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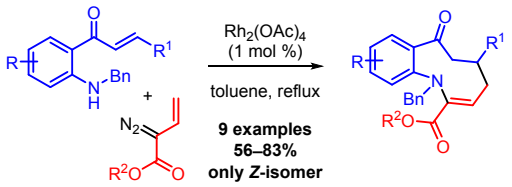

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Trapping Rhodium Vinylcarbenoids with Aminochalcones for the Synthesis of Medium-Sized Azacycles

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ABSTRACT

A rhodium carbenoid initiated cascade has been developed for the stereoselective synthesis of medium-sized azacycles. The cascade approach utilizes readily accessible N-benzyl protected aminochalcones and vinyldiazo compounds to access 9-membered azacycles through a carbene-nitrogen insertion/aldol/oxy-Cope sequence. The cascade reaction has proven general with a range of N-benzyl protected aminochalcones and vinyldiazos to provide diverse medium-sized azacycles.

1. Introduction

Medium-sized (8-12-membered) heterocycles are commonly found in bioactive natural products and cyclic peptides.[1] The cyclic constraints within these molecules leads to improved binding affinity compared to their linear counterparts.[2] Furthermore, medium-sized heterocycles often exhibit improved pharmacokinetics due to their larger ring sizes and conformational constraints.[3] Still, medium-sized rings remain underrepresented among approved pharmaceuticals compared to their smaller-sized ring (4-7 membered) counterparts.[4]

The lack of prevalence in drug molecules could be attributed to the challenges associated with the synthesis of medium-sized rings.[5] Many of the methods for constructing medium-sized rings rely on intramolecular cyclization strategies, which often pose challenges due to the entropic and enthalpy barriers, and also require high dilution conditions to reduce polymerization.[6] Although, there are other methods such as olefin metathesis [7a] and transition metal coupling reactions [7b] for the synthesis of these scaffolds, they often require conformational constraint to promote cyclization (Figure 1a, 1b).[8] Ring expansion reactions that are insensitive to substrate conformational effects provide an alternative to conventional cyclization approaches.[9] However, construction of an appropriate precursor for a ring expansion reaction often requires multiple steps, and limits the synthetic utility (Figure 1c, 1d).[10]

To overcome this synthetic challenge, we recently reported a rhodium carbenoid initiated convergent cascade approach, which provides access to the functionalized medium-sized oxacycles with high stereoselectivity.[11a] The cascade reaction begins with carbene-oxygen insertion followed by an intramolecular aldol cyclization to provide a substituted tetrahydrofuran intermediate, which undergoes an oxy-Cope rearrangement to provide 9-membered oxacycles. We also extended this cascade reaction to the synthesis of corresponding medium-sized lactones.[11b]

Building upon these findings, we envision extending the carbene cascade approach to the synthesis of 9-membered azacycles, which are found in a variety of natural products, medicinally relevant compounds, and drug molecules (Figure 2)[12]

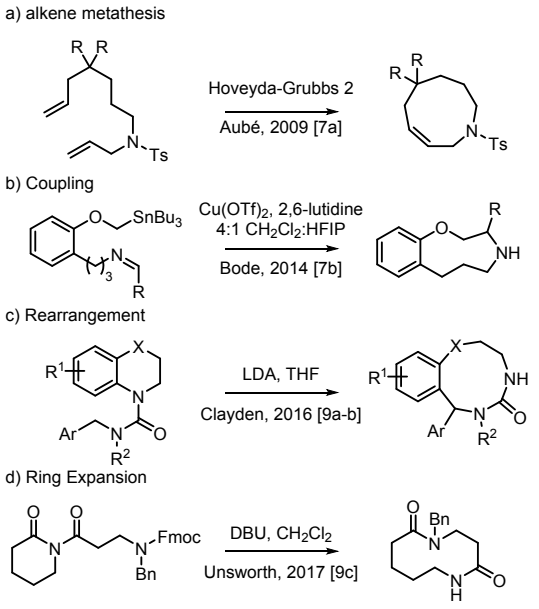


Figure 1. Previous synthetic approaches towards nine-membered azacycles

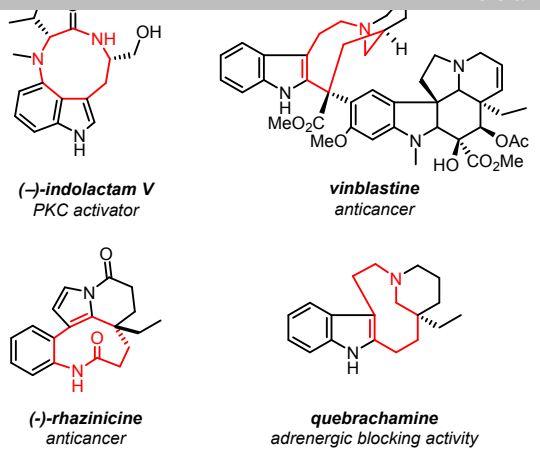
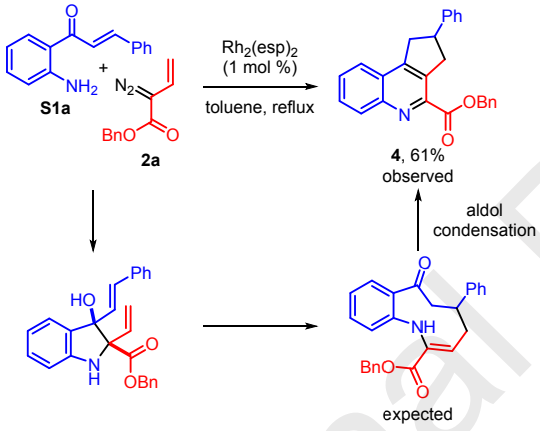


Figure 2. Nine-membered azacycle natural products

For the initial optimization to access 9-membered azacycles, aminochalcone **S1a** and vinyldiazo **2a** were selected as model substrates. The syringe pump addition of vinyldiazo **2a** to 2'-aminochalcone **S1a** in the presence of $Rh_2(esp)_2$ in refluxing toluene provided a major product, in which the characteristic enamine proton in ^{1}H-NMR, and ketone peak in ^{13}C-NMR spectrum were missing. Further structural analyses suggested the formation of an unexpected quinoline scaffold **4** (Scheme 1).[13]

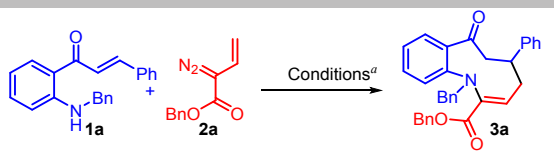


Scheme 1. Rhodium carbenoid initiated unexpected cascade leading to the formation of tricyclic quinoline **4**

Mechanistic analyses revealed that the quinoline forms from the corresponding azacycles via an aldol type condensation due to the driving force of aromatization.[13] Inspiring from these results, we thought of stopping the cascade at the azacycle stage using *N*-benzyl protected aminochalcones.

2. Results and discussion

For the initial catalyst screening, *N*-benzyl protected aminochalcone **1a** and vinyl diazo benzoate **2a** were selected as model substrates and exposed to $Rh_2(esp)_2$ in toluene (boiling point 110 °C) at reflux, which obtained the desired 9-membered azacycle **3a**, albeit in low conversion (Table 1, entry 1). Encouraged by this result, we screened other rhodium carboxylates catalysts to improve the yield of the transformation (Table 1, entries 2−5). Among them, $Rh_2(OAc)_4$ was found to be the most efficient catalyst for the cascade sequence and provided the corresponding nine-membered azacycle **3a** (entry 2).



Entry	Catalyst	Mol (%), t	Yield (%)[b]
1	$Rh_2(esp)_2$	1.0, 3 h	38
2	**$Rh_2(OAc)_4$**	**1.0, 3 h**	**67**
3	$Rh_2(TPA^c)_4$	1.0, 3 h	NR
4	$Rh_2(TFA^d)_4$	1.0, 3 h	10

[a]All optimization reactions were performed by adding a 0.45 M solution of **2a** (2.0 equiv) into a 0.1 M solution of **1a** (1.0 equiv) with catalysts *via* a syringe pump over 2.5 h, after the addition of diazo, all reaction were refluxed for an additional 30 min. [b]Isolated yields after column chromatography. [c]TPA = triphenylacetate; [d]TFA = trifluoroacetate; NR = no reaction.

With conditions in hand, we then investigated the scope of this cascade sequence using $Rh_2(OAc)_4$ as a catalyst (Figure 3). Using vinyldiazo **2a** as a standard substrate, the scope of *N*-benzyl protected aminochalcones was explored and found to be broad, encompassing a range of electron-rich and electron-deficient substituents on the aromatic side chain of *N*-benzyl protected aminochalcones.

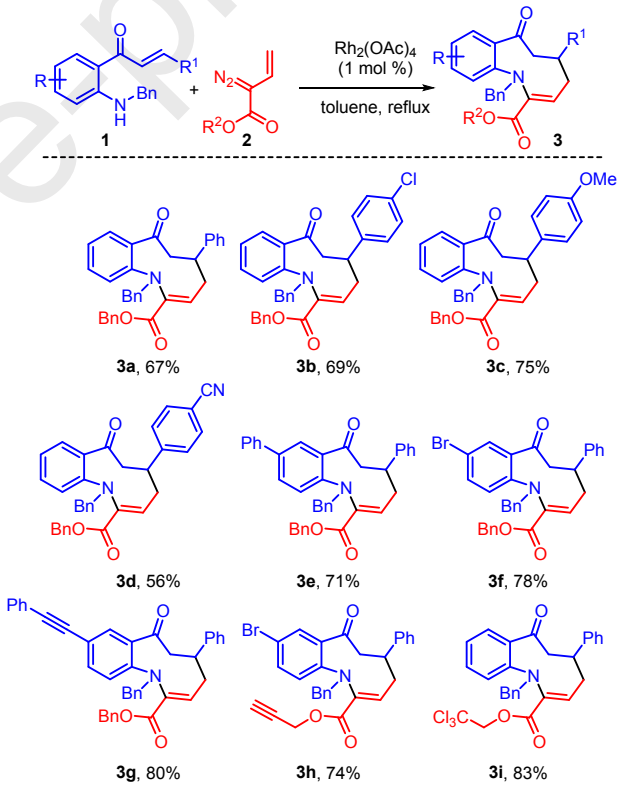


Figure 3. Scope of $Rh_2(OAc)_4$-catalyzed cascade for the synthesis of functionalized quinolines; all reactions were performed by adding a 0.45 M solution of **2** (2.0 equiv) into a 0.1 M solution of **1** (1.0 equiv) over 2.5 h *via* a syringe pump; after the addition of diazo compound, all reactions were refluxed for an additional 30 min.

In the case of electron-rich (**3b**) and neutral (**3c**) substituents worked very well, but a cyano- substituted aromatic side chain of *N*-benzyl protected aminochalcone resulted in a low yield (**3d**). We were pleased to find that the cascade sequence tolerated equally well the substitution at the aniline ring of *N*-benzyl protected aminochalcones (Figure 3, **3e–3g**). We did not observe any major side products resulting from alkyne functionality (**3g**,

3h), as well as carbene-alkyne metathesis[15] with rhodium carbenoids. The structure of the compound **3g** was further confirmed by the single crystal X-ray structure and the geometry of the double bond is found to be *Z*-isomer (Figure 4).[16a] Finally, the cascade was attempted with vinyldiazo **2c** bearing a trichloroethyl ester side-chain. To our delight, the cascade proceeded in high yield to provide azacycle scaffold **3i**. Moreover, the structure of the compound **3i** was also confirmed by the single crystal X-ray structure (Figure 4).[16b]

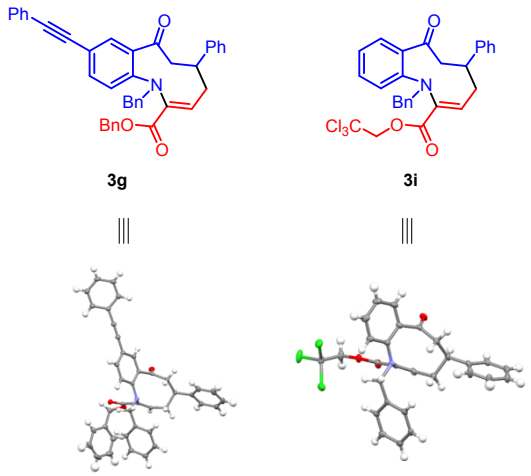
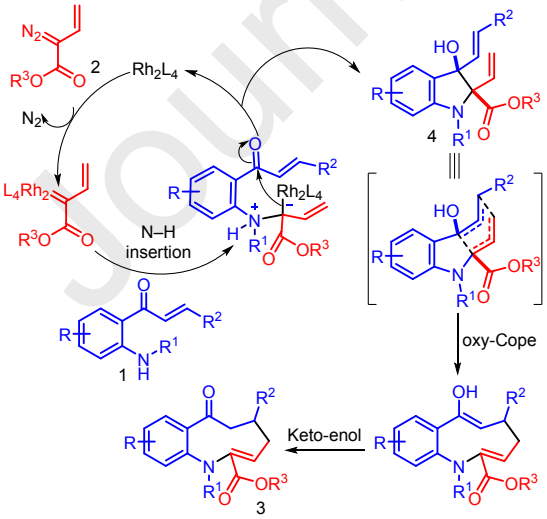


Figure 4. X-ray crystal structure of azacycle **3g** and **3i**

The reaction pathway for the synthesis of azacycles can be plausibly rationalized by the following mechansim (Scheme 2).[13] First, vinyldiazo **2** is decomposed by the dirhodium carboxylate to form a rhodium vinylcarbenoid that undergoes a chemoselective nitrogen insertion/aldol cyclization to provide indoline **4**.[17a] The indoline intermediate **4** sets the stage for a thermally driven concerted oxy-Cope rearrangement, which results in an enol-form. The enol-form then rearranges to the thermodynamically more stable keto-form **3**. Moreover, the formation of *Z*-isomer could be explained based on the boat transition state of the cycloadduct intermediate. In addition to this proposed mechanism, it is also plausible that the reaction proceeds through a metal dissociated ammonium ylide trapping mechanism.[17b]



Scheme 2. Plausible reaction mechanism for the synthesis of azacycles

3. Conclusion

In summary, the reported rhodium carbenoid initiated cascade approach is convergent in nature and uses readily accessible important feature of this transformation is its high chemo- and regio-selectivity. Furthermore, the straightforward synthesis of medium-sized azacycles would allow exploration of this less-charted area of chemical space, which is currently occupied with heterocycles having small (4-7 atoms) rings and macrocycles.

Acknowledgments

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

- A convergent approach to 9-membered azacycles is described.
- The rhodium carbene initiated three step cascade utilizes readily accessible starting materials.
- The cascade reaction accommodates a variety of functional groups.
- The reaction provides high chemo- and regio-selectivity affording only z-isomer azacycles.