Merging Rh-catalyzed C-H Functionalization and Cascade Cyclization to Enable Propargylic Alcohols as Three-Carbon Synthons: Experimental and Computational Investigations

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Abstract: Reported herein is an unprecedented reactivity of propargyl alcohols as "*Three-Carbon Synthons*" in a Rh(III)-catalyzed C-H functionalization of acetanilides, leading to the synthesis of core structures of isocryptolepine, γ–carbolines, dihydrochromeno[2,3-b]indoles, and diindolylmethanes derivatives. The transformation involves a Rh(III)-catalyzed C-H functionalization and heteroannulation to yield indoles followed by a cascade cyclization with both external and internal nucleophiles to afford diverse products. The role of the hydroxy group, the key function of the silver additive, the origin of the unique reverse regioselectivity and the rate-determining step, are rationalized in conformity with the combination of experimental, noncovalent interaction analysis and DFT studies. This protocol is endowed with several salient features, including one-pot multistep cascade approach, exclusive regioselectivity, high bond-forming efficiency, and synthesis of a variety of molecular frameworks.

Introduction

The potential of a cascade process lies in making complex molecular frameworks *via* several transformations in a single stroke, starting with a simple substrate with predetermined functionality. The development and execution of new cascade processes is a challenging aspect in organic chemistry. It brings with it novelty, along with improved practical efficiency, and an aesthetic appeal to synthetic planning.[1] This is because cascade methodologies are atom- and step-economical, and in the same sense economical in terms of time, labor, and generation of waste materials. These have therefore captivated the attention of synthetic chemists, resulting in them being utilized in the synthesis of several biologically relevant heterocycles.[2] Tricyclic scaffolds possessing the indole framework find widespread application in bioscience, medicinal, and organic chemistry.

One of the naturally occurring indoloquinoline alkaloid, isocryptolepine (Figure 1), which possesses the γ-carboline core present in many natural products, was isolated from the roots of the West African plant *Cryptolepis sanguinolena*.[3a] It shows diverse biological activities, comprising anti-inflammatory, anti-malarial, anti-plasmodial, antitumor and neuropharmacological properties. Along with γ-carbolines, chromeno[2,3-b] indoles and diindolylmethanes show potent applications in the medical domain (Figure 1).[3]

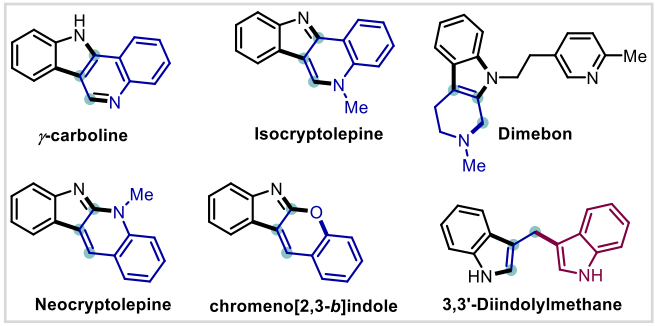
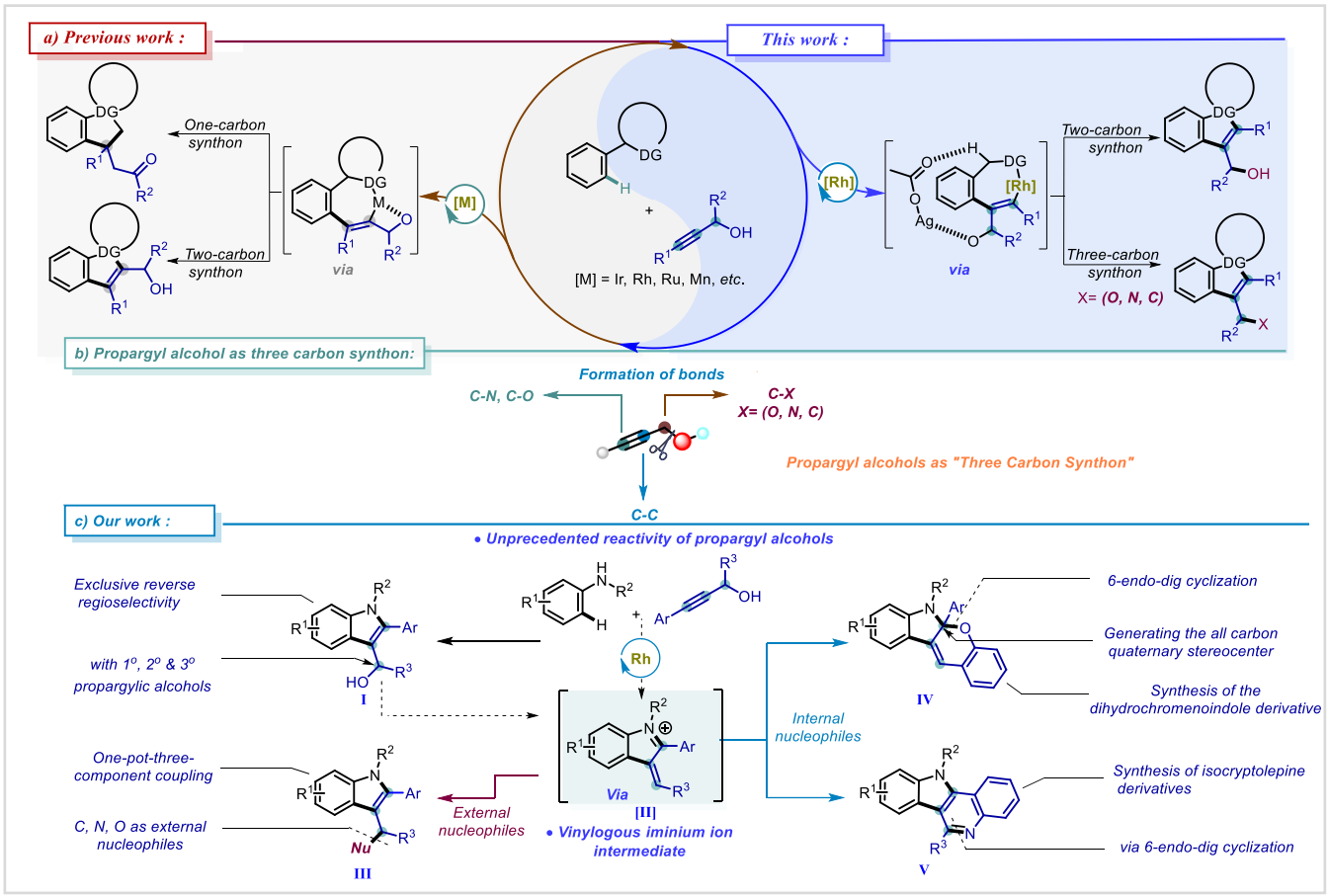


Figure 1. Selected examples of molecular frameworks possessing fused indole skeletons.

In recent years, propargyl alcohols have emerged as unique coupling partners in C–H functionalization reactions to achieve the rapid construction of complex molecular frameworks.[4] Coordination of the hydroxy group of the propargyl alcohol with the transition metal catalyst in the metallacycle plays a decisive role in varied reactivity, chemo- and regioselectivity of the functionalization.[5] Propargyl alcohols can switch reactivities between being two-carbon synthons and one-carbon synthons. (Scheme 1(a)). Generally, the propargyl alcohol acts as a two-carbon synthon wherein the hydroxy group of the propargyl alcohol coordinates with the transition metal resulting in the hydroxy group being placed at the α-position of the directing group upon C–H functionalization.[5–8]

In continuation to our research in the area of C-H functionalizations,[9] our study began with the investigation of C-H functionalization of acetanilide with an unactivated propargyl alcohol as a coupling partner. Interestingly, we observed exclusive reverse regioselectivity for the propargyl alcohol insertion in the metallacycle. This resulted in an annulated product possessing a good leaving group at the benzylic position *i.e.* 1-(3-(hydroxymethyl)-1H-indol-1-yl)ethan-1-one (**I**, (Scheme 1(c)). This is a well-known precursor of the vinylogous iminium ion

Scheme 1. Various reactivity modes for propargylic alcohols in C-H functionalization and present work



intermediate (**II**) and is prone to react with nucleophiles at the benzylic position.[10] We hypothesized that it would be possible to make this vinylogous intermediate (**II**) *in situ* from the annulated indole (**I**, (Scheme 1(c)) and employ external as well as internal nucleophiles to capture this reactive intermediate (**II**, (Scheme 1(c)) and utilize the propargyl alcohol as a three-carbon synthon. If successful, such a route would represent a new one-pot approach for the synthesis of indole containing tricyclic scaffolds (**IV** and **V**, (Scheme 1(c)). Although external nucleophiles were expected to the potentially reactive at the specific (benzylic) position (**III**, (Scheme 1(c)), we were apprehensive whether the regioselectivity would be maintained by the internal nucleophile (owing to the propargyl alcohols (internal) of this type being prone to the rearrangement and self-cyclization).[11a, 12] This unusual regioselectivity with respect to the propargyl alcohol insertion prompted us to design a simple and inexpensive method for the synthesis of nitrogen-containing tricyclic scaffolds.

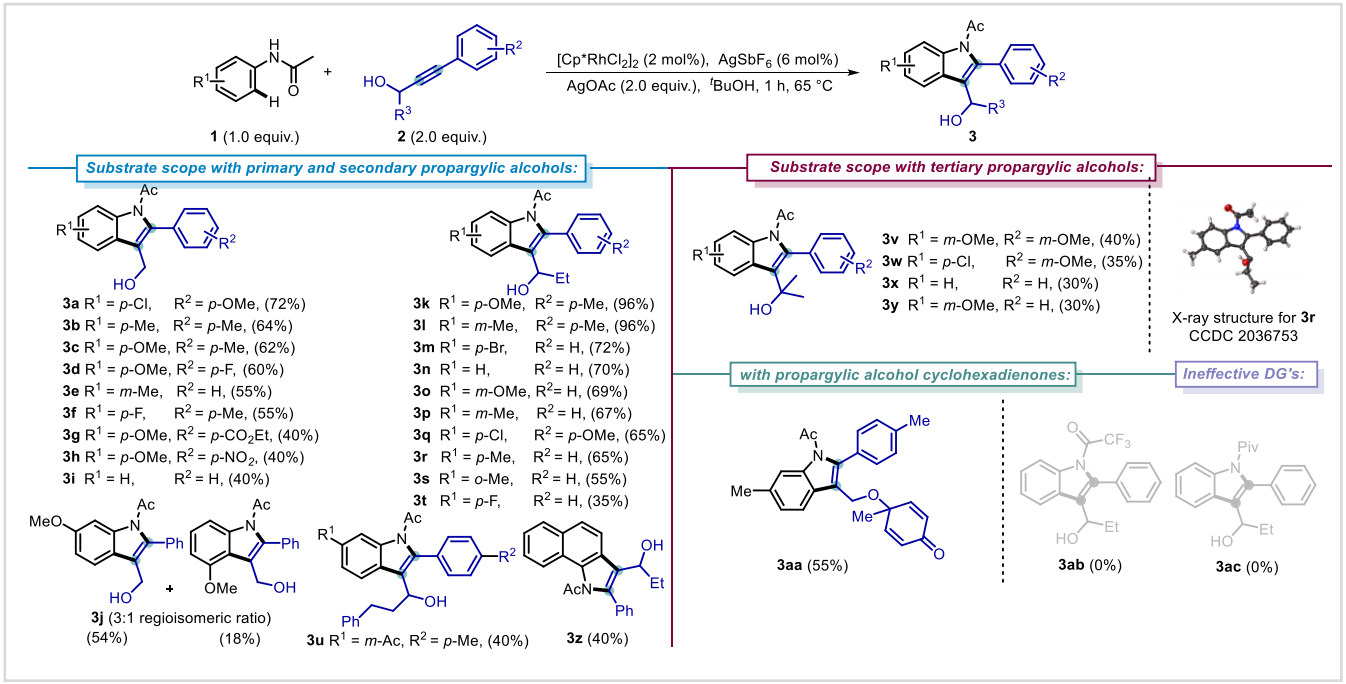
Herein, we report the successful realization of our goal of utilizing propargyl alcohols as a three-carbon synthon *via* vinylogous iminium ion intermediate **II** (Scheme 1(c)). We have successfully designed a practical method that provides diversified scaffolds in a minimal number of steps, a new system in which we are able to switch the reactivities between these substrates to yield important core structures of tricyclic natural products. Another highlight of the present work is the ability of the transformation to show opposite regioselectivity with primary, secondary and tertiary propargylic alcohols. This selectivity is rather rare and previously has been demonstrated only with tertiary propargylic alcohols.[5,8]

Results and Discussion

Optimizing Reaction Conditions. Considerable literature is available with activated propargylic alcohols,[6a–e] therefore we sought to utilize unactivated alcohols for our coupling reaction instead. Upon extensive optimization (see the Supporting Information for details), the desired transformation was found to work best with the following conditions: $[Cp^*RhCl_2]_2$ (2 mol%), $AgSbF_6$ (6 mol%), AgOAc (2.0 equiv.) in ^{t}BuOH as the solvent. AgOAc was more effective than $Cu(OAc)_2$ and others. ^{t}BuOH was found to be the best solvent for this reaction when compared to other polar or non-polar solvents. Other catalytic systems (using Pd, Ru, Co and Mn) did not yield the desired transformation as effectively as the Rh-catalyst.

Exploring the substrate scope. With the optimized conditions in hand, we sought to explore the versatility of the transformation (Table 1). Most of the anilides and propargyl alcohols worked well with high chemo- and regioselectivity, with good functional group tolerance and the site selectivity remained

Table 1. Substrate scope for synthesis of indole from anilides and propargyl alcohols



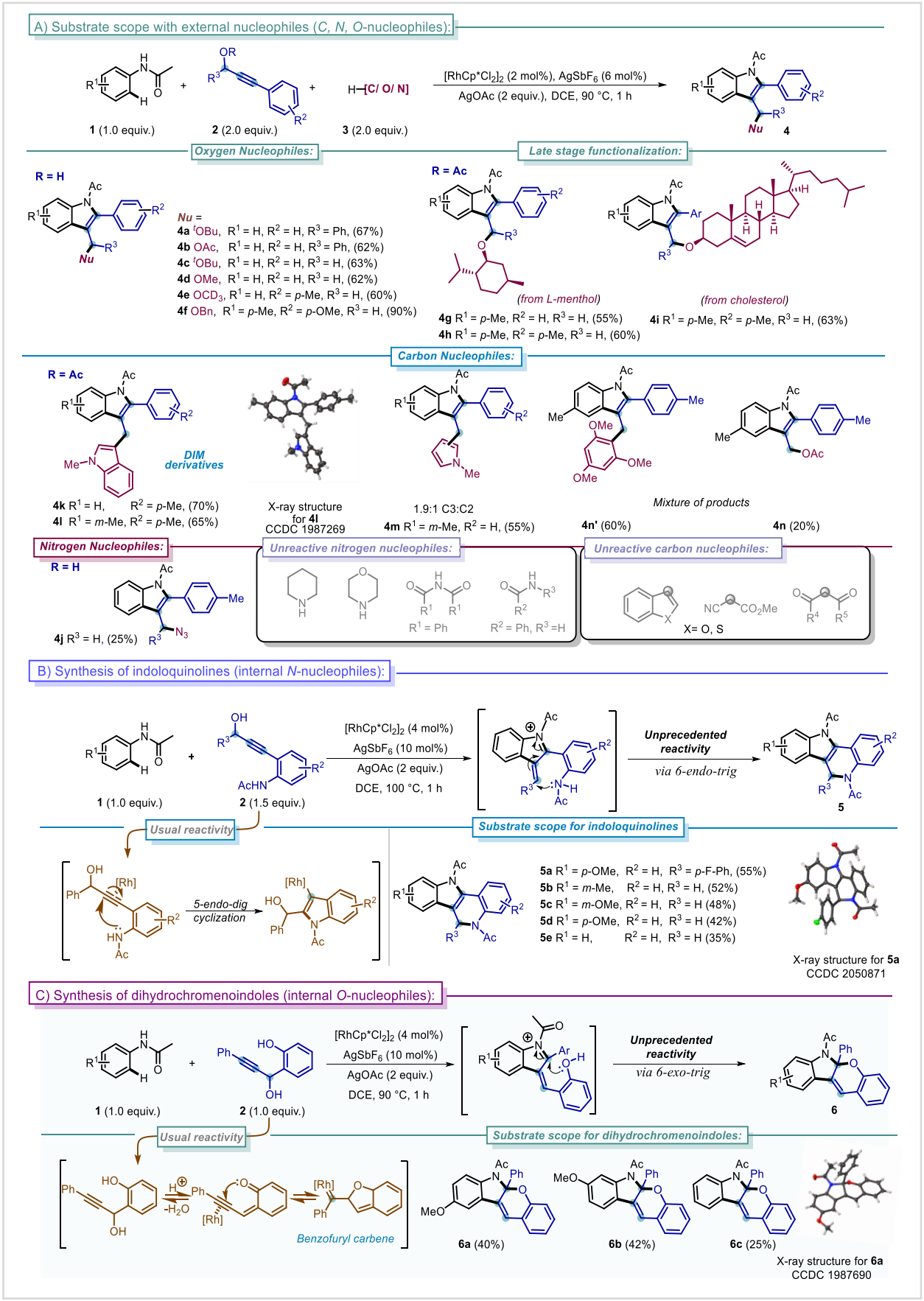
intact in all the substrates scanned. The reaction worked very well with primary and secondary propargylic alcohols. The reaction with tertiary propargylic alcohols was only moderately successful and this could most probably be attributed to steric effects. Electronic variability was well-tolerated in this transformation although sluggish rates were observed for electron-withdrawing substituents (**3g**, **3h**, **3t**, **3u**, Table 1). In the case of *m*-methoxy acetanilide, a mixture of regioisomeric products was expectedly obtained (**3j**, Table 1). The regioselectivity was confirmed by X-ray crystallography of **3r**. Other directing groups like pivaloyl and trifluoroacetylanilide failed to yield the desired transformation, which could be attributed to the poor coordination ability of the trifluoroacetanilide (**3ac**, Table 1).

We had postulated that this annulated indole product (**3**, Table 1) could be attacked by a nucleophile in the reaction system and when we prolonged the reaction beyond the completion of the annulation, the -OH group in **3** was displaced by a -O^{t}Bu group (**4a**, Table 2(A)). This observation prompted us to check if the reaction could be generalized with a variety of nucleophiles (Table 2(A)). By changing the solvent to a non-nucleophilic one like DCE, the acetate substituted product was observed (**4b**, Table 2(A)). A variety of *O*-nucleophiles were screened (**4c**–**4f**, Table 2(A)) resulting in products in good to moderate yields. Furthermore, the versatility of the established one-pot, three-component protocol was successfully demonstrated by its application in late-stage functionalization, where L-menthol (**4g–h**, Table 2(A)) and cholesterol (**4i**, Table 2(A)) were found to be potent *O*-nucleophiles to generate the desired products with acceptable yields. Unfortunately for us, *N*-nucleophiles had very limited success and in only one case, the product was isolable (**4j**, Table 2(A)). We then tested the versatility of the reaction with carbon nucleophiles using activated propargyl alcohols. To our delight, indoles, pyrroles and 1,3,5 trimethoxybenzene all resulted in products in good to moderate yields (**4k–4n**, Table 2(A)), although in the case of **4n**, the acetate competed with trimethoxybenzene to afford a mixture of separable products. The potency of the nucleophile plays a key role in the formation of the desired product. Thus, *O*-nucleophiles (**4a–f**, Table 2(A)) worked well with unactivated propargyl alcohols whereas soft nucleophiles (**4k–n**, Table 2(A)) required activated propargyl alcohols for a successful outcome. For reasons not yet clear, the reaction did not work when furans, thiophenes and cyclic amines were employed as nucleophiles. In these cases, the displacement of the -OH or the acetate group from the indole was not observed.

Following up on these results, we sought to explore the heteroannulation with internal nucleophiles. We therefore designed propargylic alcohols bearing potentially reactive internal nucleophiles at various positions. To initiate our study, we incorporated an *N*-acetyl group (**2**, Table 2(B)) on the phenyl ring for an internal cyclization. This was challenging, since these types of alkyne coupling partners tend to undergo self-cyclization as well as rearrangements in the presence of transition metals or Brønsted acids.[12]

After an extensive screening of various catalyst systems, we found that the Rh-catalyst (4 mol%) in DCE, at 90 °C, was the best combination for obtaining the desired product. Under these conditions, only a trace amount of the Meyers-Schuster rearrangement product was observed. Electron-donating and withdrawing substituents on either of the aryl rings resulted in moderate yields (**5a–e**, Table 2(B)). The regioselectivity was confirmed by X-ray crystal structure of compound **5a** (Table 2(B)). We thus established an unprecedented domino-approach in

Table 2. Substrate scope with external and internal nucleophiles

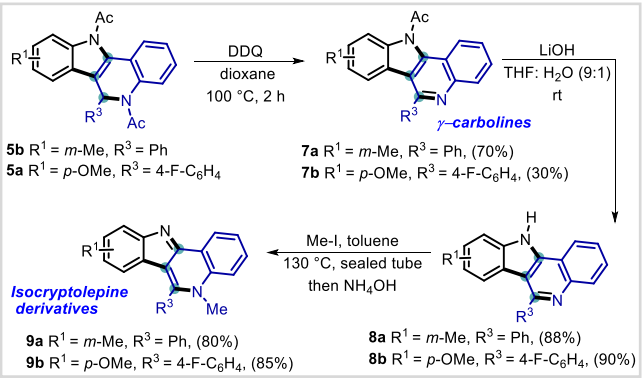


achieving indolo[3,2-c]quinolines (**5**, Table 2(B)) *via* a *6-endo-trig* cyclization in a one-pot fashion where the C-H activation predominates over rearrangement or self-cyclization.

To further explore this chemistry, we designed hydroxyphenyl propargyl alcohols (**2**, Table 2(C)) to achieve an internal cyclization. Normally, propargyl alcohols of this type are benzofuryl carbene precursors, arising from the dual catalysis of the acid and the transition metal.[11a,12] To our delight, instead of this reactivity, we obtained the desired product *via* a *6-exo-trig* cyclization, with the generation of quaternary centers. We did not observe any self-cyclization or by-products arising from rearrangements. The regioselectivity was confirmed by the X-ray crystal structure of compound **6a** (Table 2(C)). This approach provides dihydrochromenoindoles a minimal number of steps.[3a]

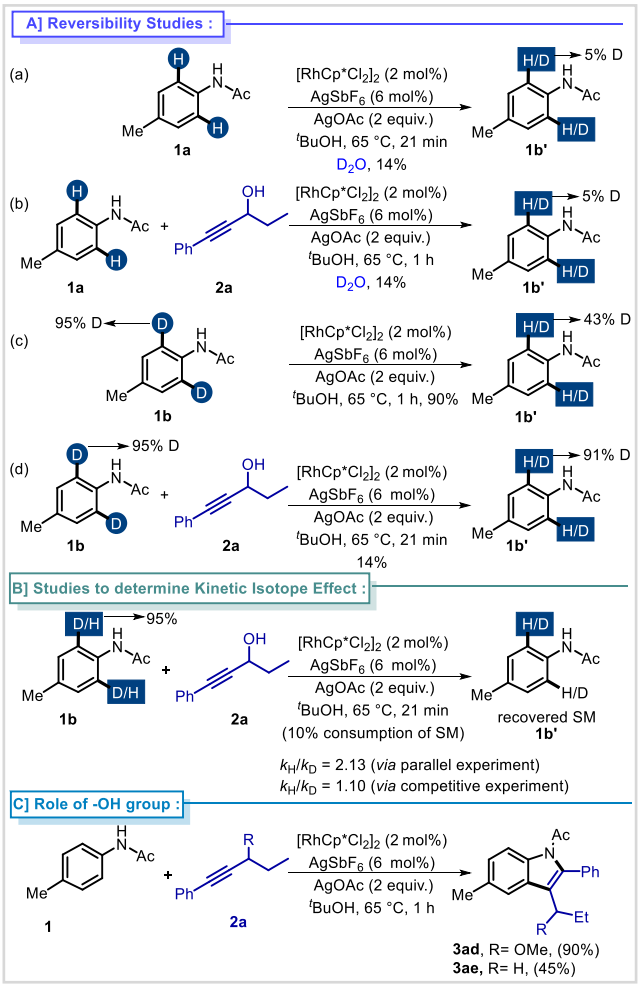
To further highlight the synthetic application of this methodology, indoloquinolines that were synthesized (**5**, Table 2(B)), were aromatized with DDQ to yield γ-carbolines (**7**, Table 3) which on *N*-deacylation and subsequent *N*-methylation[12] led to isocryptolepine derivatives (**9**, Table 3), in acceptable yields. We were thus able to develop a new approach to achieve the synthesis of isocryptolepine derivatives in a minimal number of steps.[3a]

Table 3. Synthesis of Isocryptolepine Derivatives



To obtain mechanistic insights into the transformation, various control experiments were carried out (Scheme 2). To check for the reversibility of the C−H metallation, the reaction was performed with added D_2O, resulting in a significant amount of deuteration at the *ortho*-positions of the recovered anilide (Scheme 2A). This indicated that the C–H activation was a reversible process. This was also confirmed by the D−H exchange experiment (Scheme 2A(c)) in which a significant loss of the deuterated label was observed when the reaction was carried out in ^{t}BuOH. Subsequently, to investigate whether the C−H metallation step was rate-limiting, studies were conducted to check for a kinetic isotope effect. Parallel reactions indicated that the C−H bond cleavage was the rate-limiting step (k_H/k_D = 2.13), however competition reactions indicated otherwise (k_H/k_D = 1.10) (Scheme 2B). However, due to the reversibility in the protic solvent, the KIE studies *via* the parallel reaction seem more reliable.[14]

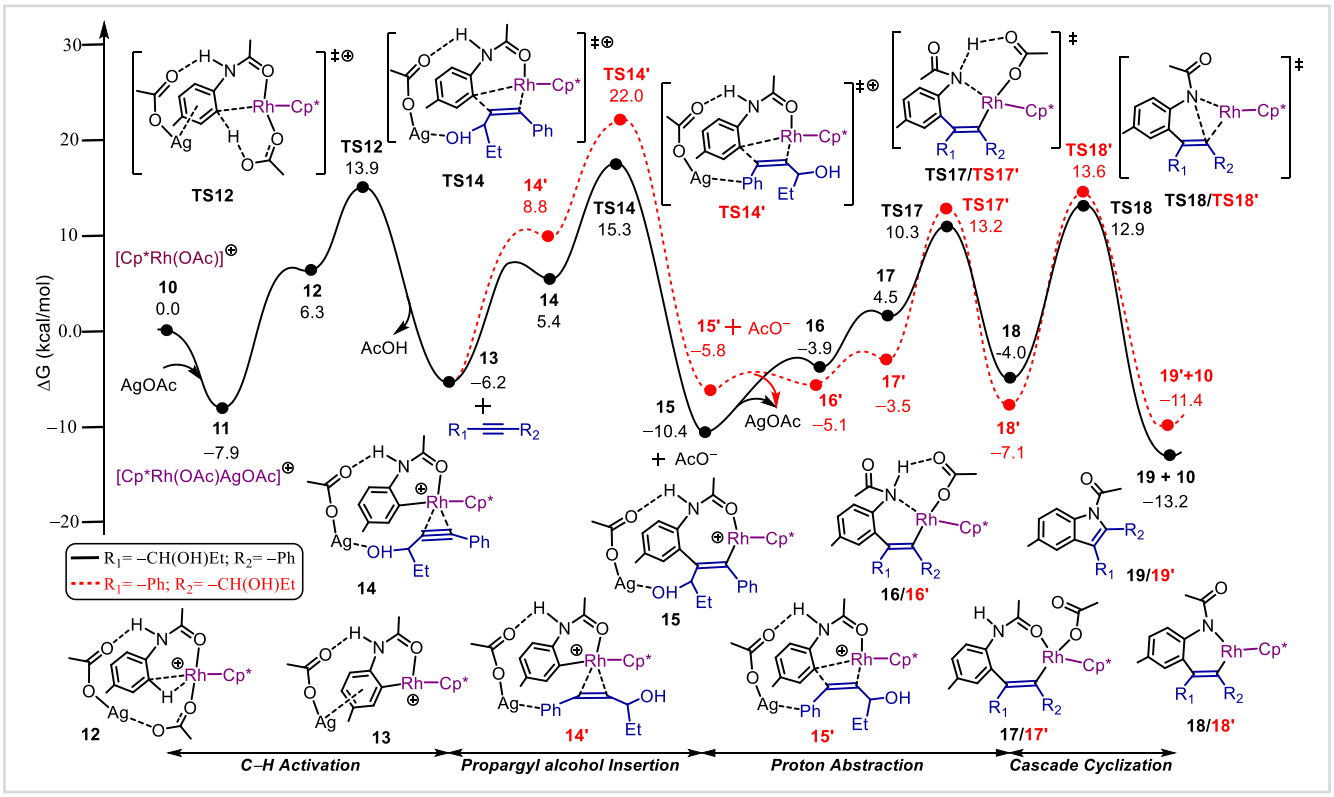
Scheme 2. Control Experiments and Studies to Check for a Kinetic Isotope Effect



Our observed regioselectivity for propargyl insertion is unusual and opposite to that reported previously in literature.[4] To better probe the regioselectivity of the propargyl insertion a diverse array of propargyl alcohols was then scrutinized under the standard conditions. In this regard, a control experiment was carried out to check for the role of the -OH functionality, by employing the acetylene lacking the propargylic -OH and by using a propargyl ether (Scheme 2(C)). The fact that the same regioselectivity was obtained for the alkyne insertion indicated that the regioselectivity in migratory insertion was catalyst driven and binding interactions with oxygen may not be essential.

Computational studies. To gain additional insights into the possible reaction mechanism and origin of the regioselectivity, we performed DFT calculations.[15] First, ligand exchange of the pre-catalyst $[Cp^*RhCl_2]_2$ with AgOAc is predicted to occur to get the cationic active catalyst $[Cp^*Rh(OAc)]^+$ (**10**, Figure 2). The excess amount of AgOAc plays a vital role in coordinating to the active catalyst and formation of complex **11**, $[Cp^*Rh(OAc)AgOAc]^+$, which is predicted to be 7.9 kcal/mol lower in energy than active catalyst $[Cp^*Rh(OAc)]^+$. After coordination of substrate, the C–H activation step is predicted to proceed through a concerted metalation−deprotonation (CMD).[16] In this process, intermediate **12** undergoes CMD through 6-membered transition state **TS12** (Figure 2) to afford a

Figure 2. Proposed mechanism for the Rhodium-catalyzed heteroannulation and cascade cyclization of 4'-methylacetanilide with 1-phenylpent-1-yn-3- ol.(Method: M06(SMD)/def2TZVP/SDD(Rh, Ag)//PBE0/def2SVP(H,C,O,N)/SDD(Rh, Ag)



rhodacycle (**13**). As shown in Figure 2, the overall free energy barrier for the CMD process is predicted to be 21.8 kcal mol^{-1}, followed by the dissociation of acetic acid to form intermediate **13**.

Once acetic acid has dissociated, the propargyl alcohol can bind to **13** to form complexes **14** and **14'** prior to the insertion. Two modes of insertion are possible for the propargyl alcohol: the propargylic OH-group can be either distal or proximal to the Rh-bound arene. Complexes **14** and **14'** can undergo propargyl insertion *via* 4-membered cyclic transition states **TS14** (Figure 2) and **TS14'** to form the 8-membered rhodacycles **15** and **15'**, respectively. It is this step that dictates the regioselectivity observed for the reaction. The transition state for the insertion that leads to the experimentally observed product (**TS14**) is computed to be approximately ~7 kcal mol^{-1} lower in energy than the **TS14'** (red) that leads to the product that is not observed. The overall barrier *via* transition state **TS14** is predicted to be 23.2 kcal mol^{-1}, which is consistent with the experimental conditions. Rhodacycles **15** and **15'** can then bind another acetate to form **16/16'**, which are in equilibrium with higher energy isomers **17/17'**. This isomerization leads to *N*-bound rhodacycles **18/18'** upon elimination of acetic acid *via* **TS17/TS17'** (Figure 2), *i.e.*, in this model, the bound acetate serves as the base for amide deprotonation. Complexes **18/18'** are now set up for reductive elimination to form the indole products **19/19'** *via* **TS18/TS18'** (Figure 3). While **TS18'** is higher in energy than **TS18**, the regioselectivity was already determined in the alkyne insertion step, *i.e.*, formation of structures **18/18'** are not predicted to be rapidly reversible.

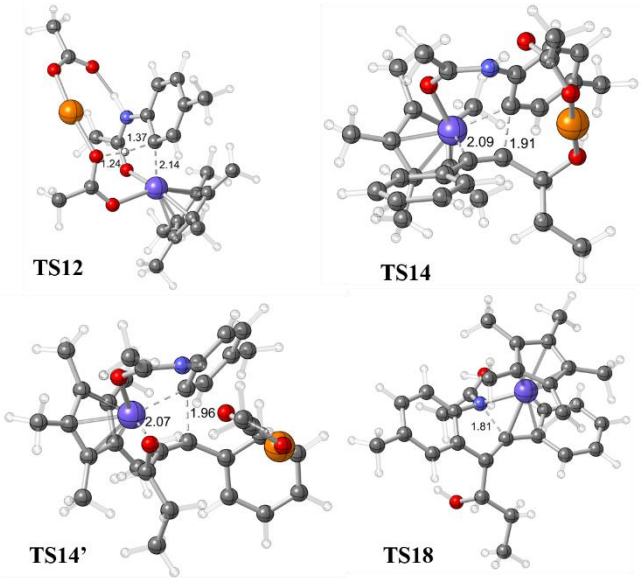


Figure 3. Optimized geometries of transition state structures with key nuclear distances for the rhodium-catalyzed heteroannulation and cascade cyclization of 4'-methylacetanilide with 1-phenylpent-1-yn-3-ol. The bond distances are in angstroms (Å). Color code: C gray, O red, H white, N blue, Rh purple, Ag orange. To reduce congestion, only the experimentally favored pathway (blue) is shown.

Theoretical explanations for selective olefin insertions into metal–carbon bonds based on the different electron densities at the two carbon atoms of the olefin have been reported previously.[17] In general, when substituents are electronically similar, the larger group prefers to be *β* to the Rh atom in the metallacycle to avoid unfavorable steric interactions.[23b, 18–20] However, when they are electronically different, the more electron-donating group prefers to be α to the electron-poor rhodium.[23b, 18–21] Here, we find that the aliphatic group (ethanol or isopropanol) prefers a position distal to the Rh atom to avoid a steric clash with the bulky Cp* group (Figure 4). In addition, the propargylic alcohol coordinates with silver acetate, which hydrogen bonds with the N-H of the anilide.

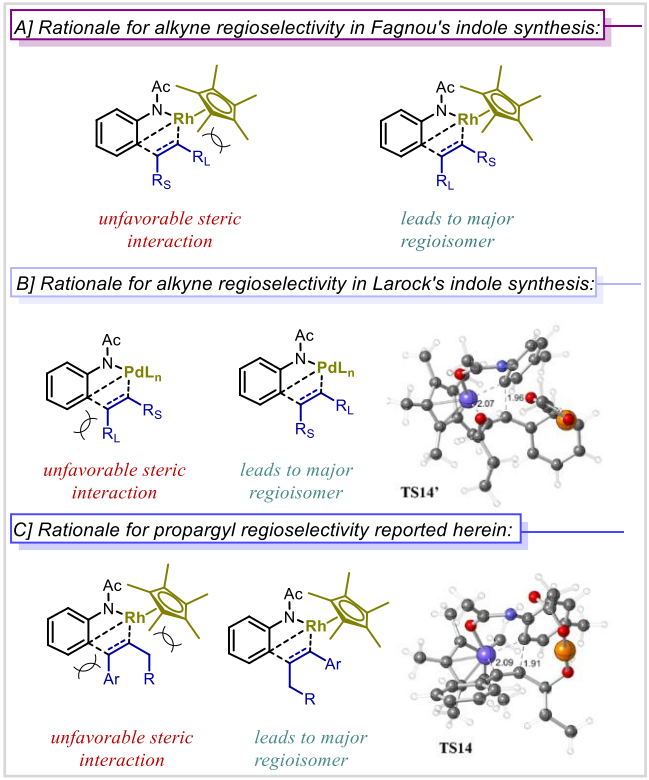


Figure 4. Rationale for regioselectivity of alkyne insertion based on steric effects. Hydrogens hidden for clarity. The bond distances and dihedral angels are in angstroms (Å) and degrees (°), respectively. Color code: C gray, O red, H white, N blue, Rh purple, Ag orange.

Thus, the observed regioselectivity likely results from the combination of both steric and electronic effects. Our observed regioselectivity matches that reported by Fagnou[23b] assuming that the CH_2R group is effectively larger than the aryl group in this context but is opposite to that previously reported by Larock[22] (Figure 4). In addition, one can see a greater degree of favorable, stabilizing non-covalent interactions (green; primarily dispersion interactions) in **TS14** because of the propargylic alcohol motif proximal to the phenyl ring, an effect that is less pronounced in **TS14'** when distal (Figure 5).

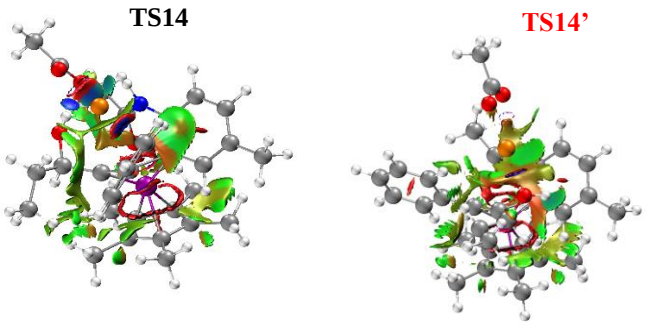
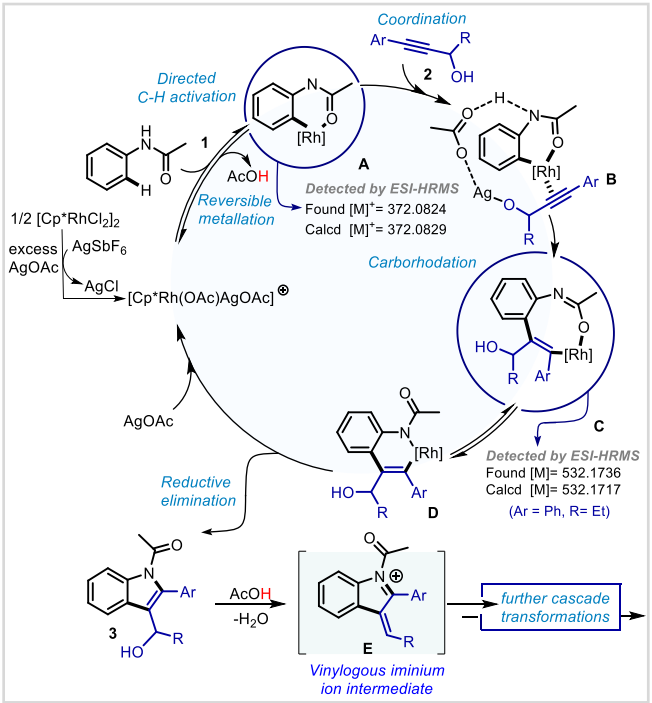


Figure 5. Noncovalent interaction analyses for the transitions states TS14 and TS14'. Blue, green, and red surfaces represent the strong attraction, weak interaction, and steric effect, respectively. Color code: C gray, H white, Rh purple, Ag orange, O red, N blue.

Based on our mechanistic investigations and previous literature reports,[10,23] we propose the plausible catalytic cycle for the transformation (Scheme 3). The first step is the formation of active catalyst species through ligand exchange with AgOAc. Next, directed *ortho* C–H activation, assisted by the weakly coordinating anilide **1**, results in the rhodacycle intermediate **A**. Coordination and regioselective migratory insertion (carborhodation) of the propargyl alcohol leads to the eight-membered rhodacycle intermediate **C**. Equilibration (exchange of ligand binding modes) followed by reductive elimination from intermediate **D** gives rise to the product **3**. Molecules with masses corresponding to those of intermediates **A** and **C** (Scheme 3) were detected in ESI-HRMS (see the SI for details).

Scheme 3. Proposed Mechanism:



Conclusion

To conclude, in this work, we have presented an approach for the utilization of propargyl alcohols as three-carbon synthons in an unprecedented heteroannulation of indoles by merging C-H activation with a cascade cyclization. The noteworthy characteristic of this study is the unusual reversed regioselectivity of the insertion of the propargyl alcohol. This methodology leads to the synthesis of diverse heterocycles in a one-pot fashion. The transformation proceeds smoothly with a broad range of *C*-, *N*- and *O*- based external nucleophiles. By choosing appropriate coupling partners, we can switch the reactivities in these substrates to synthesize γ-carbolines and dihydrochromenoindoles. The cascade process opens a synthetically novel route for constructing isocryptolepine derivatives, γ-carbolines and potential drug molecules based on these molecular frameworks. The role of the hydroxy group, rate-determining step, the origin of the reverse regioselectivity, and the key function of silver acetate were clarified using a combination of experimental and DFT studies. The application of this methodology in the synthesis of several indole-based alkaloids is currently in progress in our laboratory.

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Keywords: Propargyl alcohol • Three-carbon synthon • Heteroannulation reaction • C-H functionalization • DFT studies.

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