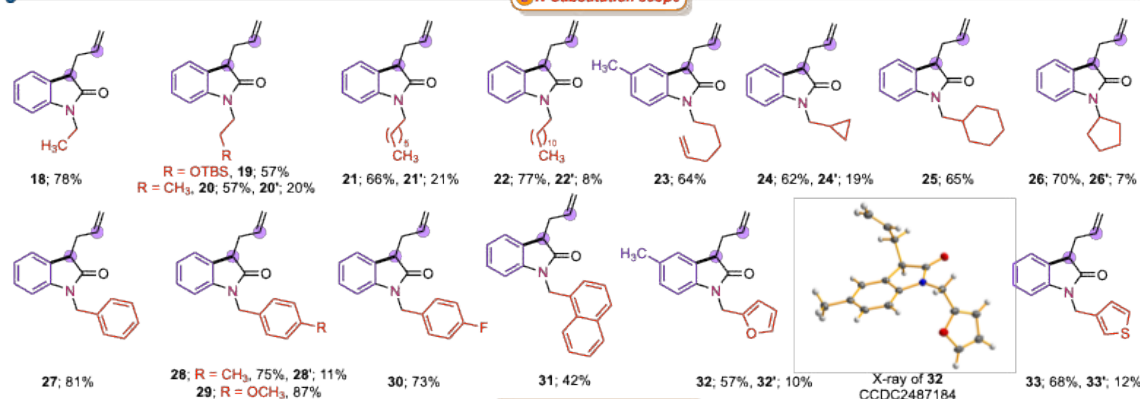
1	None	66 (63)^c	24 (18)^c
2	Rh ₂ (esp) ₂ in lieu of Rh ₂ (OAc) ₄	28	24
3	Rh ₂ (Oct) ₄ in lieu of Rh ₂ (OAc) ₄	38	32
4	Rh ₂ (TFA) ₄ in lieu of Rh ₂ (OAc) ₄	12	8
5	Cu(OTf) ₂ in lieu of Rh ₂ (OAc) ₄	14	12
6	[Rh(CO) ₂ Cl] ₂ , DPPE (4 mol%) in lieu of Rh ₂ (OAc) ₄	ND	ND
7	Without Rh ₂ (OAc) ₄	ND	ND
8	110 °C in lieu of 120 °C	60	24
9	150 °C in lieu of 120 °C	54	22
10	40, 60 and 80 °C in lieu of 120 °C	NR	NR



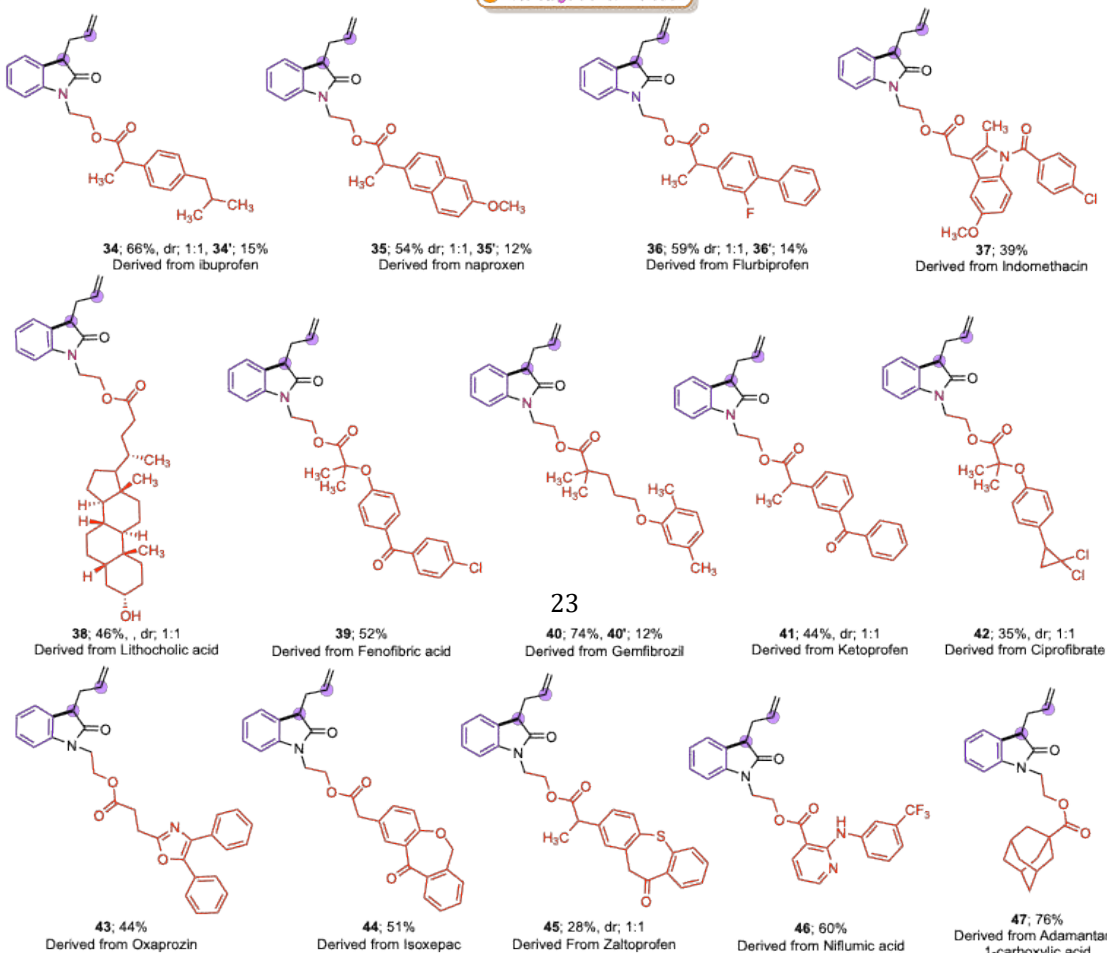
Aryl substitution scope



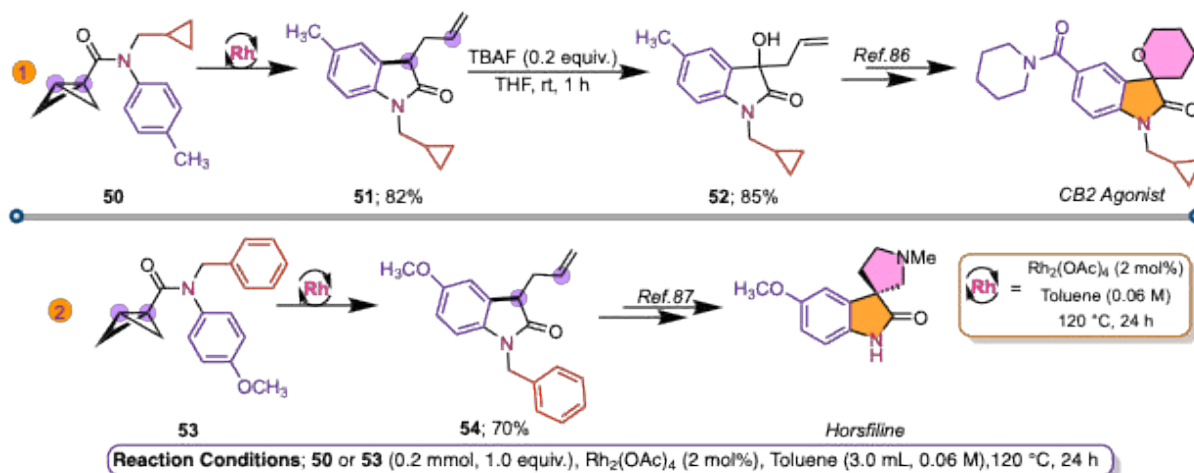
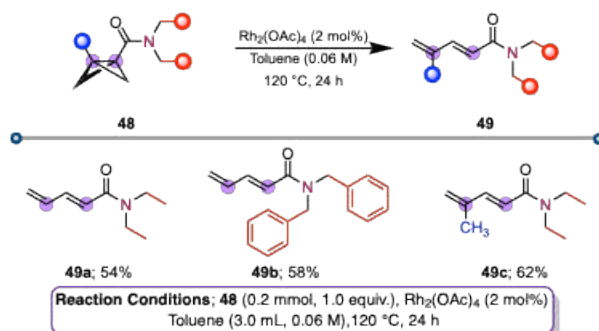
N-Substitution scope

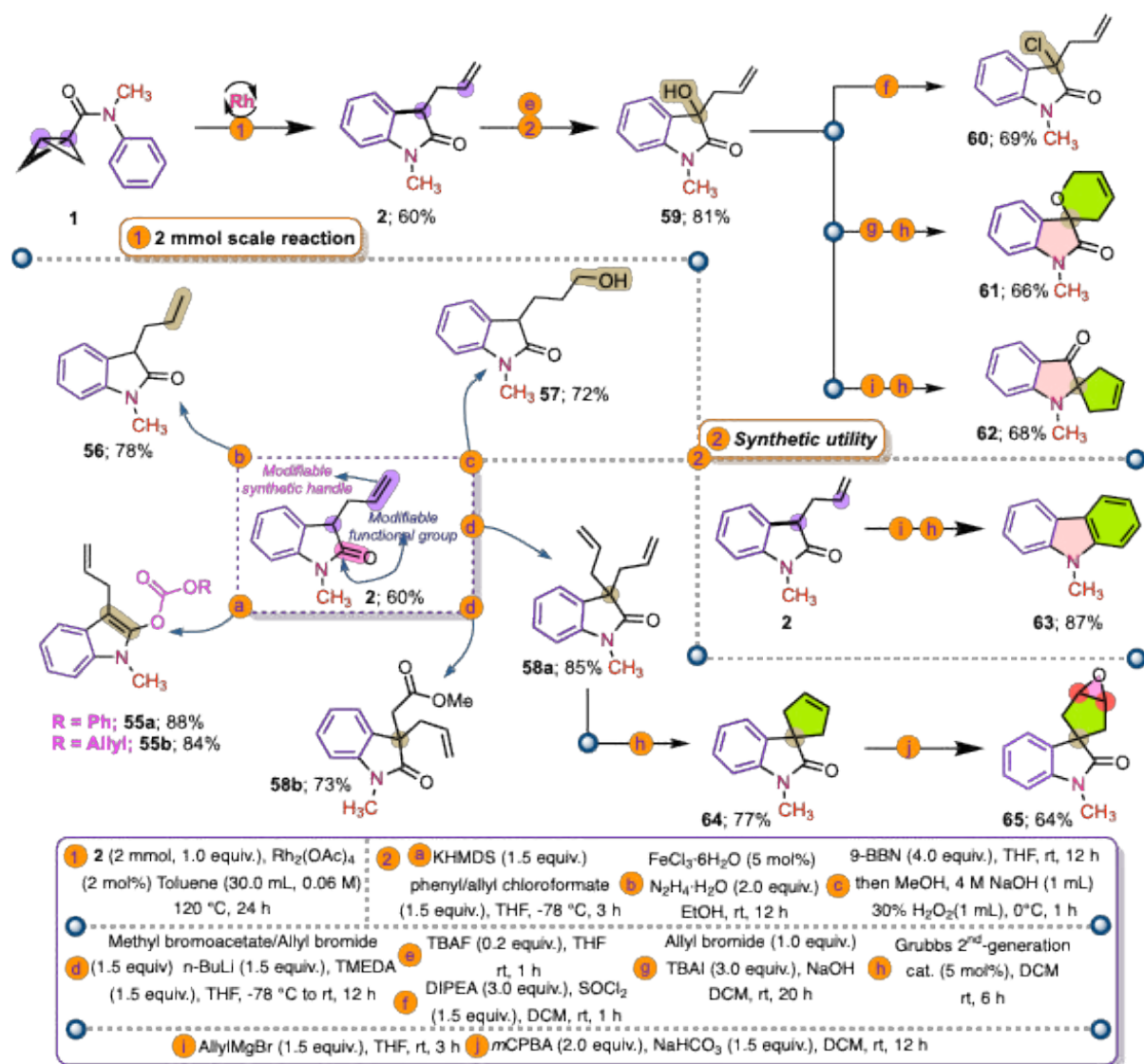


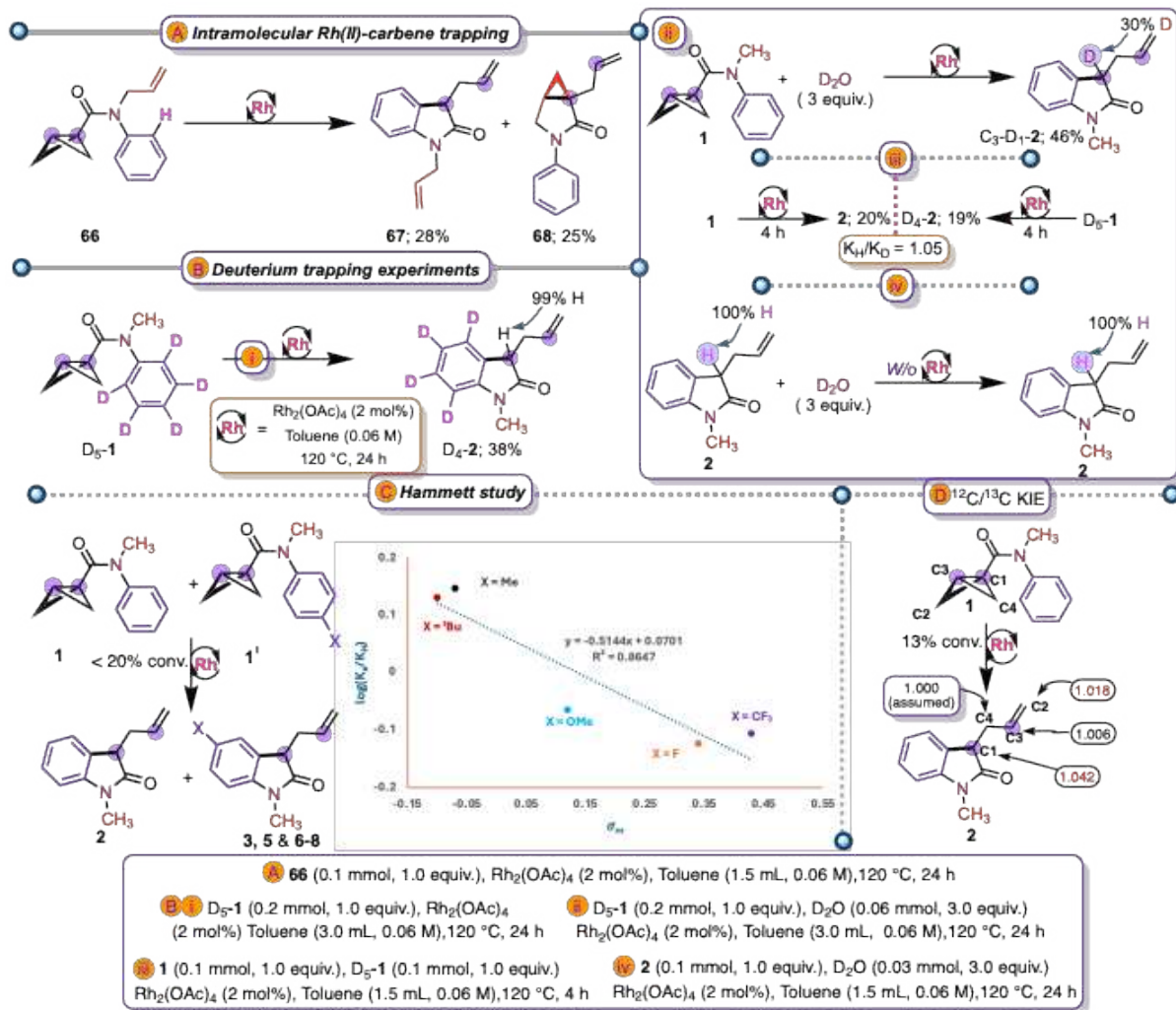
Late-stage transannulation

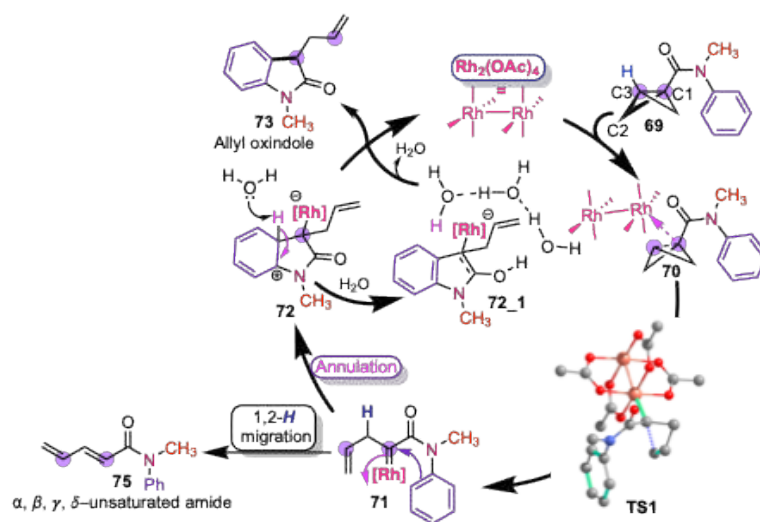
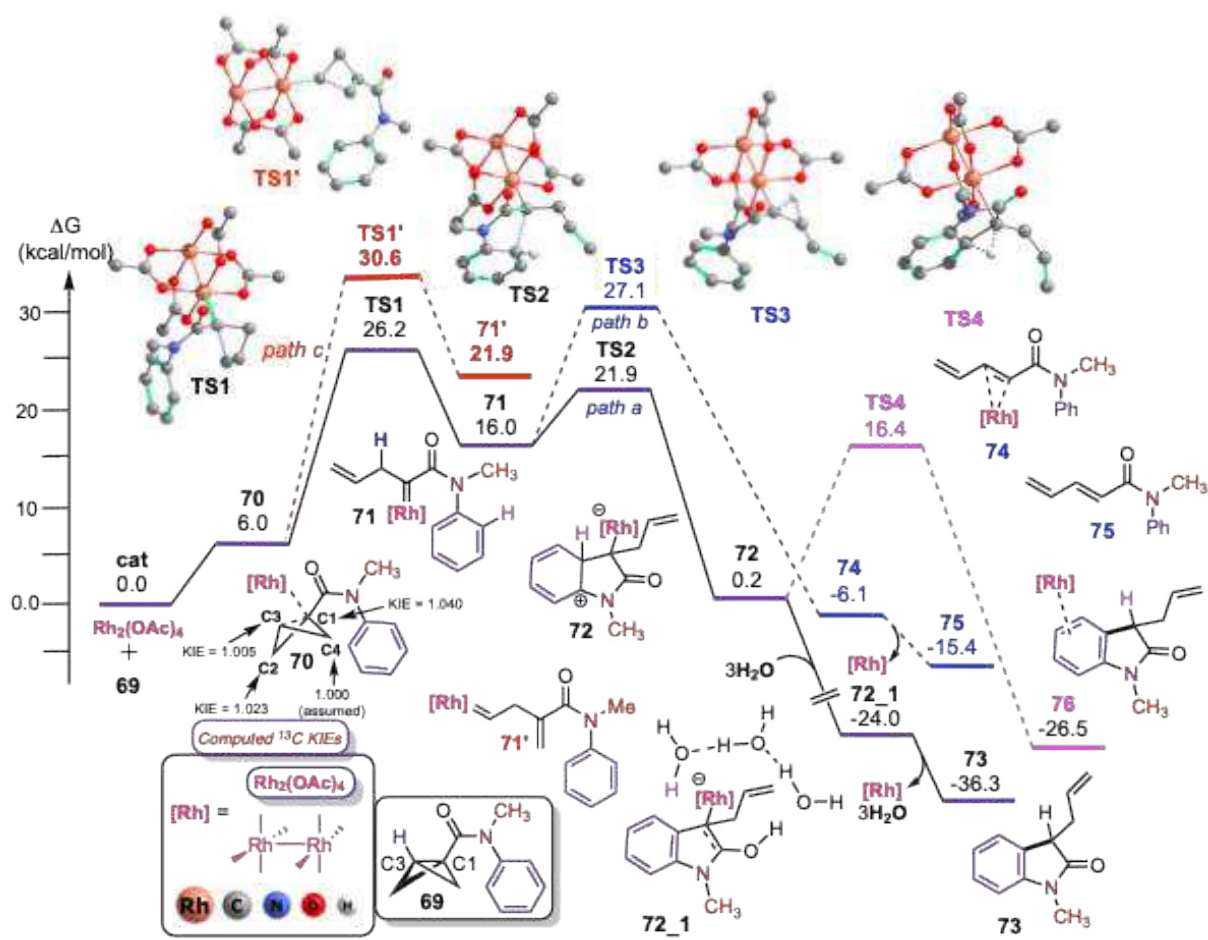


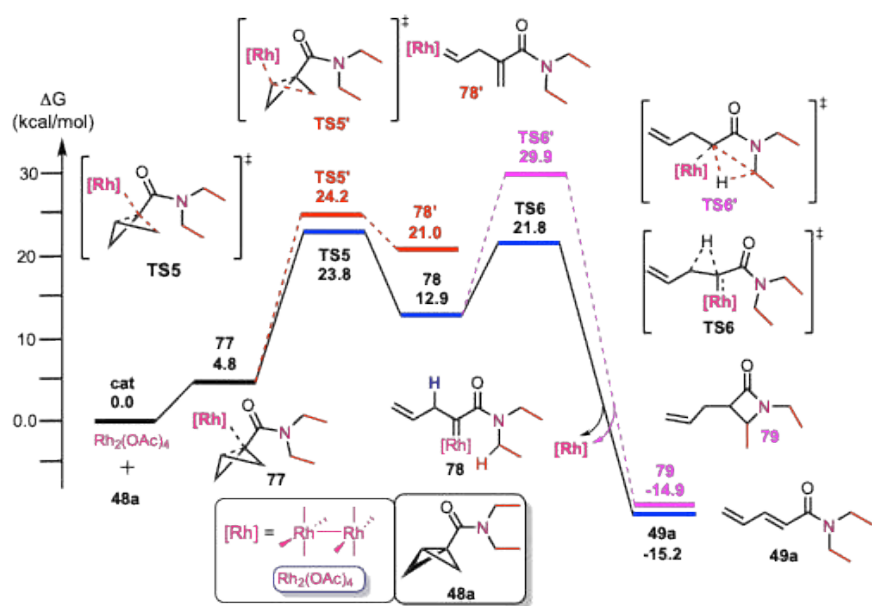
Reaction Conditions: **1** (0.2 mmol, 1.0 equiv.), $\text{Rh}_2(\text{OAc})_4$ (2 mol%), Toluene (3.0 mL, 0.06 M), 120 °C, 24 h











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