

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

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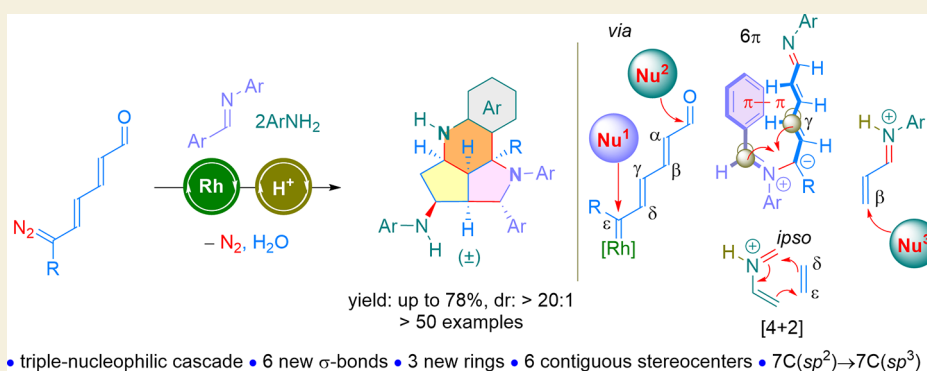
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ABSTRACT: Reported herein are the bench stable (2*E*,4*E*)-diazohexa-2,4-dienals (diazodienals) and their unprecedented polycyclization with aldimine and arylamines enabled by Rh(II)/Brønsted acid relay catalysis. This scalable and atom-economical 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.

KEYWORDS: aza-polycycles, azomethine ylide, carbene, cascade polycyclization, catalysis, diazodienal, π – π interactions

Cyclopentane-fused polycyclic alkaloids having an azatricyclo[6.2.1.0^{4,11}]undecane core are prevalent in various plant species (e.g., Figure 1A).^{1–5} 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 toward developing novel strategies to total synthesis.^{6–26} However, the direct approaches for constructing azatricyclo[6.2.1.0^{4,11}]undecane fused scaffolds from simple precursors have remained challenging.^{25,27}

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.^{28–34} 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 (Figure 1B) to access a variety of 5–6 membered monocyclic and fused carbo/heterocycles.^{35–41} 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,^{35–49} we have designed a conceptually new building blocks “conjugated diazoenals” in which enal and diazo motif is integrated through π -conjugation (Figure 1C).

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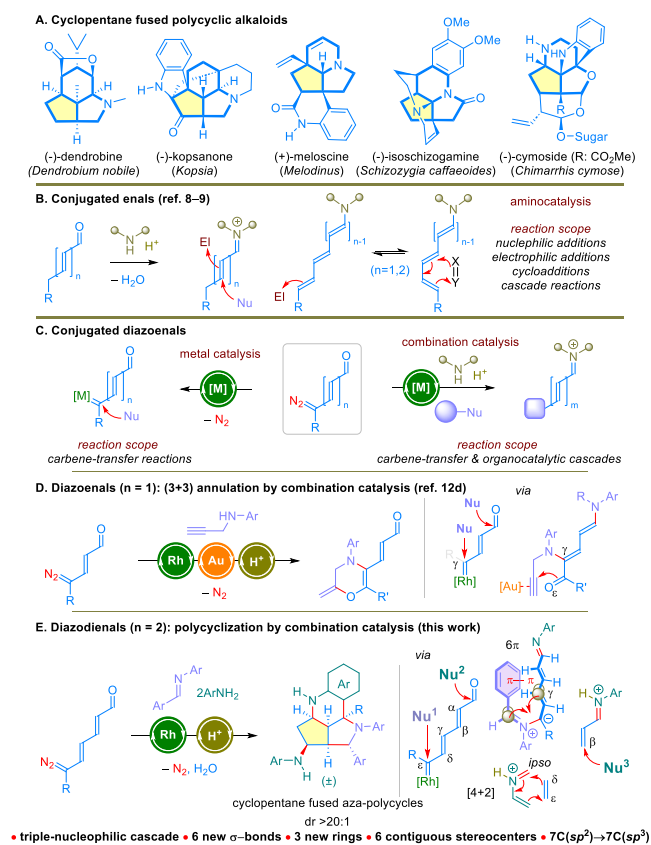


Figure 1. (A) Azatricyclo[6.2.1.0^{4,11}]undecane fused natural products. (B–E) Reactivity of conjugated enals and diazoenals.

We 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.^{50–58}

Initial investigations by us and others revealed that (2E)-diazoenals (n = 1) are versatile substrates for metal catalysis and combinations catalysis.^{59–68} Rh-enalcarbenoid reacts with a variety of π - and heteroatom nucleophiles resulting in the (4 + 2),^{59,61,63,68} (4 + 1),⁶⁰ (1 + 1 + 3),⁶⁴ (3 + 3),⁶⁷ and (3 + 2)⁶⁵ annulations, olefination,⁶⁴ and enal-transfer⁶⁶ 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 dianimine catalysis (Figure 1D).⁶²

Herein we report the novel (2E,4E)-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 (Figure 1E).^{69–71} 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, 6 π -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 by using inexpensive sorbic acid (Figure 2A). Most of these compounds are orange-colored crystalline solids with good thermal stability (see 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 a deep red solution of novel unstable dienal azomethine ylide (DAY) 5 (Figure 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-nitroaniline could be detected by TLC. However, they isomerize to (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 the 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 ¹³C 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 6 π -electrocyclization and iminium/enamine cascade reactions via 6 and 7 to access privileged pyrrolidine heterocyclic scaffolds (Figure 2C). However, we realized two significant challenges in our proposed plan— uncontrolled Mannich/aldol reactions of DAY, and interrupted 6 π -electrocyclization due to the isomerization of DAY to the unproductive (E,E,E)-trienolate 5^a or (E,E,E)-trienamine 6^a (see SI for details). We envisioned that aza-trienyl azomethine ylide 9 would offer two advantages— prevents side reactions due to reduced nucleophilicity and satisfies electronic and geometrical requirements of 6 π -electrocyclization to access dihydropyrrole 10 for further elaborations. To our surprise, in the presence of a Brønsted acid catalyst diphenyl phosphate (DPP), the *in situ* formed DAY 5 reacted with arylamine 3a to give a polycyclization product (\pm)-11-1 as a single diastereomer (24%, dr >20:1) instead of dihydropyrrole 10/8 (Figure 2D). The structure of (\pm)-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 equiv 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.^{72–81}

Inspired by this remarkable result, we designed control experiments to gain insight into the details of the polycyclization reaction (Figure 2E). In the absence of aldimine, 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 -diazoinime 12a. However, isolated diazoimine 12a failed to give the polycyclization product (\pm)-11-1; instead, it slowly decomposed. This result suggests that compound 12a is not

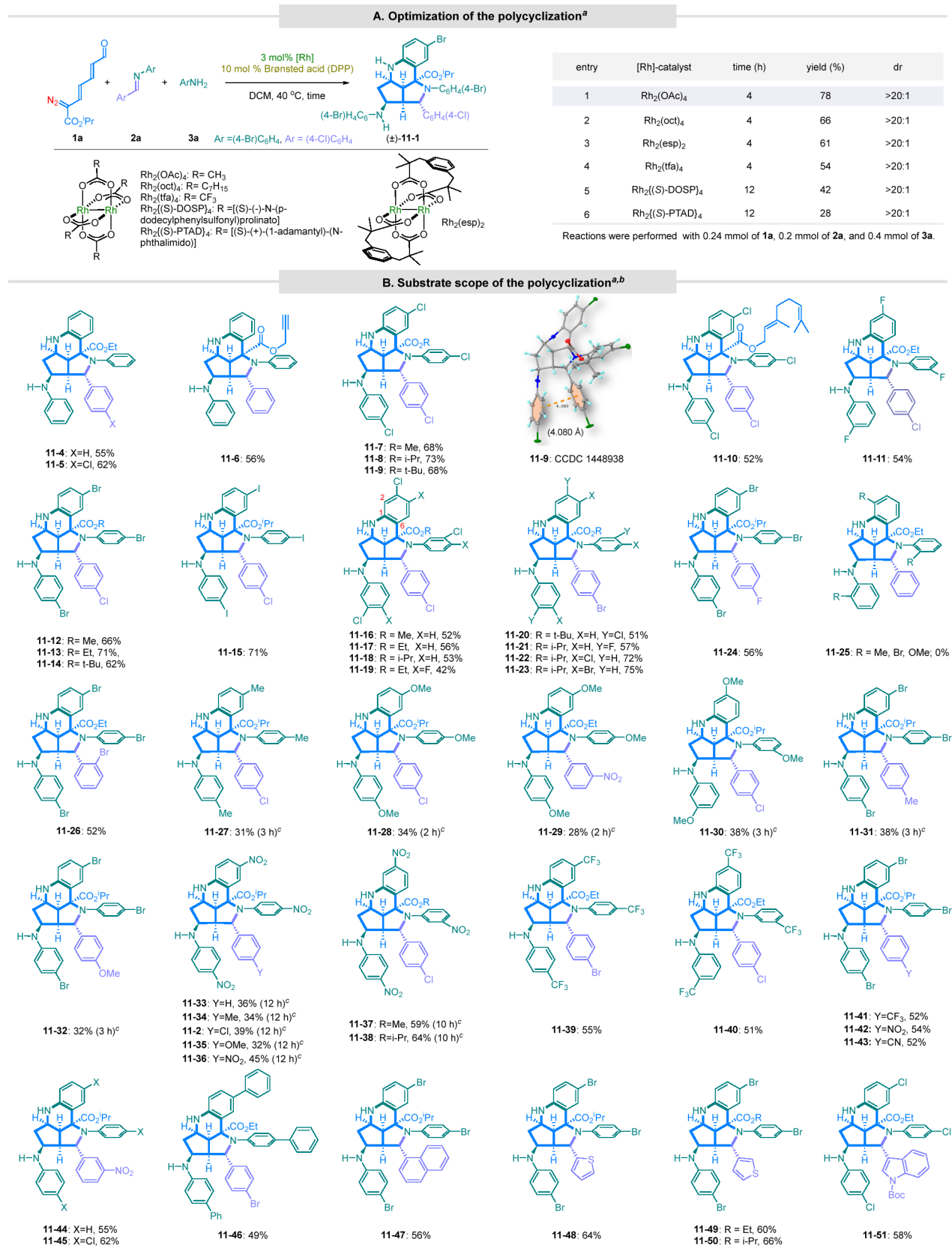


Figure 3. (A) Optimization and (B) substrate scope of the polycyclization. ^aYield of isolated product. ^bReactions were performed using optimized conditions. All compounds are racemic. ^cReaction time.

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).⁸⁸⁻⁹⁰ Finally, rearomatization

of **19** delivers the aza-polycyclic product (\pm)-**11**. The molecular conformation of (\pm)-**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 further optimized the polycyclization reaction (Figure 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 $\text{Rh}_2(\text{OAc})_4$ 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 $\text{Rh}_2(\text{oct})_4$, $\text{Rh}_2(\text{esp})_2$, and $\text{Rh}_2(\text{tfa})_4$ are also effective (entries 2–4). Sterically hindered $\text{Rh}_2\{(\text{S})\text{-DOSP}\}_4$ and $\text{Rh}_2\{(\text{S})\text{-PTAD}\}_4$ resulted in a sluggish reaction and reduced yields (entries 5–6). 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 SI for full optimization details).

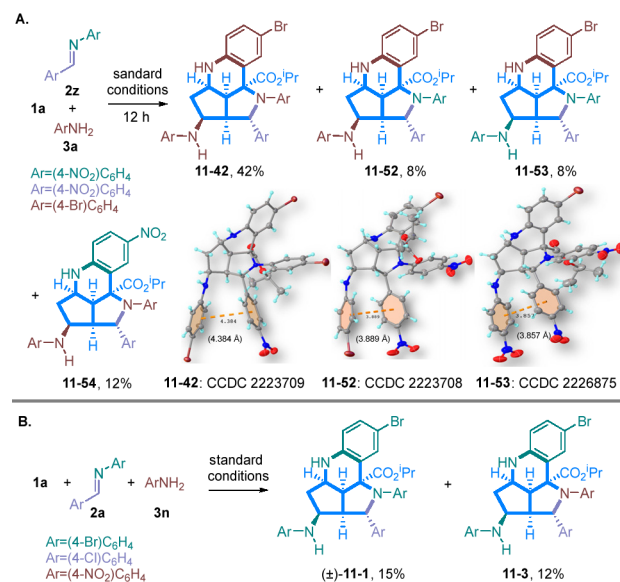
With the optimized conditions, the scope of the polycyclization was evaluated with diverse diazodienals **1**, aldimines **2**, and arylamines **3** (Figure 3B). Alkyl ester diazodienals, including the bulky *t*-Bu ester, gave good yields of tetracycles (e.g., **11-4** to **11-10**, 55–73%). Interestingly, 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.⁴² The polycyclization was highly compatible with halo-aldimines and halo-anilines, resulting in 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 C_1 - C_6 -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, or OMe). In contrast, the reaction was successful with 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-carbene 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-nitroaniline and its aldimine gave high yields despite a 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** (Figure 2F, where 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** (Figure 2F, where 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 the corresponding tetracycles in high yield (**11-48** to **11-51**, 58–66%).

Inspired by the formation of cross-product **11-3** (Figure 2E), we further investigated the use of different aniline components in polycyclization (Scheme 1A,B). The use of 4-bromoaniline

Scheme 1. Cross Experiments

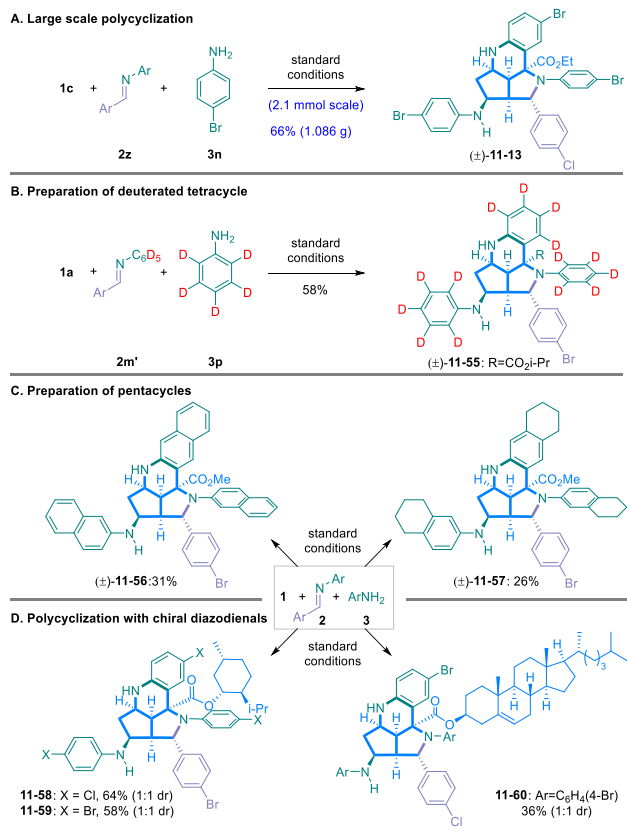


3a and electron-deficient dinitroimine **2z** gave a mixture of four tetracycles **11-42** (42%), **11-52** (8%), **11-53** (8%), and **11-54** (12%). In contrast, 4-nitroaniline **3n** and dihaloimine **2a** gave tetracycles **11-1** (15%) and **11-3** (12%). The cross-product formation could be rationalized through *in situ* transimination processes catalyzed by DPP (see SI for details). The relative yields of the products further support that haloanilines 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.

The scalability of the polycyclization was demonstrated through the gram-scale synthesis of tetracycle **11-13** (1.086 g, 66%, Scheme 2A). Reaction with aniline- D_5 and its aldimine provided deuterium incorporated tetracycle **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 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 include the efficient electronic communication between the

Scheme 2. Applications



diazo and enal functionalities through π -conjugation which offer controlled catalytic activations and hence controlled reactivity to deliver cleaner reactions. The Rh(II)/Bronsted acid relay catalysis efficiently assembled the biologically important azatricyclo[6.2.1.0^{4,11}]undecane fused polycycles in a single step from the benchtop 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

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacsau.4c00134>.

Experimental procedures, characterization data (PDF)
NMR spectra (PDF)

Crystallographic data of 1a (CIF)

Crystallographic data of 11-1 (CIF)

Crystallographic data of 11-9 (CIF)

Crystallographic data of 11-42 (CIF)

Crystallographic data of 11-52 (CIF)

Crystallographic data of 11-53 (CIF)

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Author Contributions

‡H.C., K.S.R., S.C., and P.K.M. contributed equally. The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript. CRediT: Haribabu Chennamsetti formal analysis, methodology, validation; Kuldeep Singh Rathore formal analysis, validation; Saikat Chatterjee data curation, formal analysis, investigation, methodology, validation, writing-review & editing; Pratap Kumar Mandal data curation, formal analysis, investigation, methodology, validation, writing-review & editing; Sreenivas Katukojvala conceptualization, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, visualization, writing-original draft, writing-review & editing.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) Mou, Z.; Zhao, Y.; Ye, F.; Shi, Y.; Kennelly, E. J.; Chen, S.; Zhao, D. Identification, biological activities, and biosynthetic pathway of Dendrobium alkaloids. *Front. Pharmacol.* **2021**, *12*, No. 605994.
- (2) Hop, N. Q.; Son, N. T. A comprehensive review on phytochemistry and pharmacology of genus *Kopsia*: monoterpene alkaloids—major secondary metabolites. *RSC Adv.* **2022**, *12*, 19171–19208.

- (3) Bernauer, K.; Englert, G.; Vetter, W.; Weiss, E. Constitution of the Melodinus alkaloids (+)-meloscine, (+)-epimeloscine, and (+)-scandine. *Helv. Chim. Acta* **1969**, *52*, 1886–1905.
- (4) Kariba, R. M.; Houghton, P. J.; Yenesew, A. Antimicrobial Activities of a New Schizozygane Indoline Alkaloid from *Schizozygia coffaeoides* and the Revised Structure of Isoschizogaline. *J. Nat. Prod.* **2002**, *65*, 566–569.
- (5) Lémus, C.; Kritsanida, M.; Canet, A.; Genta-Jouve, G.; Michel, S.; Deguin, B.; Grougnet, R. Cymoside, a monoterpene indole alkaloid with a hexacyclic fused skeleton from *Chimarrhis cymose*. *Tetrahedron Lett.* **2015**, *56*, 5377–5380.
- (6) Yamada, K.; Suzuki, M.; Hayakawa, Y.; Aoki, K.; Nakamura, H.; Nagase, H.; Hirata, Y. Total synthesis of *dl*-dendrobine. *J. Am. Chem. Soc.* **1972**, *94*, 8278–8280.
- (7) Kende, A. S.; Bentley, T. J.; Mader, R. A.; Ridge, D. Simple total synthesis of (+)-dendrobine. *J. Am. Chem. Soc.* **1974**, *96*, 4332–4334.
- (8) Borch, R. F.; Evans, A. J.; Wade, J. J. Synthesis of 8-epi-dendrobine. *J. Am. Chem. Soc.* **1977**, *99*, 1612–1619.
- (9) Roush, W. R. Total synthesis of (±)-dendrobine. *J. Am. Chem. Soc.* **1980**, *102*, 1390–1404.
- (10) Lee, C. H.; Westling, M.; Livinghouse, T.; Williams, A. C. Acyltrilium ion-initiated heteroannulations in alkaloid synthesis. An efficient, stereocontrolled, total synthesis of the Orchidaceae alkaloid (±)-dendrobine. *J. Am. Chem. Soc.* **1992**, *114*, 4089–4095.
- (11) Sha, C.-K.; Chiu, R.-T.; Yang, C.-F.; Yao, N.-T.; Tseng, W.-H.; Liao, F.-L.; Wang, S.-L. Total Synthesis of (–)-Dendrobine via α -Carbonyl Radical Cyclization. *J. Am. Chem. Soc.* **1997**, *119*, 4130–4135.
- (12) Cassayre, J.; Zard, S. Z. A Short Synthesis of (–)-Dendrobine. *J. Am. Chem. Soc.* **1999**, *121*, 6072–6073.
- (13) Gallagher, T.; Magnus, P. Synthesis of (±)-Kopsanone and (±)-10,22-Dioxokopsane, Heptacyclic Indole Alkaloids. *J. Am. Chem. Soc.* **1983**, *105*, 2086–2087.
- (14) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. Collective synthesis of natural products by means of organocascade catalysis. *Nature* **2011**, *475*, 183–188.
- (15) Leng, L.; Zhou, X.; Liao, Q.; Wang, F.; Song, H.; Zhang, D.; Liu, X.-Y.; Qin, Y. Asymmetric Total Syntheses of Kopsia Indole Alkaloids. *Angew. Chem., Int. Ed.* **2017**, *56*, 3703–3707.
- (16) Jia, X.; Lei, H.; Han, F.; Zhang, T.; Chen, Y.; Xu, Z.; Nakliang, P.; Sun, C.; Guo, Y.; Ye, T. Asymmetric Total Syntheses of Kopsane Alkaloids via a PtCl₂-Catalyzed Intramolecular [3 + 2] Cycloaddition. *Angew. Chem., Int. Ed.* **2020**, *59*, 12832–12836.
- (17) Qin, B.; Wang, Y.; Wang, X.; Jia, Y. Total synthesis of kopsine, fruticosine, and structurally related polycyclic caged *Kopsia* indole alkaloids. *Org. Chem. Front.* **2021**, *8*, 369–383.
- (18) Overman, L. E.; Robertson, G. M.; Robichaud, A. J. Use of Azacope Rearrangement-Mannich Cyclization Reactions to Achieve a General Entry to Melodinus and Aspidosperma Alkaloids. Stereocontrolled Total Syntheses of (±)-Deoxoapodine, (±)-Meloscine, and (±)-Epimeloscine and a Formal Synthesis of (±)-1-Acetylspidoalbidine. *J. Am. Chem. Soc.* **1991**, *113*, 2598–2610.
- (19) Selig, P.; Bach, T. Enantioselective Total Synthesis of the Melodinus Alkaloid (+)-Meloscine. *Angew. Chem., Int. Ed.* **2008**, *47*, 5082–5084.
- (20) Zhang, H.; Curran, D. P. A Short Total Synthesis of (±)-Epimeloscine and (±)-Meloscine Enabled by a Cascade Radical Annulation of a Divinylcyclopropane. *J. Am. Chem. Soc.* **2011**, *133*, 10376–10378.
- (21) Hayashi, Y.; Inagaki, F.; Mukai, C. Total Synthesis of (±)-Meloscine. *Org. Lett.* **2011**, *13*, 1778–1780.
- (22) Hubbs, J. L.; Heathcock, C. H. Total Synthesis of (±)-Isoschizogamine. *Org. Lett.* **1999**, *1*, 1315–1317.
- (23) Miura, Y.; Hayashi, N.; Yokoshima, S.; Fukuyama, T. Total Synthesis of (–)-Isoschizogamine. *J. Am. Chem. Soc.* **2012**, *134*, 11995–11997.
- (24) Xu, Z.; Bao, X.; Wang, Q.; Zhu, J. An Enantioselective Total Synthesis of (–)-Isoschizogamine. *Angew. Chem., Int. Ed.* **2015**, *54*, 14937–14940.
- (25) Dou, Y.; Kouklovsky, C.; Gandon, V.; Vincent, G. Enantioselective Total Synthesis of Cymoside through a Bioinspired Oxidative Cyclization of a Strictosidine Derivative. *Angew. Chem., Int. Ed.* **2020**, *59*, 1527–1531.
- (26) Sakamoto, J.; Umeda, Y.; Rakumitsu, K.; Sumimoto, M.; Ishikawa, H. Total Syntheses of (–)-Strictosidine and Related Indole Alkaloid Glycosides. *Angew. Chem., Int. Ed.* **2020**, *59*, 13414–13422.
- (27) Marques, A.-S.; Duhail, T.; Marrot, J.; Chataigner, I.; Coeffard, V.; Vincent, G.; Moreau, X. A. Fused Hexacyclic Ring System: Diastereoselective Polycyclization of 2,4-Dienals through an Interrupted iso-Nazarov Reaction. *Angew. Chem., Int. Ed.* **2019**, *58*, 9969–9973.
- (28) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis from Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley: New York, 2005.
- (29) Watson, A. J. B.; MacMillan, D. W. C. *Enantioselective Organocatalysis Involving Iminium, Enamine, Somo, and Photoredox Activation. Catalytic Asymmetric Synthesis*, 3rd ed.; Ojima, I., Ed.; 2010; pp 39–57.
- (30) Kampen, D.; Reisinger, C. M.; List, B. Asymmetric Organocatalysis. *Top. Curr. Chem.* **2010**, *291*, 1.
- (31) *Science of Synthesis: Asymmetric Organocatalysis 1*; List, B., Ed.; Thieme: Stuttgart, Germany, 2012.
- (32) Anebuselvy, K.; Ramachary, D. B.; Kumar, I. *Dienamine Catalysis for Organic Synthesis*; Royal Society of Chemistry, 2018. ASIN: B07JV85S4N.
- (33) *N-Heterocyclic Carbenes in Organocatalysis*; Biju, A. T., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA, 2019.
- (34) Burke, A. J. Asymmetric organocatalysis in drug discovery and development for active pharmaceutical ingredients. *Expert Opin. Drug Dis.* **2023**, *18*, 37–46.
- (35) Arceo, E.; Melchiorre, P. Extending the Aminocatalytic HOMO-Raising Activation Strategy: Where Is the Limit? *Angew. Chem., Int. Ed.* **2012**, *51*, S290–S292.
- (36) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. The Diarylprolinol Silyl Ether System: A General Organocatalyst. *Acc. Chem. Res.* **2012**, *45* (2), 248–264.
- (37) Jiang, H.; Albrecht, L.; Jørgensen, K. A. Aminocatalytic remote functionalization strategies. *Chem. Sci.* **2013**, *4*, 2287–2300.
- (38) Kumar, I.; Ramaraju, P.; Mir, N. A. Asymmetric Trienamine Catalysis: New Opportunities in Amine Catalysis. *Org. Biomol. Chem.* **2013**, *11*, 709–716.
- (39) Donslund, B. S.; Johansen, T. K.; Poulsen, P. H.; Halskov, K. S.; Jørgensen, K. A. The Diarylprolinol Silyl Ethers: Ten Years After. *Angew. Chem., Int. Ed.* **2015**, *54*, 13860–13874.
- (40) Curti, C.; Battistini, L.; Sartori, A.; Zanardi, F. New Developments of the Principle of Vinylogy as Applied to π -Extended Enolate-Type Donor Systems. *Chem. Rev.* **2020**, *120*, 2448–2612.
- (41) Pawar, T. J.; Mitkari, S. J.; Peña-Cabrera, E.; Gómez, C. V.; Cruz, D. C. Polyenals and Polyenones in Aminocatalysis: A Decade Building Complex Frameworks from Simple Blocks. *Eur. J. Org. Chem.* **2020**, *2020*, 6044–6061.
- (42) Doyle, M. P.; McKervey, M. A.; Tao, Y. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley-VCH: Weinheim, 1998; pp 238–279.
- (43) Doyle, M. P. Catalytic methods for metal carbene transformations. *Chem. Rev.* **1986**, *86*, 919–939.
- (44) Padwa, A.; Weingarten, M. D. Cascade Processes of Metallo-Carbenoids. *Chem. Rev.* **1996**, *96*, 223–270.
- (45) Davies, H. M. L.; Beckwith, R. E. J. Catalytic Enantioselective C–H Activation by Means of Metal–Carbenoid-Induced C–H Insertion. *Chem. Rev.* **2003**, *103*, 2861–2904.
- (46) Gillingham, D.; Fei, N. Catalytic X–H insertion reactions based on carbenoids. *Chem. Soc. Rev.* **2013**, *42*, 4918–4931.
- (47) Guo, X.; Hu, W. Novel Multicomponent Reactions via Trapping of Protic Onium Ylides with Electrophiles. *Acc. Chem. Res.* **2013**, *46*, 2427–2440.

- (48) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. Modern Organic Synthesis with α -Diazocarbonyl Compounds. *Chem. Rev.* **2015**, *115*, 9981–10080.
- (49) Qiu, D.; Wang, J. Recent Developments of Diazo Compounds in Organic Synthesis. *World Scientific* **2021**, 584.
- (50) Shao, Z.-H.; Zhang, H.-B. Combining Transition Metal Catalysis and Organocatalysis: A Broad New Concept for Catalysis. *Chem. Soc. Rev.* **2009**, *38*, 2745–2755.
- (51) Allen, A. E.; MacMillan, D. W. C. Synergistic Catalysis: A Powerful Synthetic Strategy for New Reaction Development. *Chem. Sci.* **2012**, *3*, 633–658.
- (52) Du, Z. T.; Shao, Z.-H. Combining Transition Metal Catalysis and Organocatalysis—an Update. *Chem. Soc. Rev.* **2013**, *42*, 1337–1378.
- (53) Chen, D.-F.; Han, Z.-Y.; Zhou, X.-L.; Gong, L.-Z. Asymmetric Organocatalysis Combined with Metal Catalysis: Concept, Proof of Concept, and Beyond. *Acc. Chem. Res.* **2014**, *47*, 2365–2377.
- (54) Afewerki, S.; Córdova, A. Combinations of Aminocatalysts and Metal Catalysts: A Powerful Cooperative Approach in Selective Organic Synthesis. *Chem. Rev.* **2016**, *116*, 13512–13570.
- (55) Zhou, Q.-L. Transition-Metal Catalysis and Organocatalysis: Where Can Progress Be Expected? *Angew. Chem., Int. Ed.* **2016**, *55*, 5352–5353.
- (56) Arndtsen, B. A.; Gong, L.-Z. *Topics in Current Chemistry Collections: Asymmetric Organocatalysis Combined with Metal Catalysis*; Springer Nature: Cham, Switzerland, 2020.
- (57) Gong, L.-Z. *Asymmetric Organo-Metal Catalysis: Concepts, Principles, and Applications*; Wiley-VCH: Weinheim, Germany, 2021.
- (58) Chen, D.-F.; Gong, L.-Z. Organo/Transition-Metal Combined Catalysis Rejuvenates Both in Asymmetric Synthesis. *J. Am. Chem. Soc.* **2022**, *144*, 2415–2437.
- (59) 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.
- (60) Kanchupalli, V.; Joseph, D.; Katukojvala, S. Pyridazine N-Oxides as Precursors of Metallocarbenes: Rhodium-Catalyzed Transannulation with Pyrroles. *Org. Lett.* **2015**, *17* (23), 5878–5881.
- (61) Dawande, S. G.; Kanchupalli, V.; Lad, B. S.; Rai, J.; Katukojvala, S. Synergistic Rhodium(II) Carboxylate and Bronsted Acid Catalyzed Multicomponent Reactions of Enalcarbenoids: Direct Synthesis of α -Pyrrolylbenzylamines. *Org. Lett.* **2014**, *16*, 3700–3703.
- (62) 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.
- (63) Rathore, K. S.; Lad, B. S.; Chennamsetti, H.; Katukojvala, S. An unprecedented benzannulation of oxindoles with enalcarbenoids: a regioselective approach to functionalized carbazoles. *Chem. Commun.* **2016**, *52*, 5812–5815.
- (64) 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.
- (65) 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.
- (66) Kanchupalli, V.; Thorbole, L. A.; Kalepu, J.; Joseph, D.; Arshad, M.; Katukojvala, S. Rhodium-Catalyzed Enal-Transfer with N-Methoxy-pyridazinium Salts. *Org. Lett.* **2022**, *24*, 3850–3854.
- (67) 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*, No. e202303862.
- (68) Wu, J.-Q.; Yang, Z.; Zhang, S.-S.; Jiang, C.-Y.; Li, Q.; Huang, Z.-S.; Wang, H. From Indoles to Carbazoles: Tandem Cp* Rh(III) -Catalyzed C–H Activation/Bronsted Acid-Catalyzed Cyclization Reactions. *ACS Catal.* **2015**, *5*, 6453–6457.
- (69) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. Cascade Reactions in Total Synthesis. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186.
- (70) Ardkhean, R.; Caputo, D. F. J.; Morrow, S. M.; Shi, H.; Xiong, Y.; Anderson, E. A. Cascade polycyclizations in natural product synthesis. *Chem. Soc. Rev.* **2016**, *45*, 1557–1569.
- (71) Jiang, Y.; McNamee, R. E.; Smith, P. J.; Sozanschi, A.; Tong, Z.; Anderson, E. A. Advances in polycyclization cascades in natural product synthesis. *Chem. Soc. Rev.* **2021**, *50*, 58–71.
- (72) Pinho e Melo, T. M. V. D. Conjugated Azomethine Ylides. *Eur. J. Org. Chem.* **2006**, 2873–2888.
- (73) Anaç, O.; Güngör, F. Ş. Electrocyclization reactions of vinyl, styryl, and butadienyl conjugated carbonyl/azomethine ylides. *Tetrahedron* **2010**, *66*, 5931–5953.
- (74) De, N.; Yoo, E. J. Recent Advances in the Catalytic Cycloaddition of 1,n-Dipoles. *ACS Catal.* **2018**, *8*, 48–58.
- (75) Lee, D. J.; Han, H. S.; Shin, J.; Yoo, E. J. Multicomponent [5 + 2] Cycloaddition Reaction for the Synthesis of 1,4-Diazepines: Isolation and Reactivity of Azomethine Ylides. *J. Am. Chem. Soc.* **2014**, *136*, 11606–11609.
- (76) Lee, D. J.; Ko, D.; Yoo, E. J. Rhodium(II)-Catalyzed Cycloaddition Reactions of Non-classical 1,5-Dipoles for the Formation of Eight-Membered Heterocycles. *Angew. Chem., Int. Ed.* **2015**, *54*, 13715–13718.
- (77) De, N.; Ko, D.; Baek, S.-Y.; Oh, C.; Kim, J.; Baik, M.-H.; Yoo, E. J. Cu(I)-Catalyzed Enantioselective [5 + 1] Cycloaddition of N-Aromatic Compounds and Alkynes via Chelating-Assisted 1,2-De芳香ative Addition. *ACS Catal.* **2020**, *10*, 10905–10913.
- (78) Potowski, M.; Bauer, J. O.; Strohmman, C.; Antonchick, A. P.; Waldmann, H. Highly Enantioselective Catalytic [6 + 3] Cycloadditions of Azomethine Ylides. *Angew. Chem., Int. Ed.* **2012**, *51*, 9512–9516.
- (79) Liu, H.; Wu, Y.; Zhao, Y.; Li, Z.; Zhang, L.; Yang, W.; Jiang, H.; Jing, C.; Yu, H.; Wang, B.; Xiao, Y.; Guo, H. Metal-Catalyzed [6 + 3] Cycloaddition of Tropone with Azomethine Ylides: A Practical Access to Piperidine-Fused Bicyclic Heterocycles. *J. Am. Chem. Soc.* **2014**, *136*, 2625–2629.
- (80) Teng, H.-L.; Yao, L.; Wang, C.-J. Cu(I)-Catalyzed Regio- and Stereoselective [6 + 3] Cycloaddition of Azomethine Ylides with Tropone: An Efficient Asymmetric Access to Bridged Azabicyclo[4.3.1]decadienes. *J. Am. Chem. Soc.* **2014**, *136*, 4075–4080.
- (81) Li, Q.-H.; Wei, L.; Wang, C.-J. Catalytic Asymmetric 1,3-Dipolar [3 + 6] Cycloaddition of Azomethine Ylides with 2-Acyl Cycloheptatrienes: Efficient Construction of Bridged Heterocycles Bearing Piperidine Moiety. *J. Am. Chem. Soc.* **2014**, *136*, 8685–8692.
- (82) Doyle, M. P.; Yan, M.; Hu, W.; Gronenberg, L. S. Highly Selective Catalyst-Directed Pathways to Dihydropyrroles from Vinyl diazoacetates and Imines. *J. Am. Chem. Soc.* **2003**, *125*, 4692–4693.
- (83) Lopez-Calle, E.; Keller, M.; Eberbach, W. Access to Isolable Azomethine Ylides by Photochemical Transformation of 2,3-Dihydroisoxazoles. *Eur. J. Org. Chem.* **2003**, 2003, 1438–1453.
- (84) Lee, D. J.; Han, H. S.; Shin, J.; Yoo, E. J. Multicomponent [5 + 2] Cycloaddition Reaction for the Synthesis of 1,4-Diazepines: Isolation and Reactivity of Azomethine Ylides. *J. Am. Chem. Soc.* **2014**, *136*, 11606–11609.
- (85) de Lera, A. R.; Alvarez, R.; Lecea, B.; Torrado, A.; Cossío, F. P. On the Aromatic Character of Electrocyclic and Pseudopericyclic Reactions: Thermal Cyclization of (2Z)-Hexa-2,4–5-trienes and Their Schiff Bases. *Angew. Chem., Int. Ed.* **2001**, *40*, 557–561.
- (86) Duncan, J. A.; Calkins, D. E. G.; Chavarha, M. Secondary Orbital Effect in the Electrocyclic Ring Closure of 7-Azahepta-1,2,4,6-tetraenes—A CASSCF Molecular Orbital Study. *J. Am. Chem. Soc.* **2008**, *130*, 6740–6748.
- (87) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970.

(88) Krenske, E. H.; Houk, K. N. Aromatic Interactions as Control Elements in Stereoselective Organic Reactions. *Acc. Chem. Res.* **2013**, *46*, 979–989.

(89) Kennedy, C. R.; Lin, S.; Jacobsen, E. N. The Cation– π Interaction in Small-Molecule Catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 12596–12624.

(90) Yamada, S. Cation– π Interactions in Organic Synthesis. *Chem. Rev.* **2018**, *118*, 11353–11432.