C–C Activation

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Intermolecular [5+2] Annulation between 1-Indanones and Internal Alkynes by Rhodium-Catalyzed C–C Activation

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Dedicated to Professor Robert H. Grubbs on the occasion of his 80th birthday

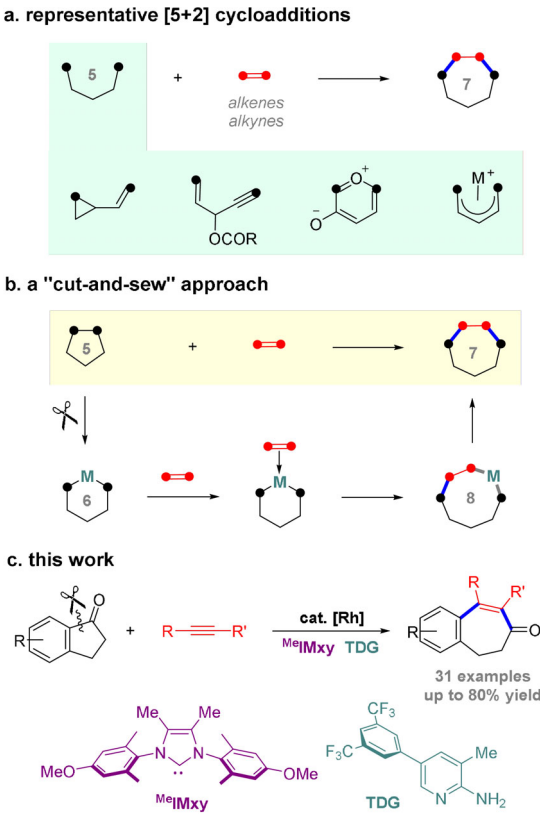
Abstract: *Herein, we report a [5+2] cycloaddition between readily accessible 1-indanones and internal alkynes through Rh-catalyzed activation of less strained C–C bonds. The reaction is enabled by a strongly σ-donating NHC ligand and a carefully modified temporary directing group. A wide range of functional groups is tolerated, and the method provides straightforward access to diverse benzocycloheptenones that are hard to access otherwise. DFT studies of the reaction mechanism imply the migration insertion as the turnover-limiting step and suggest beneficial π–π interactions in the transition states.*

Introduction

Seven-membered carbocycles are prevalent in natural products and other biologically important molecules.[1] They also frequently appear in emerging non-planar organic materials.[2] Compared to five or six-membered rings, significant challenges remain for synthesizing medium-sized cycloheptanes due to limited disconnection approaches and increased activation enthalpy during the ring-forming processes. Among established seven-membered-ring construction methods,[3] formal [5+2] cycloadditions-the annulations between a five-carbon synthon and a two-carbon one-have proved to be highly versatile and effective (Scheme 1a).[4] They render multiple C–C bond formations in one step in an atom-economical,[3] regio- and stereo-selective manner, and have found wide success in elegant syntheses of complex natural products.[4] While the two-carbon synthons generally come from readily available alkenes and alkynes, the corresponding five-carbon moieties, such as vinylcyclopropanes,[5] (oxido)pyrylium ions,[6] 3-acyloxy-1,4-enynes[7] and pentadienyl-metal complexes,[8] are less accessible, which typically contain high-energy or special functional groups (FGs) and need to be prepared through multi-step sequences. Thus, it could be attractive to use common, more native FGs as the five-carbon building blocks in constructing seven-membered carbocycles.

One complementary and straightforward [5+2] approach would be to directly employ an easily accessible five-membered ring as the synthon.[9] One can imagine that, through oxidative addition with a low-valent transition metal, the relatively inert C–C bond in a five-membered ring is cleaved and converted into two reactive C-M (M = transition metal) termini, which then add across unsaturated 2π-units to provide a 7-membered carbocycle (Scheme 1b).[10] Such so-called a "cut-and-sew" strategy has shown good efficiency with three- or four-membered-ring substrates.[11,12] It was only until recently that a preliminary study on the catalytic insertion of ethylene gas into 1-indanone C–C bonds was reported by us.[13] This transformation provides a benzene-fused cycloheptanone in a rapid and byproduct-free manner; however, it requires high-pressure ethylene gas and other alkenes were not effective at this stage, which hampers forming α- or β-substituted products. In addition, mechanistic understanding of this C–C activation method remains elusive.

Hence, we conceived exploring alkynes as the coupling partner in the C–C activation-mediated [5+2] cycloaddition for preparing α- or β-substituted seven-membered-ring ketones. In contrast to alkenes, alkynes with a smaller HOMO/



Scheme 1. [5+2] reactions for constructing seven-membered carbocycles.

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LUMO gap typically show high coordination affinity with transition metals, which could ease 2π-insertion.[14] Besides, the resulting enone moiety can provide a convenient handle to permit further functionalizations of the products. However, compared to the prior ethylene insertion, substantial challenges can be envisioned for using alkynes as the 2π-units in an intermolecular [5+2] cycloaddition: 1) due to the high reactivity of the triple bond, alkynes easily undergo various catalyzed dimerization or trimerization pathways;[15] 2) the strong binding affinity of alkynes will compete with the C–C σ-bond coordination to the metal center, which is the key intermediate for C–C activation; and 3) the bulkiness of internal alkynes (versus simple ethylene) during the steric demanding carbometallation step cannot be overlooked. Herein, we describe the development of a catalytic intermolecular [5+2] cycloaddition between 1-indanones and internal alkynes and show how the aforementioned challenges could be addressed through careful selection of ligands and temporary directing groups (TDGs) (Scheme 1c). Furthermore, computational studies have been carried out to provide useful information about the reaction mechanism and reveal important roles of the π–π ligand/substrate interactions in this transformation.

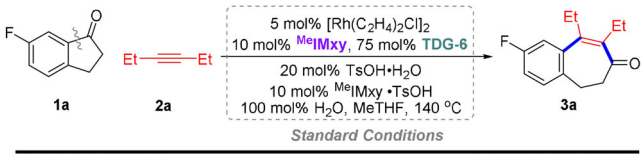
Results and Discussion

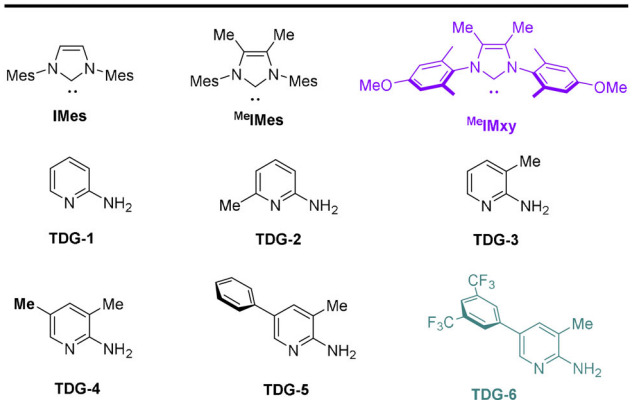
Our study started with using 6-fluoro-1-indanone (**1a**) and 3-hexyne (**2a**) as the model substrates (Table 1). After an extensive survey of various reaction parameters, the desired [5+2] product **3a** was obtained in 80% isolated yield (entry 1), using 5 mol% $[Rh(C_2H_4)_2Cl]_2$, 10 mol% ^{Me}IMxy, 75 mol% **TDG-6**, 20 mol% TsOH·H_2O, 10 mol% ^{Me}IMxy·TsOH and 100 mol% H_2O in 2-methyltetrahydrofuran (MeTHF). Control experiments showed that both the Rh catalyst and the TDG are essential to this reaction (entries 2 and 3). Given the important role of TDG in activation of less strained C–C bonds,[16] different TDGs were then examined (entries 4–8). While simple 2-aminopyridine (**TDG-1**)[17] or 2-amino-6-methylpyridine (**TDG-2**) proved ineffective, the 3-substituted aminopyridines were found to greatly enhance the reactivity (entries 4–6). Further improvement was observed when having an additional substituent at the C5 position (entries 7 and 8); ultimately, the optimal **TDG-6** was identified with an electron-deficient 3,5-ditrifluoromethylphenyl group.[18] Reducing the TDG loading decreased the yield to some extent (entry 9).

The reaction can proceed in the absence of the *N*-heterocyclic carbene (NHC) ligand (entry 10), suggesting that $[Rh(C_2H_4)_2Cl]_2$ alone can catalyze the "cut-and-sew" reaction, albeit in lower efficiency. Compared with the more electron-rich ^{Me}IMxy ligand, IMes and ^{Me}IMes gave slightly lower yields. TsOH was indispensable to this transformation (entry 13), which is anticipated to promote forming the key ketimine intermediate. The addition of H_2O increased the reaction efficiency (entry 14), possibly by accelerating the hydrolysis of the 7-membered-ring ketimine product to minimize side reactions.[13] Notably, the ^{Me}IMxy·TsOH additive proved beneficial (entry 15), and the effect was more evident for more challenging substrates (see Supporting Information, Scheme S2). Other solvents besides MeTHF, such as toluene and 1,4-dioxane, were less effective (entries 15 and 16). Finally, somewhat lower yields were obtained when running the reaction at lower temperature or in a shortened period (entries 17–20).

With the optimized conditions in hand, the substrate scope was then studied (Scheme 2).[19] Both the electron-withdrawing (**3b–g**) and -donating groups (**3h–3k**) at the C6-position of 1-indanones were tolerated. In the presence of other carbonyl moieties, such as linear ketone or ester (**3d**, **3e**), the C–C activation selectively took place on the indanone ring. Relatively reactive FGs, including ester (**3d**), ketone (**3e**), benzyl ether (**3g**), alkene (**3j**), trimethylsilyl (**3k**), thienyl (**3l**), cyano (**3m**), and amide (**3n**), were compatible in this transformation. 1-Indanones with substituents at the C5

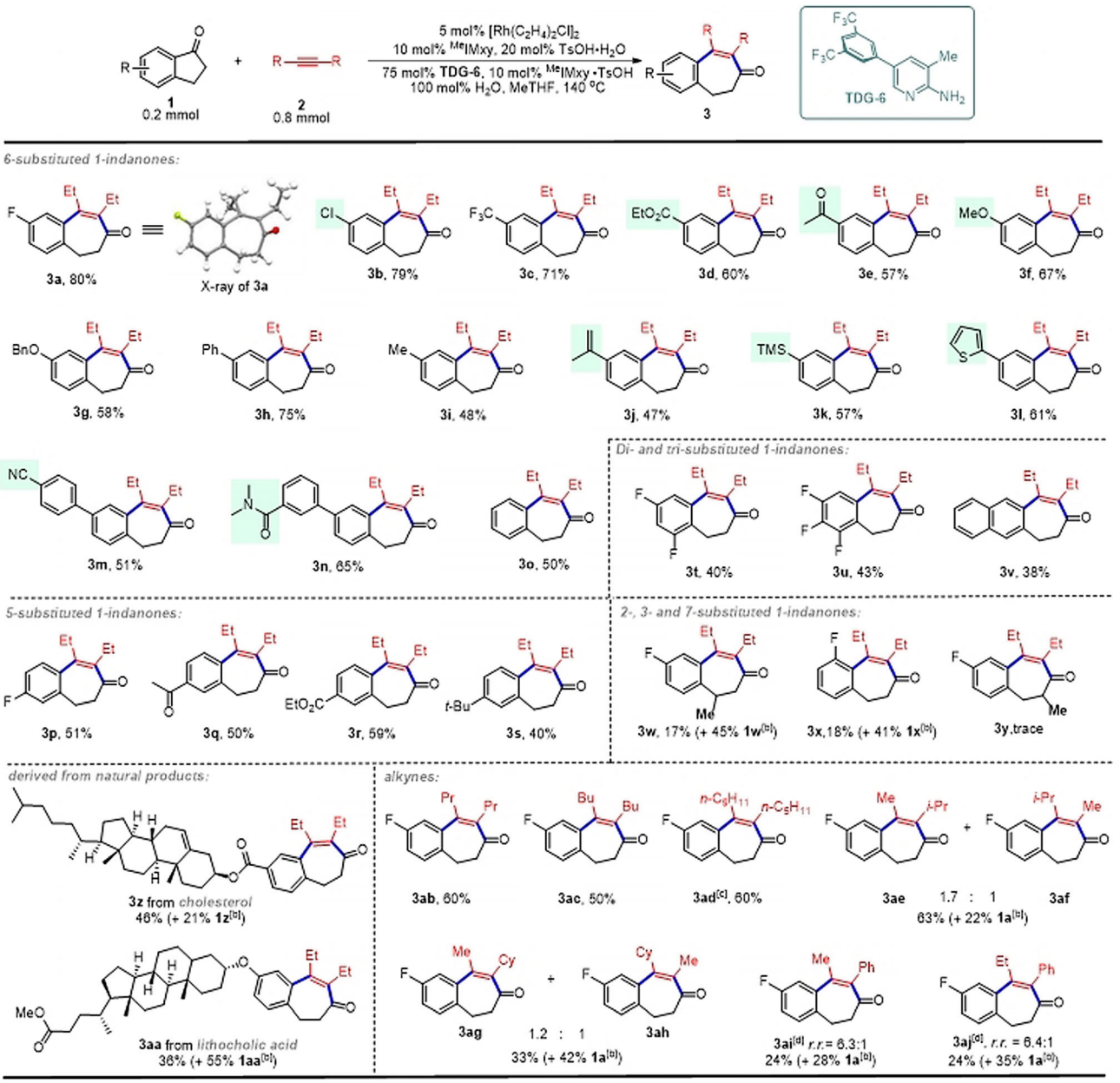
Table 1: Selected optimization of the [5+2] reaction.[a]





Entry	Variation	Yield[b]	Entry	Variation	Yield[b]
1	none	82%(80%[d])	11	IMes instead of ^{Me}IMxy[c]	69%
2	w/o $[Rh(C_2H_4)_2Cl]_2$	<5%	12	^{Me}IMes instead of ^{Me}IMxy[c]	76%
3	w/o TDG-6	<5%	13	w/o TsOH·H_2O	<5%
4	TDG-1 instead of TDG-6	trace	14	w/o H_2O	56%
5	TDG-2 instead of TDG-6	trace	15	w/o ^{Me}IMxy·TsOH	78%
6	TDG-3 instead of TDG-6	46%	16	toluene instead of MeTHF	57%
7	TDG-4 instead of TDG-6	48%	17	1,4-dioxane instead of MeTHF	47%
8	TDG-5 instead of TDG-6	61%	18	130°C	60%
9	50 mol% TDG-6	53%	19	24 h	51%
10	w/o ^{Me}IMxy[c]	36%	20	48 h	73%

[a] All the reactions were run with 0.2 mmol of **1a**, 0.8 mmol of **2a**, 0.15 mL MeTHF in a 4 mL vial at 140°C for 72 h. [b] Yields were determined by ^{1}H-NMR analysis of the crude mixture with 1,1,2,2-tetrachloroethane as the internal standard. [c] Without 10 mol% ^{Me}IMxy·TsOH as the additive. [d] Isolated yield.



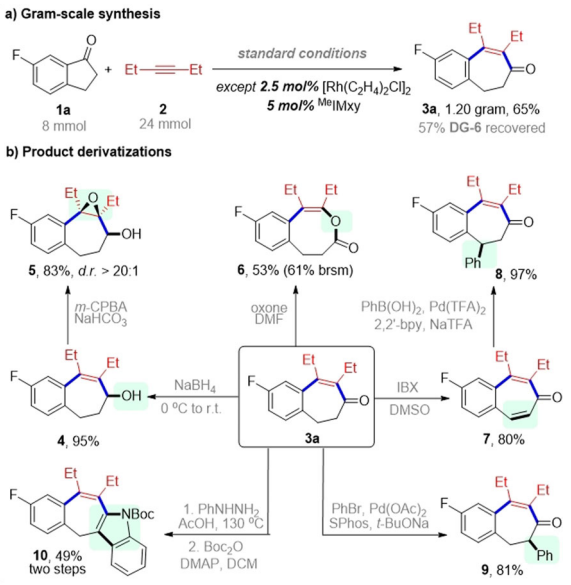
Scheme 2. Scope of the [5+2] reaction[a] [a] Unless otherwise mentioned, all reactions were carried out on 0.2 mmol scale in 72 h under the standard conditions. [b] Conversions were determined by ^{1}H-NMR with 1,1,2,2-tetrachloroethane as the internal standard. [c] 2 equiv of the alkyne **2d** was added first before another 2 equiv of **2d** was added after 6 h. [d] The reactions were run under 160 °C.

(**3p**, **3q**, **3r**, **3s**) or C4 positions (**3t**, **3u**) and the one derived from naphthalene (**3v**) were also competent substrates. More steric demanding substrates with either the C3 (**3w**) or C7 (**3x**) substitution gave much lower conversion, and the C2 substituted indanone (**3y**) was probably too bulky to react. More complex substrates, for instance, those derived from cholesterol (**3z**) and lithocholic acid (**3aa**) reacted smoothly to deliver the desired ring-expansion products. Notably, comparing to 1-indanones, saturated cyclopentanone was not reactive under the current conditions (see DFT calculations below).

Regarding the scope of the alkyne coupling partners, the reaction worked well for alkynes with different alkyl substituents (**3ab**–**3ad**). When unsymmetrical alkynes were employed, the reaction moderately favored forming the products with the bulkier substituent at the α-position (**3ae**–**3ah**). Interestingly, while diaryl-substituted alkynes did not provide the desired products (with 1-indanone substrates mostly recovered probably owing to increased steric hindrance on alkynes), the mono-aryl-alkynes were reactive with good regioselectivity, albeit in lower yields (**3ai**–**3aj**). Terminal alkynes were not suitable under the current conditions, which only led to alkyne trimerization byproducts with 1-

indanones mostly recovered.[20] Efforts of further improving alkyne compatibility are underway in our laboratory.

To show synthetic utility of this method, first, a gram-scale reaction with a reduced catalyst loading provided ring-expanded product **3a** in 65% yield with 57% of **TDG-6** recovered (Scheme 3a). The benzocycloheptenone product



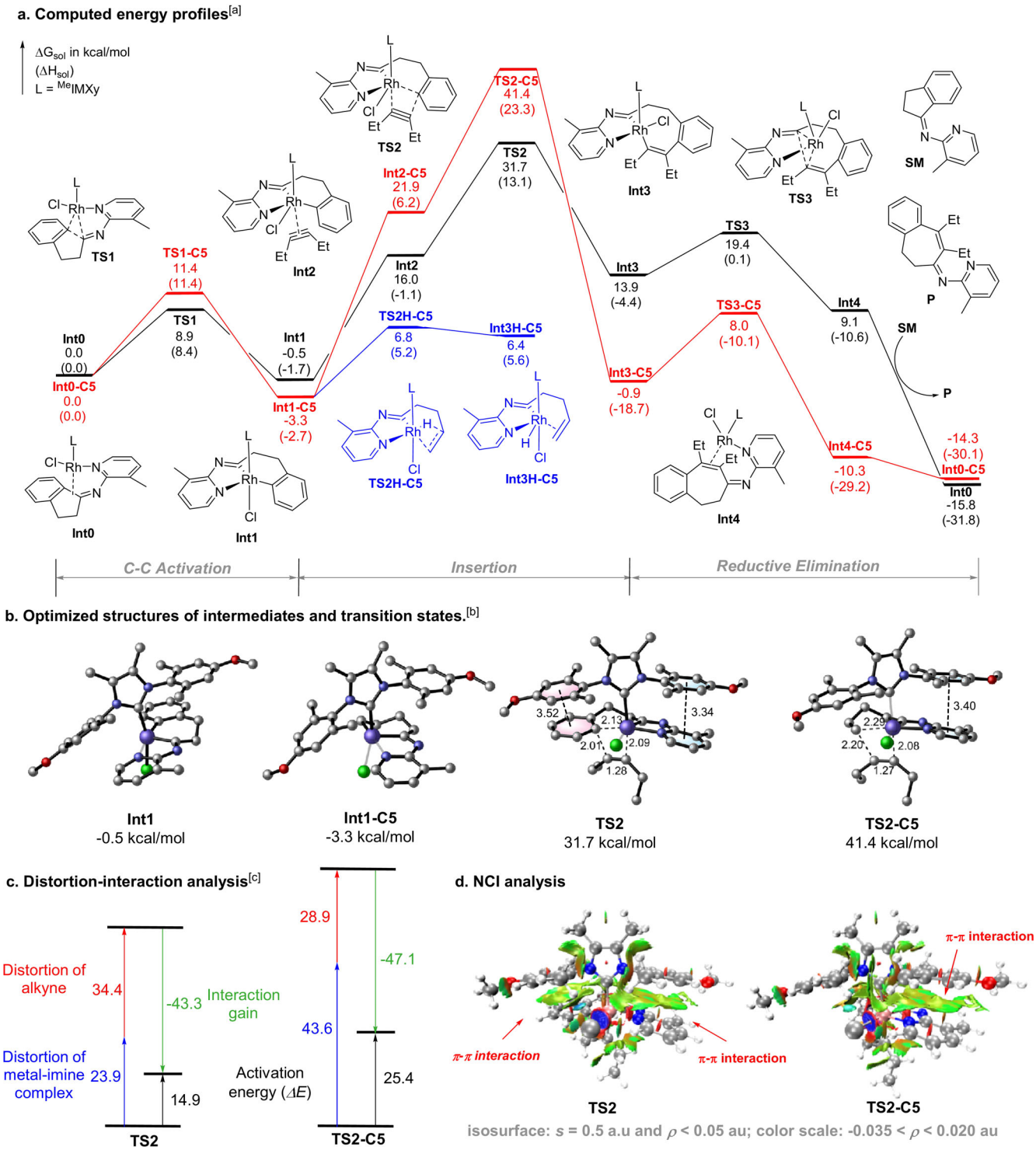
Scheme 3. Synthetic applications.

can readily undergo various transformations to access diverse structural motifs (Scheme 3b). For example, direct reduction with $NaBH_4$ gave allylic alcohol **4** in 95% yield, which can be transformed to epoxide **5** in excellent diastereoselectivity. Baeyer–Villiger oxidation with oxone[21] as the oxidant selectively gave the 8-membered-ring vinyl migration product (**6**). When IBX was used as the oxidant, the dehydration product **7** was isolated in 80% yield,[22] which further underwent the Pd-catalyzed conjugated addition to deliver the β-arylation product (**8**) in almost quantitative yield.[23] The α-arylation was smoothly realized with a Pd catalyst and Buchwald ligand (**9**).[24] Hence, both the α and β positions of the benzocycloheptenone can be efficiently functionalized. Finally, an interesting 6-7-5-6 tetracyclic compound (**10**) was obtained after subjecting **3a** to the Fischer-indole synthesis.

Finally, DFT calculation was performed to gain insights into the reaction mechanism (Scheme 4). **TDG-3** was employed instead of **TDG-6** to simplify the calculation process with limited computational resources. First, starting from the imine intermediate (**Int0**) derived from 1-indanone and **TDG-3** (see Supporting Information, Section 7.4), the C–C activation step (**TS1**) is rather facile with an activation barrier of 8.9 kcal mol^{-1} and the resulting six-membered rhodacycle **Int1** is slightly exergonic by 0.5 kcal mol^{-1}, indicating possible equilibrium between **Int0** and **Int1**. The following alkyne coordination gives an 18-electron closed-shell complex **Int2**, which is endergonic by 16.5 kcal mol^{-1}. The enhanced energy of the alkyne-coordinated complex is likely due to the increased steric repulsion between the NHC ligand and the equatorial ligands (i.e. the aryl and pyridyl groups). The subsequent migration insertion (**TS2**) was found to be the turnover-limiting step (TLS), with an activation barrier of 32.2 kcal mol^{-1}. The subsequent reductive elimination and catalyst regeneration are straightforward, and the overall process is thermodynamically favored by 15.8 kcal mol^{-1}, therefore driving the reaction to completion.

To understand why the reaction works well with 1-indanones but not with saturated cyclopentanones, the pathway for simple cyclopentanone was also computed and compared (Scheme 4, red). The C–C activation step for cyclopentanone is analogous to that of 1-indanone, while the migration-insertion step shows significant difference. The alkyne coordination is strongly disfavored, and the intermediate (**Int2-C5**) is 5.9 kcal mol^{-1} less stable than the corresponding one with 1-indanone. As such, the activation energy of the 2π-insertion step (44.7 kcal mol^{-1}) is much higher. On the other hand, as a side reaction, the β-hydrogen elimination (the blue pathway, Scheme 4a) exhibits a low barrier, though the product **Int3H-C5** is 9.7 kcal mol^{-1} uphill. In addition, distortion-interaction analysis of the 2π-insertion transition states (TSs) reveals that even with a much earlier TS (the forming C–C bond is 2.01 Å in **TS2** but 2.20 Å in **TS2-C5**), the distortion energy of the metal-imine complex in **TS2-C5** is still 19.7 kcal mol^{-1} higher than that in **TS2** (Scheme 4c). This could account for *the major* reactivity difference between the two substrates. Further distortion/interaction analysis along the intrinsic reaction coordinate (IRC) indicates that the difference mainly arises from the alkyne coordination instead of the migratory insertion step (see Supporting Information Figure S1 for details).

To gain deeper understanding of the TLS, the structures before and after alkyne coordination were carefully reexamined. As shown in Scheme 4b, before alkyne coordination (**Int1**), the chloride stays at the axial position with the NHC ligand bending towards the equatorial position to minimize unfavored steric repulsion with the imine backbone. However, in **Int2** and **TS2**, with alkyne being a much larger ligand, the chloride has to occupy an equatorial position instead, which leads to distortion of the NHC ligand to adopt a more sterically encumbered conformation. In the case of 1-indanone, one aryl ring of the NHC ligand happens to be at slipped parallel geometry with the phenyl group of 1-indanone. The centroid distance between these two aromatic rings is only 3.52 Å, thus indicating a strong π–π interaction that could partially offset the steric repulsion caused by the alkyne coordination.[25] The existence of "double π–π interactions" between the two NHC aryls and the aromatic moieties of 1-indanone and 2-aminopyridine, respectively, in this key TS was further substantiated by non-covalent interaction (NCI) analysis (Scheme 4d).[26,27] The large green areas represent weak van der Waals attractions between the arenes. For comparison, the corresponding reaction with cyclopentanone lacks stabilization by such "double π–π interactions", therefore resulting in a much higher barrier.[28,29]



Scheme 4. DFT calculations. [a] Computed energy profiles at ωB97X-V/def2-TZVPP/SMD(THF)//B3LYP-D3(BJ)/SDD-6-31G(d) level of theory. The reaction pathway of 1-indanone **1o** is shown in black. The reaction pathway of cyclopentanone is shown in red and blue, and their structures are omitted for clarity. [b] Distances are in angstroms. [c] Energies are in kcal mol^{-1}. NCI: non-covalent interaction.

Conclusion

We have disclosed a new intermolecular [5+2] cycloaddition strategy between 1-indanones and internal alkynes through the Rh-catalyzed C–C activation, which provides a straightforward access to benzocycloheptenones containing tetrasubstituted olefins. The reaction is scalable, redox-neutral, and chemoselective. Diverse structures can be obtained through derivatizing the enone products. The mechanistic insights gained through detailed DFT studies should shed light on future reaction development and better catalyst design. Efforts on expanding the reaction scope and

enhancing the reaction efficiency with new catalyst design are ongoing.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: [5+2] annulation · C–C activation · ketones · seven-membered rings · π–π interactions

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[18] The 5-substituent on **TDG**s appears to slow down the undesired alkyne trimerization side reaction. For a detailed study, see Supporting Information, Scheme S4.

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[29] The exact reason for the higher reactivity of 6-fluoro-1-indanone (**1a**), in contrast to non-substituted (**1o**) or 5-fluoro-1-indanones (**1p**), remains unclear. It is possible that, comparing to **1o**, the non-bulky and electron-withdrawing F in **1a** reduces the electron-density of the aryl group in the substrate and enhances the π–π interactions in **TS2**, thus leading to a slightly lower activation barrier. On the other hand, the reaction with **1p** forms a stronger Ar–Rh bond due to the *para*-F substituent, which can retard the turnover-limiting migratory insertion.

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Research Articles

C–C Activation

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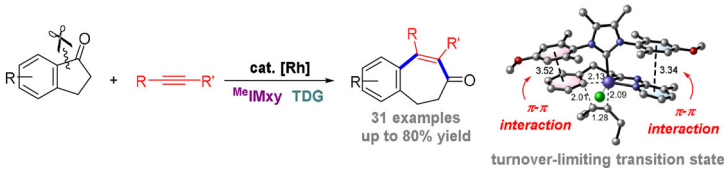
Intermolecular [5+2] Annulation between 1-Indanones and Internal Alkynes by Rhodium-Catalyzed C–C Activation



The Rh-catalyzed intermolecular [5+2] annulation between 1-indanones and alkynes is reported. It provides a rapid and straightforward entry to benzocycloheptenones. DFT calculation reveals the beneficial π–π interactions between the ligand and the substrate in the turnover-limiting migration insertion step.