Triple Nucleophilic Head-to-Tail Cascade Polycyclization of Diazodienals via Combination Catalysis: Direct Access to Cyclopentane Fused Aza-Polycycles with Six-Contiguous Stereocenters

Haribabu Chennamsetti, Kuldeep Singh Rathore,† Saikat Chatterjee, Pratap Kumar Mandal, and Sreenivas Katukojvala*

Department of Chemistry, Indian Institute of Science Education and Research, Bhopal, Madhya Pradesh, India 462066

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ABSTRACT: Reported herein are the bench stable (2*E*,4*E*)-diazohexa-2,4-dienals (diazodienals) and their unprecedented polycyclization with aldimine and arylamines enabled by Rh(II)/Brønsted acid relay catalysis. This scalable and atom-economical reaction provides direct access to the biologically important azatricyclo[6.2.1.0^{4,11}]undecane fused polycycles having six-contiguous stereocenters. Mechanistic studies revealed that polycyclization proceeds through an unusual triple-nucleophilic cascade initiated by aldimine attack on remote Rh-carbenoid, 6π-electrocyclization of aza-trienyl azomethine ylide, stereoselective aza-Michael addition *via* iminium activation and inverse electron-demand intramolecular aza Diels-Alder reaction. The π–π secondary interactions play a crucial role in the preorganization of reactive intermediates for the pericyclic reactions and hence the overall efficiency of the polycyclization.

Cyclopentane-fused polycyclic alkaloids having azatricyclo[6.2.1.0^{4,11}]undecane core are prevalent in various plant species (e.g., Fig. 1A).[1] These plant extracts are traditional herbal medicines for diverse ailments including fever, pain, inflammation, hypertension, cancer, and microbial diseases. The intriguing complexity of these polycyclic architectures, decorated with varying *N*-substitution and multiple contiguous stereocenters, has attracted significant attention towards developing novel strategies to total synthesis.[2-6] However, the direct approaches for constructing azatricyclo[6.2.1.0^{4,11}]undecane fused scaffolds from simple precursors remained challenging.[6a,7]

Stereoselective functionalization of C=C π-bonds by means of organocatalytic activation of enals is a powerful strategy that finds wide applications in chemical synthesis.[8] Pioneering studies by Jørgensen and others have shown that aminocatalytic LUMO and HOMO activation could be extended to the challenging remote functionalization of conjugated enals (Fig. 1B) to access a variety of 5-6 membered monocyclic and fused carbo/heterocycles.[9] However, the scope of the reactions is limited to the nucleophilic/electrophilic additions and cycloadditions, offered by the conjugated iminium/enamine intermediates.

Inspired by the rich chemistry of enals and diazo compounds,[9-10] we have designed a conceptually new building blocks "conjugated diazoenals" in which enal and diazo motif is integrated through π-conjugation (Fig. 1C). We

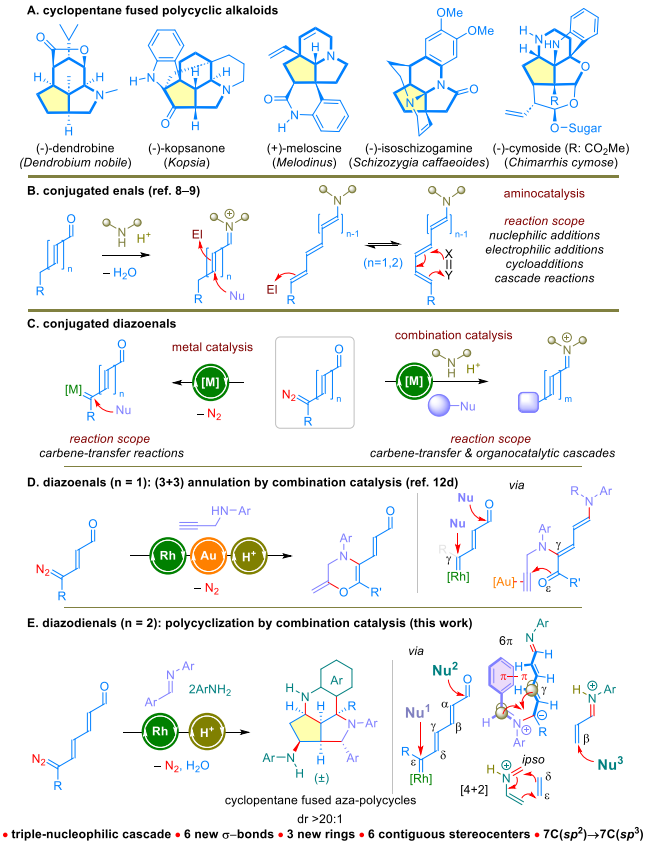


Figure 1. A. Azatricyclo[6.2.1.0^{4,11}]undecane fused natural products, B-E. Reactivity of conjugated enals and diazoenals.

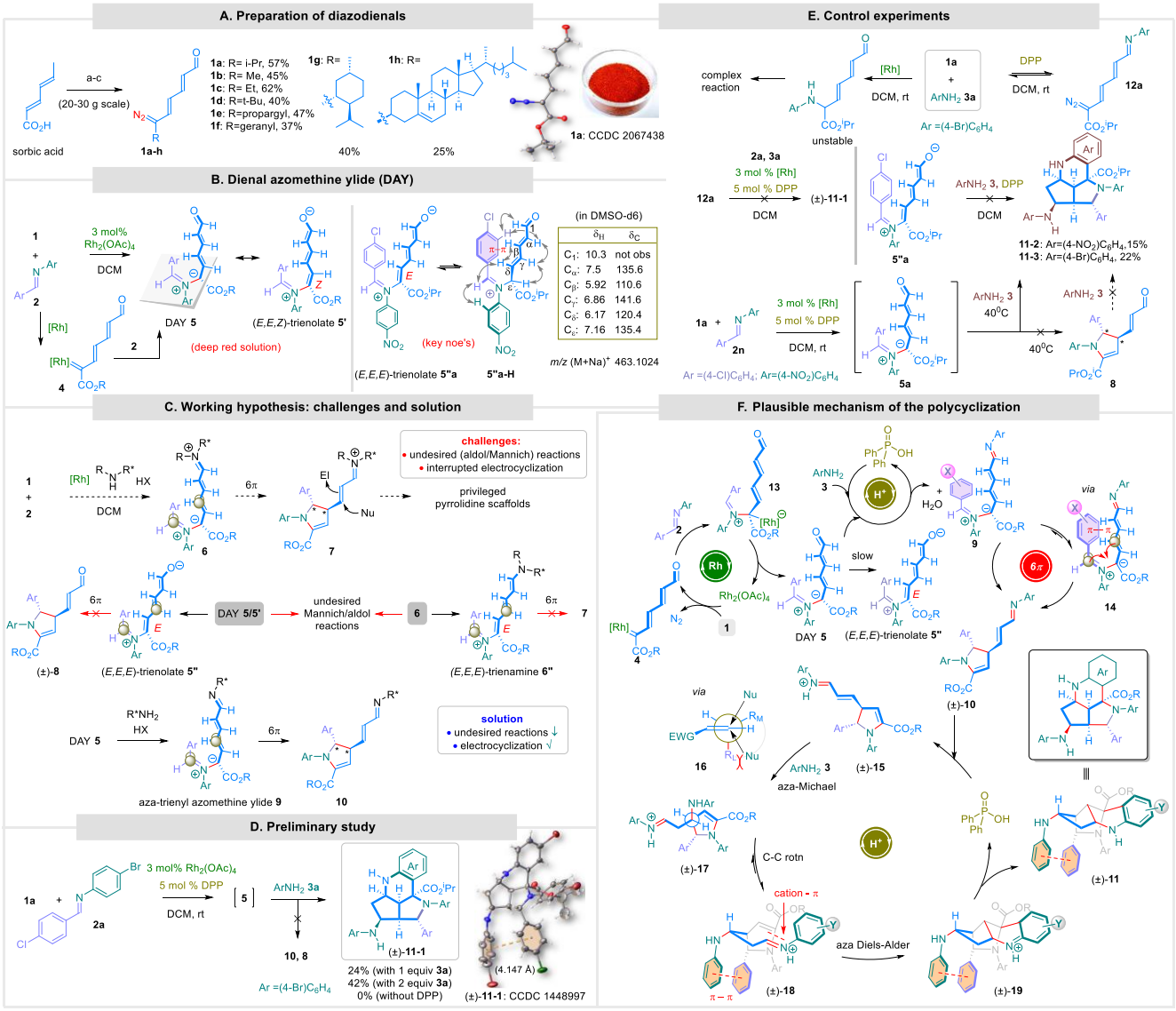


Figure 2. Inception of polycyclization of diazodienals. conditions:(a) $SOCl_2$, then ROH; (b) DBU, TsN_3; (c) $POCl_3$/DMF.

envisioned that remote functionalization of conjugated diazoenals could be accessed through distinct carbene transfer reactions such as σ-bond insertions, ylide reactions, cycloadditions, atom/group transfer, and cross-coupling reactions. More importantly, conjugated diazoenals could serve as excellent substrates for combination catalysis (metal and organocatalysis) to create rapid molecular complexity through unique cascade reactions that are not accessible by independent catalytic processes.[11]

Initial investigations by us and others revealed that (2*E*)-diazoenals (n = 1) are versatile substrates for metal catalysis and combinations catalysis.[12-13] Rh-enalcarbenoid reacts with a variety of π- and heteroatom nucleophiles resulting in the (4+2),[12a,c,13] (4+1),[12b] (1+1+3),[12f] and (3+2)[12g] annulations, olefination,[12f] and enal-transfer[12h] reactions. Notably, the reaction of diazoenal and *N*-aryl propargylamine under combination catalysis gave enal-functionalized 1,4-oxazines *via* cascade Rh-carbenoid NH-insertion and remote 6-*exo*-*dig* heterocyclization enabled by synergistic Au(I) and dienamine catalysis (Fig. 1D).[12d]

Herein we report the novel (2*E*,4*E*)-diazohexa-2,4-dienals (diazodienals, n=2) and the discovery of their unprecedented triple-nucleophilic head-to-tail cascade polycyclization with aldimine and aryl amines under Rh(II)/Brønsted acid relay catalysis (Fig. 1E).[14] The reaction gave a single diastereomer (dr >20:1) of the cyclopentane fused polycycles sharing azatricyclo[6.2.1.0^{4,11}]undecane core. The polycyclization proceeds through four distinct reaction modes- remote carbenoid azomethine ylide formation, 6π-electrocyclization, aza-Michael addition, and inverse electron demand Aza Diels-Alder reaction leading to the formation of six new σ-bonds, three new rings, and six-contiguous stereocenters.

Diazodienals were prepared in multigram quantities using inexpensive sorbic acid (Fig. 2A). Most of these compounds are orange-colored crystalline solids with good thermal stability (see the SI for the DSC study). The single crystal X-ray structure of isopropyl ester **1a** revealed the rigid (*E*,*E*)-configuration of the dienal motif.

Initial studies revealed that diazodienal **1** reacts with aldimine **2** via Rh(II)-dienalcarbenoid **4** to give deep red solution of novel unstable dienal azomethine ylide (DAY) **5** (Fig. 2B). While azomethine ylide formation was slow at room temperature, prolonged reaction times and higher temperatures resulted in complex products due to uncontrolled Mannich and self-aldol reactions (see SI). DAYs derived from the electron-deficient aldimines of 4-nitroanline could be detected by TLC. However, they isomerize to the (*E,E,E*)-trienolate **5"a**, which could be characterized in the protonated form **5"a**-H. The structure of **5"a**-H was established by 1D and 2D-NMR spectroscopy. The unusual shielding/deshielding of proton and carbon NMR signals of dienal motif [e.g., δ_H 7.5 (H_α), 5.92 (H_β), 6.86 (H_γ); δ_C 135.6 (C_α), 110.6 (C_β), 141.6 (C_γ)] suggests the ring current effect in **5"a**-H. Moreover, the NOE interactions between the dienal and C-aryl group, due to the stabilizing π–π interactions, further support the assigned geometry of **5"a**-H. The absence of aldehyde C1-carbon resonance in ^{13}C-NMR indicates an equilibrium between **5"a** and **5"a**-H.

We hypothesized that DAY **5** could serve as a valuable substrate for the subsequent aminocatalytic 6π-electrocyclization and iminium/enamine cascade reactions via **6** and **7** to access privileged pyrrolidine heterocyclic scaffolds (Fig. 2C). However, we realized two significant challenges in our proposed plan– uncontrolled Mannich/aldol reactions of DAY, and interrupted 6π-electrocyclization due to the isomerization of DAY to the unproductive (*E,E,E*)-trienolate **5"** or (*E,E,E*)-trienamine **6"** (See SI for details). We envisioned that aza-trienyl azomethine ylide **9** would offer two advantages- prevents undesired side reactions due to reduced nucleophilicity and satisfies electronic and geometrical requirements of 6π-electrocyclization to access dihydropyrrole **10** for further elaborations. To our surprise, in presence of a Brønsted acid catalyst diphenyl phosphate (DPP), the in situ formed DAY **5** reacted with arylamine **3a** to give a polycyclization product (±)-**11-1** as a single diastereomer (24%, dr >20:1) instead of dihydropyrrole **10/8** (Fig. 2D). The structure of (±)-**11-1** was confirmed by the single crystal X-ray analysis indicating that two molecules of arylamine were utilized in trapping the DAY. Repeating the reaction with two equivalents of arylamine improved the yield to 42%. In the absence of DPP, tetracycle was not obtained. To our knowledge, this is the first report on the polycyclization of conjugated azomethine ylides.[15-17]

Inspired by this remarkable result, we have designed control experiments to gain insight into the details of the polycyclization reaction (Fig. 2E). In the absence of aldimine, the diazoenal **1a** reacts with arylamine **3a** to give a complex mixture *via* the unstable carbenoid NH-insertion product. In the presence of catalytic DPP, diazodienal **1a** reacts with arylamine **3a** to establish an equilibrium with conjugated ε-diazoimine **12a**. However, the isolated diazoimine **12a** failed to give the polycyclization product (±)-**11-1**; instead, it slowly decomposed. This result suggests that **12a** is not involved in polycyclization. Notably, when (*E,E,E*)-trienolate **5"a** was treated with 4-nitroaniline **3n** and DPP, tetracycle **11-2** was not obtained, indicating that **5"a** is not involved in the polycyclization. In contrast, the in situ formed DAY **5a** under the same conditions gave **11-2** in 15% yield. Using 4-bromoaniline **3a** gave the tetracycle **11-3** in 22% yield. The low yield of tetracycles could be attributed to the competing conversion of **5a** into unproductive **5"a** and undesired side reactions. Independently, the in situ formed ylide **5a** was decomposed upon heating, and the 6π-electrocyclization product enal-dihydropyrrole **8** was not observed.[18] These results support that 6π-electrocyclization indeed proceeds via aza-trienyl azomethine ylide **9**.

Based on the control experiments, a plausible mechanism was proposed for the polycyclization (Fig. 2F). The transient Rh-dienalcarbenoid **4** generated from diazodienal **1** reacts with aldimine **2** to give metal-bound DAY **13**. Release of Rh-catalyst leads to metal-free DAY **5**, which prefers twisted non-planar structure due to steric constraints around the new C-N σ-bond.[19] A competing isomerization due to charge delocalization in **5** through dienal motif leads to the unproductive trienolate (*E,E,E*)-**5"**. In the presence of Brønsted acid, DAY **5** rapidly reacts with arylamine **3** to give aza-trienyl azomethine ylide **9**. Stereospecific disrotatory 6π-electrocyclization of **9** via conformation **14** results in *trans*-dihydropyrrole (±)-**10**. The stabilizing aryl-olefin π–π secondary orbital interactions between the electron-deficient iminium C-aryl group and electron-rich aza-trienyl motif would favor the conformation **14** and lower the transition state barrier of electrocyclization.[20-21] Next, Brønsted acid catalyzed aza-Michael addition of arylamine **3** to iminium ion **15** from the less hindered face *via* **16** leads to the adduct **17**. Intramolecular aza-Diels-Alder reaction via reactive conformation **18** results in the cyclopentannulated tetracycle **19**. The presence of cation–π and π–π secondary interactions stabilize the molecular conformation of **18,** which is *preorganized* to undergo the aza Diels-Alder reaction in a facile way, to give **19** (which is also stabilized via π–π-interactions). Finally, re-aromatization of **19** delivers the aza-polycyclic product (±)-**11**. The molecular conformation of (±)-**11-1** as determined from single crystal X-Ray data is also stabilized via π–π interactions, and this unequivocally establishes the significance of these interactions in the formation and stabilization of the different intermediates (**18** and **19**), leading to the final product.

With the preliminary results and mechanistic details, we have further optimized the polycyclization reaction (Fig. 3A). Control experiments revealed that the formation of tetracycles could be improved by minimizing the concentrations of diazodienal, aldimine, and arylamine during the reaction. Gratifyingly, the slow addition of a premixed solution of **1a**, **2a**, and **3a** to the reaction flask containing a solution of DPP and $Rh_2(OAc)_4$ at 40 °C gave the polycyclization product **11-1** in 78% yield within 4 h (entry 1, See SI for NMR study). Other rhodium(II)-catalysts such as $Rh_2(oct)_4$, $Rh_2(esp)_2$, and $Rh_2(tfa)_4$ are also effective (entries 2-4). Sterically hindered $Rh_2\{(S)\text{-DOSP}\}_4$ and $Rh_2\{(S)\text{-PTAD}\}_4$ resulted in sluggish reaction and reduced yields (entries 5-6).

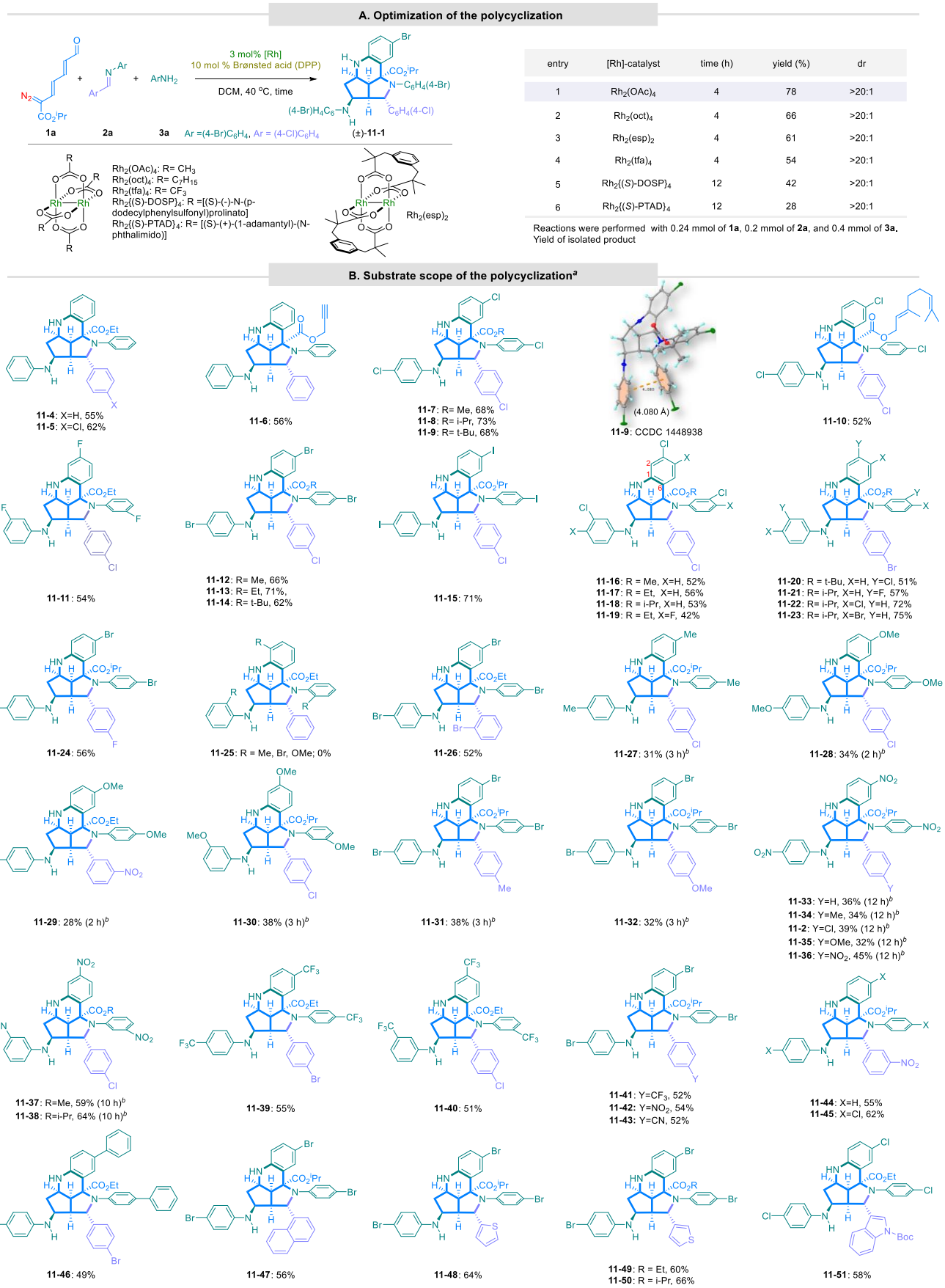


Figure 3. A. Optimization and B. Substrate Scope of the Polycyclization. [a] Reactions were performed using optimized conditions. All compounds are racemic. [b] Reaction time.

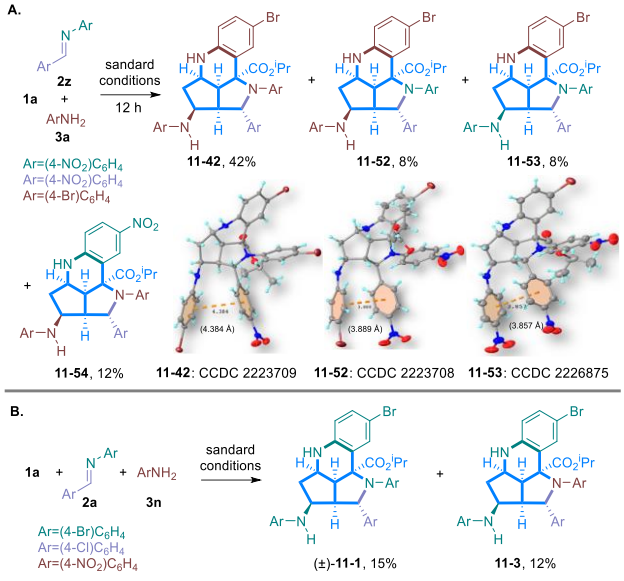
Interestingly, other Brønsted acids, such as phosphoric acid, *p*-toluenesulfonic acid, acetic acid, and *p*-nitrobenzoic acid, also promoted the reaction, albeit in low yields (see the SI for full optimization details).

With the optimized conditions, the scope of the polycyclization was evaluated with diverse diazodienals **1**, aldimines **2**, and arylamines **3** (Fig. 3B). Alkyl ester diazodienals including the bulky t-Bu ester, gave good yields of tetracycles (e.g., **11-4** to **11-10,** 55-73%). Interestingly, propargyl and geraniol esters with unsaturated side chains were also tolerated in the reaction (**11-6**, **11-10**, 52-56%) despite the potential intramolecular carbenoid cyclopropanation.[10a] The polycyclization was highly compatible with halo-aldimines and halo-anilines, resulting in the diverse halogenated (F, Cl, Br, I) tetracycles (e.g., **11-11** to **11-24**, 42-75%) which can be further functionalized through cross-coupling reactions. Notably, in the case of 3-haloanilines, only less hindered C1-C6-fused tetracycles were obtained (e.g., **11-16** to **11-21**). The polycyclization was sensitive to the steric environment on the arylamine motif. Thus, 2-substituted aniline and its aldimine are incompatible with the reaction (**11-25**, 0%, R = Me, Br, OMe). In contrast, the reaction was successful with the hindered aldimines derived from 2-bromobenzaldehyde (**11-26**, 52%) and 1-naphthaldehyde (**11-47**, 56%).

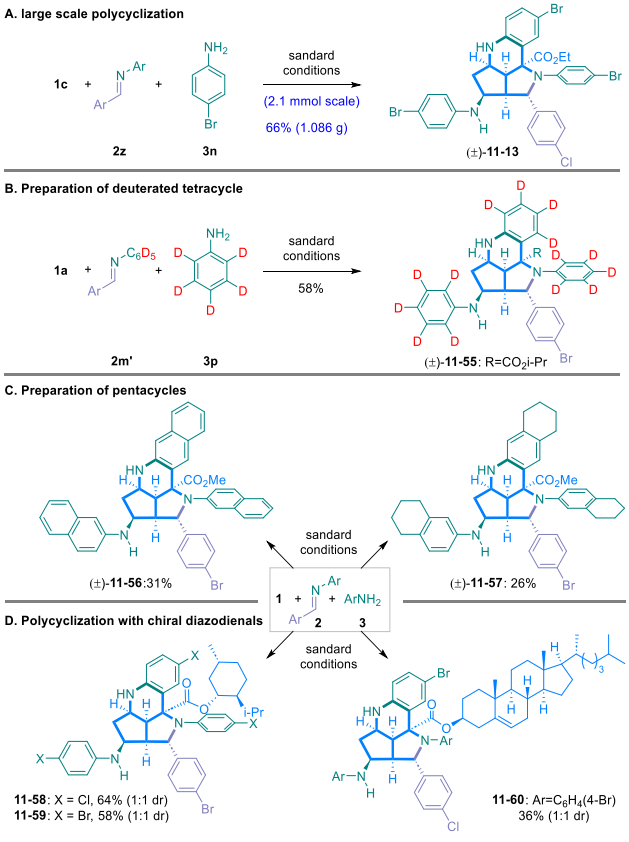
The electronic nature of arylamine and aldimine profoundly influences the efficiency of polycyclization. Electron-rich arylamine and its aldimine having alkyl or methoxy substituents resulted in faster reactions but diminished yields (**11-27** to **11-30**, 28-38%). The low yields could be attributed to the competing Rh-carbenoid NH-insertion reaction. Electron-deficient 4-nitroaniline and its aldimine showed sluggish reactivity (**11-33** to **11-36**, 32-45%). In this case, the formation of DAY and its polycyclization required a longer time due to the weak nucleophilicity of arylamine and imine. In contrast, 3-nitroanilne and its aldimine gave high yields despite longer reaction time (**11-37** to **11-38**, 59-64%). Trifluoromethyl aniline and its aldimine reacted effectively and produced valuable fluorine-containing tetracycles (**11-39** to **11-40**, 51-55%). Aldimines of electron-donating alkyl and methoxy benzaldehydes gave diminished yields (**11-31** to **11-32**, 32-38%), due to the weak donor-acceptor π–π interaction in the reactive conformation **14** (Fig. 2F, X = 4-Me, 4-OMe) leading to inefficient 6π-electrocyclization. In contrast, aldimines of electron-withdrawing trifluoromethyl, nitro, and cyanobenzaldehyde reacted efficiently (**11-41** to **11-45**, 52-62%) due to the enhanced donor-acceptor π–π–interactions in **14** (Fig. 2F, X = CF_3, NO_2, CN). 4-Phenylaniline and its aldimine gave the π-extended tetracycle in decent yield (**11-46**, 49%). Heteroaryl aldimines obtained from thiophene and indole aldehydes reacted smoothly to give corresponding tetracycles in high yield (**11-48** to **11-51**, 58-66%).

Inspired by the formation of cross-product **11-3** (Fig. 2E), we further investigated the use of different aniline components in polycyclization (Scheme 1A-B). The use of 4-bromoaniline **3a** and electron-deficient dinitroimine **2z** gave a mixture of four tetracycles **11-42** (42%), **11-52** (8%), **11-53** (8%), and **11-54** (12%). In contrast, 4-nitroaniline **3n** and dihaloimine **2a** gave tetracycles **11-1** (15%) and **11-3** (12%). The cross-products formation could be rationalized through in situ transimination processes catalyzed by DPP (See SI for details). The relative yields of the products further support that halo-anilines and their aldimines react efficiently compared to the electron-deficient anilines and their aldimines. The single crystal X-ray structures of **11-42**, **11-53** and **11-54** revealed the π–π–interactions stabilized molecular conformations.

Scheme 1. Cross Experiments.



Scheme 2. Applications.



The scalability of the polycyclization was demonstrated through the gram-scale synthesis of the tetracycle **11-13** (1.086 g, 66%, Scheme 2A). Reaction with aniline-D_5 and its aldimine provided deuterium incorporated teracycle **11-55** (58%, Scheme 2B). Fused arylamines such as 2-naphthylamine and 6-aminotetralin and their aldimines also reacted, resulting in the pentacyclic molecules **11-56** and **11-57** (26-31%) albeit in low yield due to the steric crowding (Scheme 2C). Finally, the polycyclization was evaluated with the chiral diazodienals (Scheme 2D). Menthyl ester **1g** gave the diastereomeric tetracycles **11-58** and **11-59** in decent yield (58-64%, dr 1:1), while a low yield was obtained with cholesterol ester due to poor solubility and steric crowding (**11-60**, 36%, dr 1:1).

We have demonstrated that diazodienals are valuable building blocks for combination catalysis to access unprecedented reactions that are impossible through either of the independent catalytic reactions. The key features of diazodienals includes t*he efficient electronic communication between the diazo and enal functionalities through π-conjugation which offer controlled catalytic activations and hence controlled reactivity to deliver cleaner reactions.* The Rh(II)/Brønsted acid relay catalysis efficiently assembled the biologically important azatricyclo[6.2.1.$0^{4,11}$]undecane fused polycycles in a single step from the bench-top diazodienals, aldimines and anilines. The π–π secondary interactions unequivocally establish their significance in the formation, stabilization, and reactivity of various intermediates resulting in the highly efficient polycyclization. The carbene-transfer reactions of conjugated diazoenals significantly expand the remote functionalization strategies. Further studies on the synthetic applications of diazodienals and polycyclization are ongoing.

AUTHOR INFORMATION

Corresponding Author

*sk@iiserb.ac.in

Present Addresses

†Government Arts & Science PG College, Ratlam, Madhya Pradesh, India 457001.

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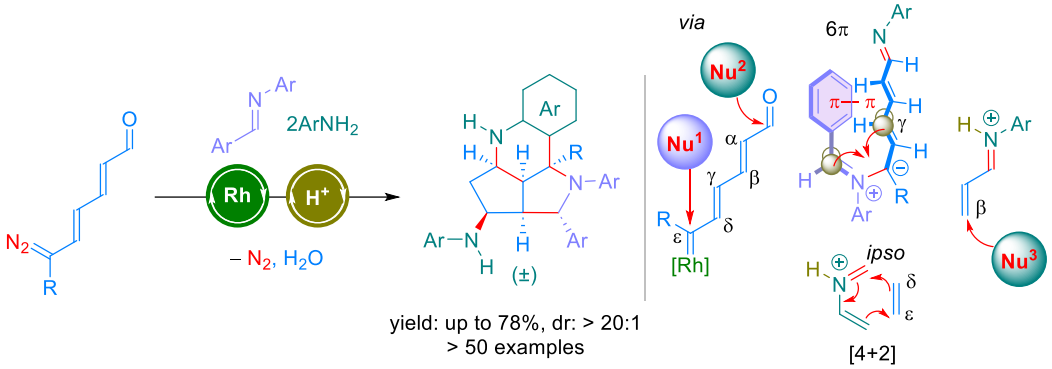

yield: up to 78%, dr: > 20:1
> 50 examples

• triple-nucleophilic cascade • 6 new σ-bonds • 3 new rings • 6 contiguous stereocenters • 7C(sp^2)→7C(sp^3)