Rhodium-Catalyzed 3-Aza-Cope Rearrangement of Protic *N*-Allyl Enammonium Ylides Enabled by Resonance Assisted H-Bonding

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ABSTRACT: Herein, we present the design of a new class of Rh-bound protic *N*-allyl enammonium ylides and its stereoselective 3-aza-Cope rearrangement. These transient ylides are generated *in situ* by the Rh-catalyzed reaction of vinyldiazo compounds and *N*-secondary-(*Z*)-*β*-enamino carbonyl compounds, under mild conditions. Mechanistic studies revealed that the resonance-assisted hydrogen bonding (RAHB) of protic enammonium ylide promotes exclusively [3,3] rearrangement by disfavouring both 1,2-proton transfer (NH-insertion) and direct carbenoid C-C bond formation. This new reaction was used in the synthesis of multi-substituted pyrroles, dihydropyrroles, deuterated pyrroles, tetrahydroindoles, and pyrroloindole scaffold of an antitumor and UV-protecting agent terreusinone.

The pericyclic 3-aza-Cope (aza-Claisen) rearrangement is a fundamentally and mechanistically important [3,3] sigmatropic reaction of *N*-allyl enamine that gives valuable γ,δ–unsaturated imine with a new C-C σ-bond and upto two new stereocenters (Figure 1a).[1-3] This atom economial reaction is a reliable way to transpose nitrogen within the 6-atom chain to create rapid skeletal diversity with regio- and stereocontrol governed by the highly ordered six-member cyclic transition state. The classical aliphatic 3-aza-Cope rearrangement requires harsh conditions (150 – 250 °C) due to the high activation barrier associated with the breaking of a relatively strong σ–sp³(C_4-N) bond.[2-3] In contrast to other related [3,3] rearrangements (Cope and Claisen),[4] the presence of a basic sp³-nitrogen in the 2π-2σ-2π network offers uniqe modes of electrophilic activation. Studies have shown that use of strong Lewis/Brønsted acids or *N*-quaternization weakens the σ-sp³(C_4-N), leading to charge-accelerated [3,3]-rearrangement at considerably reduced temperature (<120 °C).[5-6] However, the requirement of harsh thermal or acidic-conditions or additional quaternization steps limits the functional group tolerence and its wider aplications across many areas of synthesis.

In continuation of our studies on the metallocarbenes,[7] we envisioned that, reaction of vinylcarbene with enamine would provide a new class of metal-bound protic *N*-allyl enammonium ylide **Y1** (Figure 1b). This highly reactive transient ylide could undergo facile metal-assisted 3-aza-Cope rearrangemt due to the labile σ–sp³(C_4-N) bond. However, implementation of this new reaction might be challenging due to the potential competing NH-insertion and other modes of enamine reactivity.[8,9]

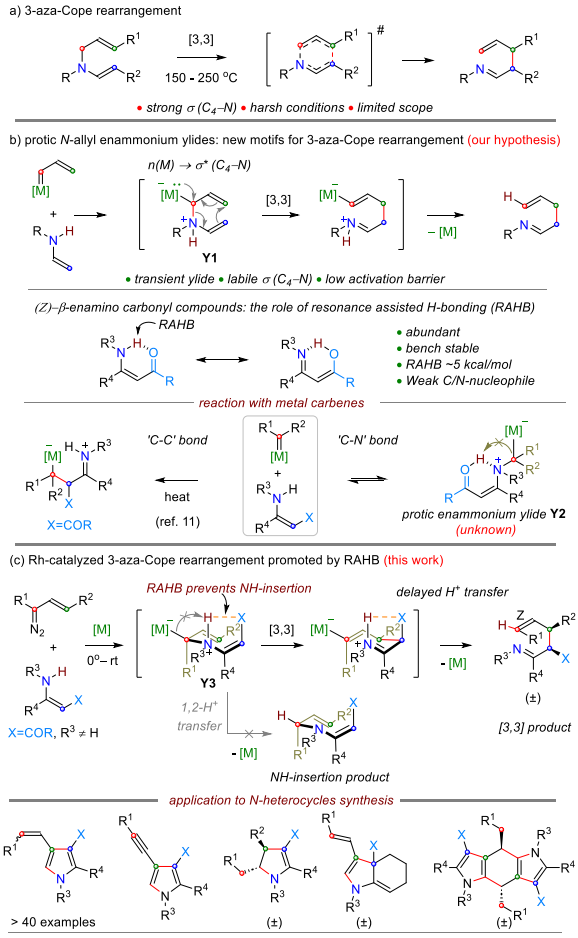

Figure 1. Inception of the protic *N*-allyl enammonium ylide 3-aza-Cope rearrangement. Construction of *N*-heterocycles.

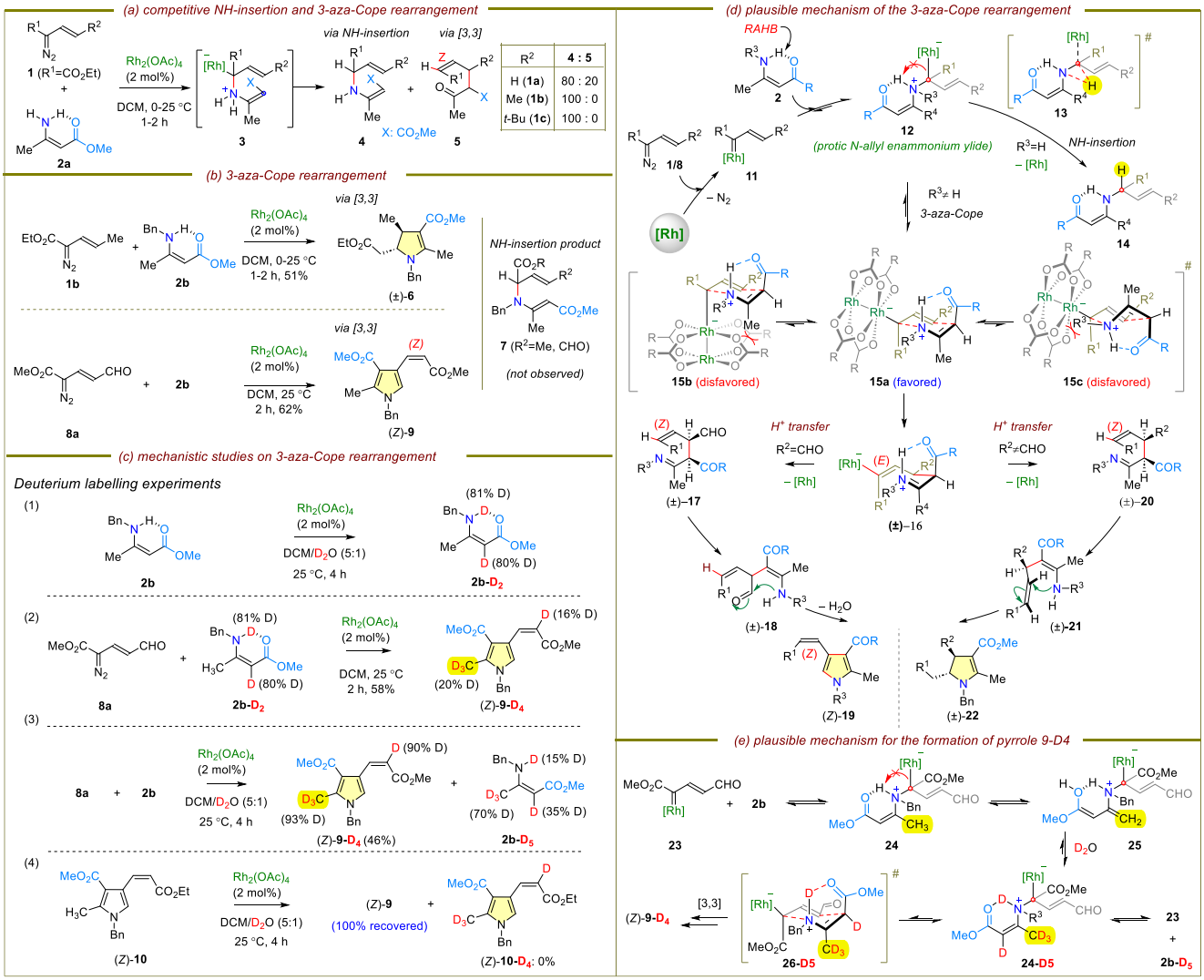

Figure 2. Development of Rh-catalyzed 3-aza-Cope rearrangement of protic *N*-allyl enammonium ylides.

To overcome these problems, we considered *N*-secondary-(*Z*)-*β*-enamino carbonyl compounds as the suitable substrates due to their resonance assisted H-bonding (RAHB) stabilization (~5 kcal/mol).[10] We reasoned that: (i) NH-proton engaged in the RAHB would be reluctant for 1,2-proton transfer of protic enammonium ylide **Y2**, thus disfavouring the undesired NH-insertion, (ii) the σ–π congugation due to RAHB significantly reduces the enamine reactivity requiring harsh conditions for direct C-C bond formation with carbenoid.[11]

Herein we disclose the first successful development of novel Rh-catalyzed and RAHB enabled stereoselective 3-aza-Cope rearrangement of vinyl diazo compounds and *β*-enamino carbonyl compounds ($R^3 \neq H$) via transient Rh-bound protic *N*-allyl enammonium ylide **Y3** (Figure 1c). The reaction gave exclusively [3,3] rearrangement product, (*Z*)-γ,δ-unsaturated imine. No other products arising from either direct NH insertion or carbenoid C-C bond formation were detected. Remarkably, the RAHB played vital role in the implementation of our hypothesis.[12,13] This new reaction has been used in the cascade (3+2)-annulation of vinyldiazo compounds and *N*-primary-*β*-enamino carbonyl compounds resulting in the densely functionalized vinyl and ethynyl pyrroles (Figure 1c). The methodology was used in the short stereoselective synthesis of dihydropyroles, tetrahydroindole and the tricyclic pyrroloindole scaffold of a UV-protecting agent terreusinone.[14]

We initiated our studies with the Rh(II)-catalyzed reaction between vinyl diazo compounds and (*Z*)-*β*-enamino esters in quest for the transient protic *N*-allyl enammonium ylide intermediates (Figure 2). The unstable terminal vinyl diazo ester **1** (R^2=H) reacted rapidly with *N*-primary-(*Z*)-*β*-enamino esters **2a** at 0 °C to give an 80:20 ratio of NH-insertion product **4a** and *in situ* hydrolyzed 3-aza-Cope rearrangement product **5a**. This result shows that the difference in transition state energies for 1,2-proton transfer (NH-insertion) and 3-aza-Cope rearrangement is marginal (~0.75 kcal/mol at 0 °C). The terminal methyl and *t*-Bu vinyldiazo esters **1b-c** disfavored the 3-aza-Cope rearrangement due to steric congestion and gave only NH-insertion product **4** (R^2=Me, *t*-Bu, Figure 2a). A dramatic change in the product selectivity was observed with the *N*-secondary-(*Z*)-*β*-enamino ester **2b** (Figure 2b). The reaction with vinyldiazo ester **1b** proceeded smoothly at 0-25

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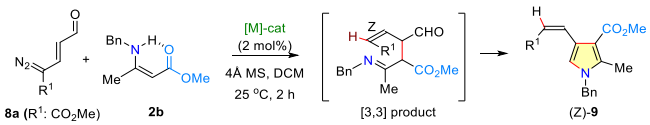
°C and produced only *trans*-2,3-dihydropyrrole (±)-**6** *via in situ* cyclization of the 3-aza-Cope product. Moreover, the enal-functionalized diazo compound (diazoenal) **8a** was also reacted successfully at the room temperature to give exclusively (*Z*)-4-vinylpyrrole **9** via 3-aza-Cope rearrangement and cyclization. The NH-insertion product **7** was not detected. These results indicate that in case of *N*-allyl enammonium ylides derived from *N*-secondary-(*Z*)-*β*-enamino ester **2b**, the barrier for 1,2-proton transfer is much higher than that of 3-aza-Cope rearrangement presumably due to the strong RAHB.

Inspired by these preliminary results, we have carried out control experiments to understand the mechanism of the 3-aza-Cope rearrangement and subesquent cyclization reactions (Figure 2c). In the presence of Rh(II) and D_2O, the *β*-enamino ester **2b** was deuterated to give enamine **2b-D₂** (Figure 2c.1). The Rh-catalyzed reaction of diazoenal **8a** and deuterated enamine **2b-D₂** gave partially deuterated (*Z*)-4-vinyl-pyrrole **9-D₄** (Figure 2c.2). Intrigued by the partial deuteration of ring-methyl group in **9-D₄**, we performed the reaction using D_2O as the co-solvent (Figure 2c.3). Surprisingly, the deuteration was increased to >90% for both ring-methyl and vinylic protons. Moreover, the deuterated enamine **2b-D₅** was also recovered. Subjecting the pyrrole **10** to the reaction conditions using D_2O as the co-solvent did not result in D-incorporated pyrrole **10-D₄** (Figure 2c.4).

Based on the preliminary studies and control experiments, a plausible mechanism for the 3-aza-Cope rearrangement and cascade cyclization was proposed (Figure 2d-e). Rhodium catalyzed denitrogenation of vinyldiazo compound **1/8** results in the rhodium vinylcarbenoid **11**. Reaction of **11** with (*Z*)-*β*-enamino carbonyl compound **2** leads to the formation of transient Rh-bound protic *N*-allyl enammonium ylide **12** stabilized by the RAHB. Based on the deuterium isotope studies this ylide formation is reversible (Figure 2c.3 and 2e). In case of ylide **12** derived from *N*-primary (*Z*)-*β*-enamino carbonyl compound (R^3=H), a competitive 1,2-proton transfer of weakly bonded NH-proton via transition state **13** leads to the NH-insertion product **14**. For the crucial [3,3]-rearrangement, the ylide **12** would prefer a six-membered chair transition state **15a** in which the bulky dirhodium paddle-wheel catalyst occupies less hindered equatorial position. The other chair TS **15b** with axially disposed Rh would be disfavored due to severe 1,3-diaxal strain. Similarly, the boat TS **15c** also disfavored due to severe destabilizing 1,2-interactions of the catalyst bulk and N-substituent. Therefore, the [3,3]-sigmatropic rearrangement is highly stereoselective resulting in the (*E*)-vinyl-Rh species γ,δ–unsaturated imine (±)-**16**. In case of enaldiazo compounds (R^2=CHO), protodemetalation of **16** leads to the (*Z*)-γ,δ–unsaturated (*E*)-imine (±)-**17**. Intramolecular cyclization of **17** via enamine (±)-**18** gives (*Z*)-4-vinylpyrrole **19**. However, in case of vinyldiazo compounds (R^2≠CHO), protodemetalation of **16** leads to the (*Z*)-γ,δ-unsaturated-imine (±)-**20**. Subsequent, stereoselective intramolecular cyclization of **20** via enamine **21** gives *trans*-2,3-dihydropyrrole (±)-**22**. In the presence of D2O, the Rh-bound protic *N*-allyl enammonium ylide **24** undergoes vinylic methyl deuteration **24**→**24-D5** via RAHB stabilized dienol form **25** (Figure 2e). The 3-aza-Cope rearrangent of **24-D5** via transition state **26-D5** and subseqent cyclization leads to the deuterated (*Z*)-4-vinylpyrrole **9-D4**. Whereas reversible nature of Rh-bound protic *N*-allyl enammonium ylide **24-D5** results in the deuterated *β*-enamino ester **2b-D5** and enalcarbenoid **23**.

With the proof of concept, we have investigated the synthetic applications of the new 3-aza-Cope rearrangement. In continuation of our studies on the enalcarbenoids,[7] we have optimized the (3+2) annulation reaction between the bench stable diazoenals **8** and *N*-secondary-(*Z*)-*β*-enamino carbonyl compounds **2**, leading to the valuable (*Z*)-4-vinylpyrroles. Slow addition of a slight excess of diazoenal **8a** in DCM, to a solution of enamine **2b**, 2 mol% $Rh_2(OAc)_4$ and 4 Å MS in DCM at room temperature (25 °C), provided the (*Z*)-4-vinyl pyrrole **9** in 74% yield. (Table 1, entry 1). Other Rh(II)-catalysts such as $Rh_2(oct)_4$, $Rh_2(esp)_2$, $Rh_2[(S)\text{-DOSP}]_4$ and $Rh_2[(S)\text{-PTAD}]_4$ also effective towards the reaction and resulted the pyrrole product in 38-68% yield (entry 2-5). The highly elctrophilic $Rh_2(tfa)_4$ and sterically hindered $Rh_2(tpa)_4$ led to slow reactivity and low yield (entry 6-7).

Table 1. Catalyst screening for the (3+2)-annulation.[a]



Entry	[M]-catalyst	(Z)-9 (%)[b]
1	$Rh_2(OAc)_4$	74
2	$Rh_2(oct)_4$	53
3	$Rh_2(esp)_2$	68
4	$Rh_2[(S)\text{-DOSP}]_4$	60
5	$Rh_2[(S)\text{-PTAD}]_4$	38
6[c]	$Rh_2(tpa)_4$	22
7[c]	$Rh_2(tfa)_4$	15

[a] Reaction conditions: **8a**:**2b** = 0.19:0.15 mmol. [b] Yield of isolated product. [c] reaction time 20 h, incomplete conversion.

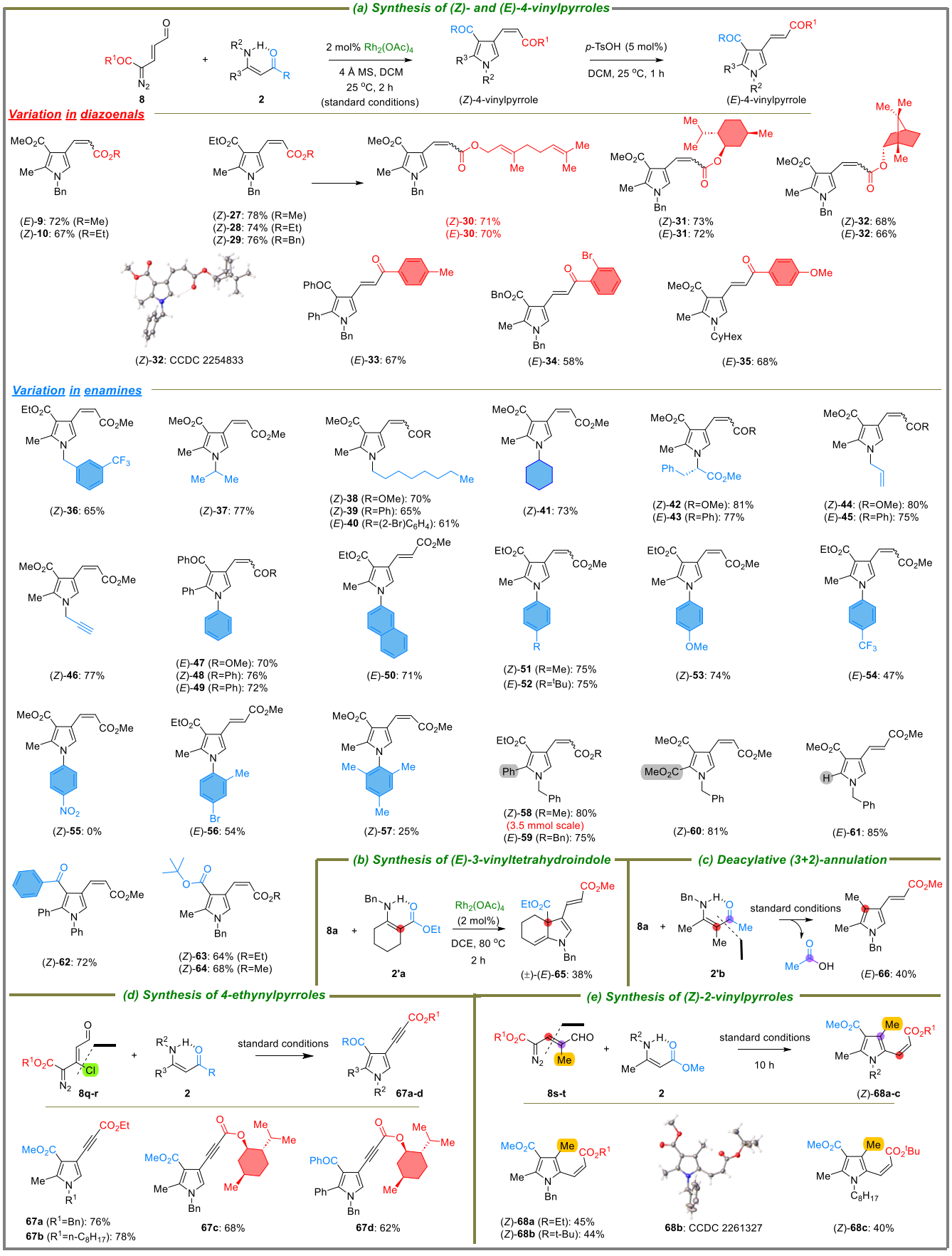


Figure 3. Substrate scope of the (3+2)-annulation.

With the optimized reaction conditions, the scope of the cascade (3+2) annulation was investigated with diverse diazoenals **8** and enamines **2** (Figure 3). Although the reaction gave exclusively (*Z*)-vinyl pyrroles, they tend to isomerize to the more stable (*E*)-vinyl pyrroles during the chromatographic purification. Complete isomerization was achieved in the same reaction flask by adding PTSA-catalyst after the first step (Figure 3a). Thus, a variety of (*Z*)- and (*E*)-vinyl pyrroles could be accessed using these protocols. Alkyl and benzyl ester diazoenals reacted efficiently with enamino esters to deliver 4-vinylpyrroles **9-10** and **27-29** in high yield (67-78%). The geraniol ester diazoenal having alkene side chain was tolerated despite the potential cyclopropanation to give pyrroles **30** in 70-71% yield. Menthyl and bornyl ester diazoenals gave chiral pyrroles **31-32** in 66-73% yield. The keto diazoenals having diverse aryl substituents were investigated. Alkyl, halo, and methoxy-substituted aryl diazoenals successfully reacted to deliver 4-vinylpyrroles **33-35** in 58-68% yield. The sterically hindered 2-bromophenyl keto-diazoenal also successfully reacted to give the pyrrole **34** in 58% yield. Next, the scope of the enamine was investigated with diverse N/C-substituents. Enamines derived from benzyl/n-alkyl/cyclohexyl amine and chiral amino esters are successfully reacted to deliver pyrrole products **36-43** in 61-81% yield. Gratifyingly, *N*-allyl/propargyl enamino esters gave pyrrole products **44-46** in excellent yield (75-80%) despite the potential [2,3]-sigmatropic rearrangement and cyclopropanation, indicating the facile [3,3] rearrangement. The electronic and steric influence of N-substituent was investigated by using enamino esters derived from diverse arylamines. The neutral and electron-rich (R: alkyl, OMe) aryl groups were compatible resulting in the *N*-arylpyrroles **47-53** in high yields (70-76%). The electron-withdrawing groups significantly impacted the pyrrole formation presumably due to the inefficiency of protic enammonium ylide formation. Although, 4-trifluoromethyl group gave pyrrole **54** in 47% yield, the highly electron-withdrawing 4-nitro substituent failed to deliver the pyrrole **55**. With respect to the steric effect, 2-methyl substituent was tolerated (**56**, 54%). In contrast, 2,6-dimethyl substitution severely hampered the reaction (**57**, 25%). Subsequently, the scope of the C-substituted enamines was evaluated. Phenyl and ester groups at *β*–carbon were tolerated resulting in the corresponding pyrroles **58-60** in 75-81% yield. The disubstituted enamino ester gave pyrrole **61** in excellent yield (85%). The aryl ketone, and the bulky *t*-Bu ester at the *α*-carbon were compatible resulting in the pyrroles **62-64** in 64-72% yield. The scalability of the reaction was demonstrated on a 3.5 mmol scale, which furnished (*Z*)-4-vinyl pyrrole **58** in 80% yield.

Further, the efficiency of [3,3]-rearrangement was investigated using sterically hindered tetrasubstituted (*Z*)-*β*-enamino esters **2'** (Figure 3b-c). The reaction of diazoenal **8a** with cyclohexene fused (*Z*)-*β*-enamino ester **2'a** required elevated temperature to give valuable (*E*)-3-vinyl-tetrahydroindole (±)-**65** having a quaternary carbon (Figure 3b and Figure 4). Interestingly, under standard conditions, the (*Z*)-*α*,*β*-dimethyl-*β*-enamino ketone **2'b** gave (*E*)-4-vinylpyrrole **66** presumably through deacylative C-C fragmentation of pyrrol-1-ium intermediate (±)-**E** via (±)-**F** (Figure 3c and Figure 4). The effect of enal-substitution on 3-aza-Cope rearrangement and subsequent pyrrole formation was investigated (Figure 3d-e). Interestingly, under the optimized conditions, *β*-chloro-diazoenals **8q-r** succesfully reacted to produce valuable 4-ethynyl pyrroles **67a-d** in 62-78% yield (Figure 3d). In this case, upon [3,3] rearrangement, the vinyl-Rh species (±)-**A** undergoes Rh-assisted *β*-chloride elimination leading to alkynyl-imine (±)-**I** (Figure 4). Subsequent, intramolecular cyclization via enamine **J** gives 3-alkynyl-pyrrole **67**. On the other hand, *α*-methyl-diazoenals **8s-t** gave fully substituted-(*Z*)-2-vinylpyrroles **68a-c** in moderate yield involving diazoenal *sp*² C-C fragmentation (Figure 3e). As shown in Figure 4, intramolecular cyclization of [3,3]-rearrangement product (±)-**D** (Y=Me, R⁴=H) gives (*Z*)-3-vinyl-3H-pyrrol-1-ium ion (±)-**G**. Selective migration of vinyl group via [1,5]-sigmatropic rearrangement and aromatization produces the (*Z*)-2-vinylpyrrole **68**.

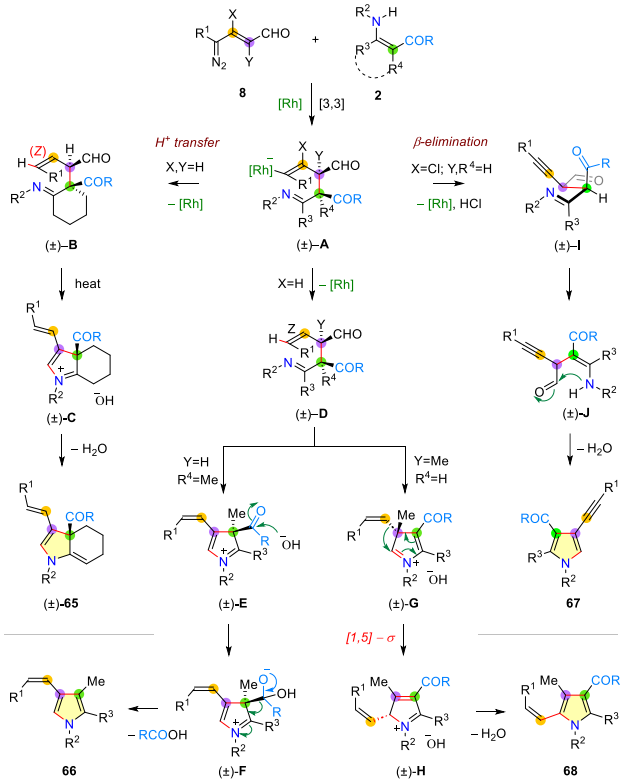


Figure 4. Plausible mechanism for the formation of pyrroles **65-68**.

Finally, we have studied other synthetic applications of (3+2) annulation and pyrrole products (Figure 5). Intrigued by the deuterium labeling studies, we further extended the scope of (3+2)-annulation by preparing a few deuterated 4-vinyl and 4-alkynylpyrroles **69-72** with upto >99% ring-Me deuteration (Figure 5a). Rh-catalyzed reaction between vinyldiazo ester **1** and enamine **2b** gave 2,3-dihydropyrroles (±)-**73-74** in 55-67% yield (Figure 5b). Reaction of (*E*)-4-vinylpyrrole **33** with Corey-Chaykovsky reagent furnished the cyclopropylketone (±)-**75** in 77% yield (Figure 5c).

Exposure of **75** to Lewis acid $TiCl_4$ at room temperature resulted in 7-arylindole **76** in 62% yield (Figure 5c). Gratifyingly, in the presence of $TiCl_4$, 4-vinylpyrroles **9/58** undergone stereoselective dimerization to give valuable 1,5-dibenzyl-1,4,5,8-tetrahydropyrrolo[2,3-f]indole scaffold (±)-**77** and (±)-**78** in good yields (Figure 5d). This tricyclic motif is a core structure of novel anti-tumour and UV-A protecting agent terreusinone **79**.[14]

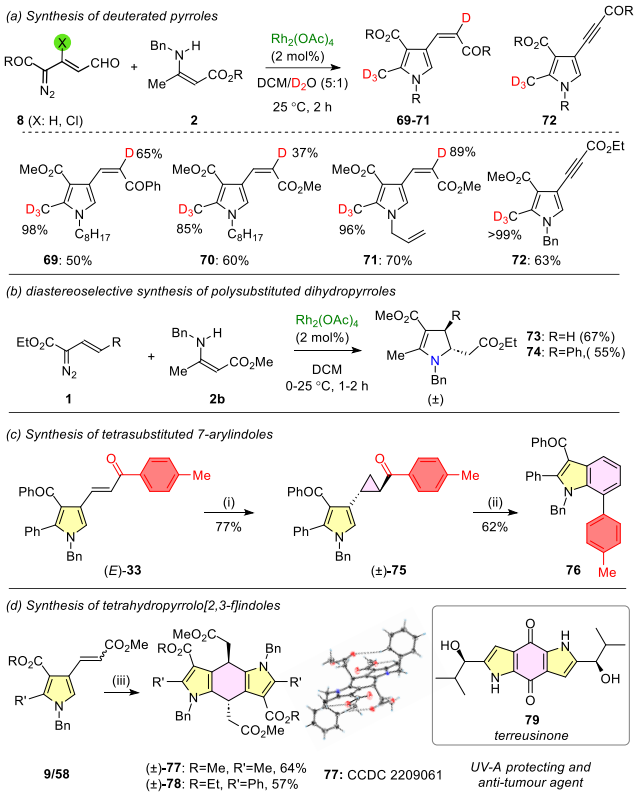


Figure 5. Synthetic applications. Conditions: (i) NaH, $Me_3S(O)I$, THF/DMF (5:1); (ii) $TiCl_4$, DCM, 25 °C, 12 h; (iii) $TiCl_4$, DCE, 60 °C, 4 h.

In conclusion, we have reported the new class of Rh-bound protic *N*-allyl enammonium ylides. These ylides are generated *in situ via* Rh-catalyzed reaction of *N*-secondary-(*Z*)-*β*-enamino carbonyl compounds and vinyldiazo compounds at ambient conditions. These highly reactive transient ylides undergo facile Rh-assisted and RAHB enabled stereoselective 3-aza-Cope rearrangement via chair transition state. The utility of 3-aza-Cope rearrangement was demonstrated by the synthesis of multi-substituted vinyl and alkynyl pyrroles, dihydropyrroles, deuterated pyrroles, and tetrahydroindoles via cascade (3+2) annulation. The pyrrole products allowed short synthesis of a tricyclic core of an anti-tumour and UV-A protecting agent terreusinone. Further studies on the asymmetric 3-aza-Cope rearrangement and synthetic applications of (3+3)-annulation are ongoing in our laboratory.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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REFERENCES

(1) (a) Opitz, G.; Mildenberger, H. Einfache Synthese von Aldehyden mit quartärem α-Kohlenstoffatom. *Angew. Chem.* **1960**, *72*, 169. (b) Opitz, G. Verlauf Der Allyl- Und Propargyl-Allenyl-Umlagerungen Bei Der Alkylierung Von Enamine. *Justus Liebigs Ann. Chem.* **1961**, *650*, 122-132. (c) Brannock, K. C.; Burpitt, R. D. The Chemistry of Isobutenylamines. II. Alkylation with Allylic and Benzyl Halides. *J. Org. Chem.* **1961**, *26*, 3576-3577.

(2) Nubbemeyer, U. Aza-Claisen Rearrangement. *The Claisen Rearrangement: Methods and Applications*. Hiersemann, M.; Nubbemeyer, U. (Eds), Wiley-VCH Weinheim, 2007, 461-523.

(3) (a) Majumdar, K. C.; Bhattacharyya, T.; Chattopadhyay, B.; Sinha, B. Recent Advances in the Aza-Claisen Rearrangement. *Synthesis* 2009, 2117-2142. (b) Jung, J.-W.; Kim, S.-H.; Suh, Y.-G. Advances in Aza-Claisen-Rearrangement-Induced Ring-Expansion Strategies. *Asian J. Org. Chem.* **2017**, *6*, 1117–1129. (c) Wei, L.; Wang. C.-J. Recent advances in catalytic asymmetric aza-Cope rearrangement. *Chem. Commun.* **2021**, 57, 10469–10483.

(4) (a) Rhoads, S. J.; Raulins, N. R. The Claisen and Cope Rearrangements. *Org. React.* **1975**, *22*, 1-252. (b) Lutz, R. P. Catalysis of the Cope and Claisen Rearrangements. *Chem. Rev.* **1984**, *84*, 205-247. (c) Castro, A. M. M. Claisen Rearrangement over the Past Nine Decades. *Chem. Rev.* **2004**, *104*, 2939–3002. (d) Rehbein, J.; Hiersemann. M. Claisen Rearrangement of Aliphatic Allyl Vinyl Ethers from 1912 to 2012: 100 Years of Electrophilic Catalysis. *Synthesis* **2013**, *45*, 1121–1159.

(5) (a) Nubbemeyer, U. Recent Advances in Charge-Accelerated Aza-Claisen Rearrangements. *Top. Curr. Chem.* **2005**, *244*, 149–213.

(6) Selected examples of 3-aza-Cope rearrangement: (a) Fiedler, D.; van Halbeek, H.; Bergman, R. G.; Raymond, K. N. Supramolecular Catalysis of Unimolecular Rearrangements: Substrate Scope and Mechanistic Insights. *J. Am. Chem. Soc.* **2006**, *128*, 10240-10252. (b) Waetzig, S. R.; Tunge, J. A. Regio- and Diastereoselective Decarboxylative Coupling of Heteroaromatic Alkanes. *J. Am. Chem. Soc.* **2007**, *129*, 4138-4139. (c) Weston, M. H.; Nakajima, K.; Back. T. G. Tandem Conjugate Additions and 3-Aza-Cope Rearrangements of Tertiary Allyl Amines and Cyclic α-Vinylamines with Acetylenic Sulfones. Applications to Simple and Iterative Ring Expansions Leading to Medium and Large-Ring Nitrogen Heterocycles. *J. Org. Chem.* **2008**, *73*, 4630–4637. (c) Brown, C. J.; Bergman, R. G.; Raymond, K. N. Enantioselective Catalysis of the Aza-Cope Rearrangement by a Chiral Supramolecular Assembly. *J. Am. Chem. Soc.* **2009**, *131*, 17530–17531. (d) Cant, A. A.; Bertrand, G. H. V.; Henderson, J. L.; Roberts, L.; Greaney, M. F. The Benzyne Aza-Claisen Reaction. *Angew. Chem. Int. Ed.* **2009**, *48*, 5199–5202. (e) Maity, P.; Pemberton, R. P.; Tantillo, D. J.;

Tambar, U. K. Brønsted Acid Catalyzed Enantioselective Indole Aza-Claisen Rearrangement Mediated by an Arene CH–O Interaction. *J. Am. Chem. Soc.* **2013**, *135*, 16380–16383. (f) Sakai, T.; Furuhata, T.; Hosoe, K.; Umemura, K.; Mori, Y. Synthesis of Fused Tricyclic Amines Bearing Tetrasubstituted Carbons Using an Alkylation–Cyclization–Isomerization–3-aza Cope Cascade Reaction. *Org. Lett.* **2023**, *25*, 2986–2990. (g) Li, K.; Qin, W.-M.; Su, W.-X.; Hu, J.-M.; Cai, Y.-P. Chiral BINOL-phosphate assembled single hexagonal nanotube in aqueous solution for confined rearrangement acceleration. *Nat. Commun.* **2024**, 15, 2799.

(7) (a) Dawande, S. G.; Kanchupalli, V.; Kalepu, J.; Chennamsetti, H.; Lad, B. S.; Katukojvala, S. Rhodium Enalcarbenoids: Direct Synthesis of Indoles by Rhodium(II)-Catalyzed [4+2] Benzannulation of Pyrroles. *Angew. Chem. Int. Ed.* **2014**, *53*, 4076–4080. (b) Kalepu, J.; Katukojvala, S. Dienamine Activation of Diazoenals: Application to the Direct Synthesis of Functionalized 1,4-Oxazines. *Angew. Chem. Int. Ed.* **2016**, *55*, 7831-7835. (c) Kanchupalli, V.; Katukojvala, S. [1+1+3] Annulation of Diazoenals and Vinyl Azides: Direct Synthesis of Functionalized 1-Pyrrolines through Olefination. *Angew. Chem. Int. Ed.* **2018**, *57*, 5433-5437. (d) Lad, B. S.; Katukojvala, S. Piano-Stool Rhodium Enalcarbenoids: Application to Catalyst-Controlled Metal-Templated Annulations of Diazoenals and 1,3-Dicarbonyls. *ACS Catal.* **2018**, *8*, 11807–11814. (e) Mandal, P. K.; Katukojvala, S. Rh-Catalyzed Chemodivergent [3+3] Annulations of Diazoenals and α-Aminoketones: Direct Synthesis of Functionalized 1,2-Dihydropyridines and Fused 1,4-Oxazines. *Chem. Eur. J.* **2024**, *30*, e202303862. (f) [3+3] Annulation of Diazoenals and α-Mercapto Ketones via Protic Sulfonium Ylides: Direct Synthesis of 2*H*-Thiopyrans, Innovative Progenitors for Unstudied 2*H*-Thiopyran-2-ones and 4*H*-Thiopyran-4-ones. Mandal, P. K.; Chakrawarti, R.; Katukojvala, S. *Org. Lett.* **2024**, 26, 3463 – 3468. (g) Chennamsetti, H.; Rathore, K. S.; Chatterjee, S.; Mandal, P. K.; Katukojvala, S. Triple Nucleophilic Head-to-Tail Cascade Polycyclization of Diazodienals via Combination Catalysis: Direct Access to Cyclopentane Fused Aza-Polycycles with Six-Contiguous Stereocenters. *JACS Au* **2024**, *4*, 2099–2107.

(8) For NH-insertion reactions of protic ammonium ylides derived from metal carbenes, see: (a) Zhu, S.-F.; Zhou, Q.-L. Transition-Metal-Catalyzed Enantioselective Heteroatom–Hydrogen Bond Insertion Reactions. *Acc. Chem. Res.* **2012**, *45*, 1365–1377. (b) Gillingham, D.; Fei, N. Catalytic X–H insertion reactions based on carbenoids. *Chem. Soc. Rev.* **2013**, *42*, 4918-4931. For *in situ* trapping of protic ammonium ylides, see: (c) Guo, X.; Hu, W. Novel Multicomponent Reactions via Trapping of Protic Onium Ylides with Electrophiles. *Acc. Chem. Res.* **2013**, *46*, 2427–2440.

(9) (a) Lourdusamy, E.; Yao, L.; Park, C.-M. Stereoselective Synthesis of α-Diazo Oxime Ethers and Their Application in the Synthesis of Highly Substituted Pyrroles through a [3+2] Cycloaddition. *Angew. Chem. Int. Ed.* **2010**, *49*, 7963-7967. (b) Huang, F.; Liu, Z.; Wang, Q.; Lou, J.; Yu, Z. Copper-Catalyzed Formal Carbene Migratory Insertion into Internal Olefinic C═C Bonds with *N*-Tosylhydrazones To Access Iminofuran and 2(3*H*)-Furanone Derivatives. *Org. Lett.* **2017**, *19*, 3660–3663. (c) Chen, J.; Guo, P.; Zhang, J.; Rong, J.; Sun, W.; Jiang, Y.; Loh, T.-P. Synthesis of Functionalized α-Vinyl Aldehydes from Enaminones. *Angew. Chem. Int. Ed.* **2019**, *58*, 12674 – 12679. (d) Luo, K.; Mao, S.; He, K.; Yu, X.; Pan, J.; Lin, J.; Shao, Z.; Jin, Y. Highly Regioselective Synthesis of Multisubstituted Pyrroles via Ag-Catalyzed [4+1C]^{insert} Cascade. *ACS Catal.* **2020**, 10, 3733-3740. (e) Chen, J.; Han, J.; Zhang, J.; Li, L.; Zhang, Z.; Yang, Y.; Jiang, Y. Rhodium/Amine Dual Catalytic System for Reassembling C≡C Bonds of Conjugated Alkynes with Cyclopropenes via Cutting/Insertion Cascade. *ACS Catal.* **2022**, 12, 23, 14748–14753. (f) Chen, K.; Lv, J.; Chen, J.; Zhang, J.; Li, L.; Zhao, M.; Jiang, Y. Amine-Release Annulation of Enaminones: Bimetallic Co-Catalytic Synthesis of Cyclopentadienes from Alkynes. *Org. Lett.* **2023**, 25, 4688–4693. (g) Wang, E.; Luo, J.; Zhang, L.; Zhang, J.; Jiang, Y. Copper-Catalyzed Oxidative [3+2] Cycloaddition of Enamines and Pyridotriazoles toward Indolizines. *Org. Lett.* **2024**, *26*, 1249–1254.

(10) Gilli, P.; Bertolasi, V.; Ferretti, V.; Gilli, G. Evidence for Intramolecular N–H•••O Resonance-Assisted Hydrogen Bonding in β-Enaminones and Related Heterodienes. A Combined Crystal-Structural, IR and NMR Spectroscopic, and Quantum-Mechanical Investigation. *J. Am. Chem. Soc.* **2000**, *122*, 10405-10417.

(11) Vaitla, J.; Bayer, A.; Hopmann, K. H. Synthesis of Indoles and Pyrroles Utilizing Iridium Carbenes Generated from Sulfoxonium Ylides. *Angew. Chem. Int. Ed.* **2017**, *56*, 4277-4281.

(12) Synthetic applications of RAHB: (a) So, S. M.; Mui, L.; Kim, H.; Chin, A. J. Understanding the Interplay of Weak Forces in [3,3]-Sigmatropic Rearrangement for Stereospecific Synthesis of Diamines. *Acc. Chem. Res.* **2012**, *45*, 1345–1355. (b) Mahmudov, K. T.; Pombeiro, A. J. L. Resonance-Assisted Hydrogen Bonding as a Driving Force in Synthesis and a Synthon in the Design of Materials. *Chem. Eur. J.* **2016**, *22*, 16356–16398.

(13) For RAHB driven diaza-Cope rearrangement, see: (a) Chin, J.; Mancin, F.; Thavarajah, N.; Lee, D.; Lough, A.; Chung, D. S. Controlling Diaza-Cope Rearrangement Reactions with Resonance-Assisted Hydrogen Bonds. *J. Am. Chem. Soc.* **2003**, *125*, 15276-15277. (b) Kim, H.-J.; Kim, H.; Alhakimi, G.; Jeong, E. J.; Thavarajah, N.; Studnicki, L.; Koprianiuk, A.; Lough, A. J.; Suh, J.; Chin, J. Preorganization in Highly Enantioselective Diaza-Cope Rearrangement Reaction. *J. Am. Chem. Soc.* **2005**, *127*, 16370-16371. (c) Kim, H.; Nguyen, Y.; Yen, C. P.-H.; Chagal, L.; Lough, A. J.; Kim, B. M.; Chin, J. Stereospecific Synthesis of C2 Symmetric Diamines from the Mother Diamine by Resonance-Assisted Hydrogen-Bond Directed Diaza-Cope Rearrangement. *J. Am. Chem. Soc.* **2008**, *130*, 12184–12191.

(14) (a) New Dipyrroloquinones from a Plant-Derived Endophytic Fungus *Talaromyces sp*. *Molecules* **2023**, *28*, 7847. (b) Nivedithai, L.; Fu, P.; Leao, T. F.; Li, T.; Wang, T.; Poulin, R. X.; Gasper, L. R.; Naman, C. B.; Puthiyedathu, S. T. Targeted Isolation of Two New Anti-inflammatory and UV-A Protective Dipyrroloquinones from the Sponge-associated Fungus *Aspergillus tamarii* MCCF102. *Planta Med.* **2022**, *88*, 774–782. (c) Wang, C.; Sperry, J. Total Synthesis of the Photoprotecting Dipyrrolobenzoquinone (+)-Terreusinone. *Org. Lett.* **2011**, *13*, 6444-6447.