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RESEARCH

Highly stereoselective synthesis of 2-Azabicyclo[3.1.0]hex-3-ene and 5-Azatricyclo[4.1.0.0^{2,4}]heptane scaffolds via Rh-catalyzed cyclopropanation of pyrrole

Dongyan Ju[1] · Chuang Zhao[1,2] · Bowen Liu[1] · Junming Ma[1] · Shushen Chi[2] · Jinbo Zhao[1]

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Abstract

A rhodium-catalyzed cyclopropanation of pyrrole derivatives with electron-rich cyclopropenes is reported for the efficient access to vinyl functionalized cyclopropane fused pyrrolidine scaffolds, including 2-azabicyclo[3,1,0]hex-3-ene and 5-azatricyclo[4.1.0.0^{2,4}]heptane. The method features good yields and high diastereoselectivity. Electronic fine-tuning of these *N*-heterocycles via *N*-substituents proves key to the reactivity, offering a straightforward protocol for the synthesis of these cyclopropane-fused pyrrolidine scaffolds, which may have important medicinal relevance for further developments.

Keywords Pyrrole · 2-azabicyclo[3.1.0]hex-3-ene · Cyclopropanation · Rhodium · 5-azatricyclo[4.1.0.0^{2,4}]heptane

The 2-azabicyclo[3.1.0]hexane scaffold is one of the most essential *N*-heterocycle scaffolds that appear in many clinical drugs of diverse pharmacological effects (Fig. 1A) [1]. This bicyclic scaffold features a cyclopropane fused to a pyrrole/indole core [2], and is isosteric with the quinoline scaffold [3, 4]. This characteristics influences molecular biological activity by reducing the lipophilicity of the parent pyrroline and altering the electronic properties around the nitrogen center with the rigidified cyclopropane, introducing extra exiting vectors for activity improvement. There are quite a few star molecules of this type, such as SUVN-911 (**I**) [5], a potent α4β2 receptor agonist that displays high safety profile at high dosage, NIK inhibitor (**II**), [6] and Saxagliptin, [7] a highly effective and long-acting oral dipeptidyl peptidase IV inhibitor. Although not surprisingly, there are numerous compounds with this scaffold under intensive developments, closely related scaffolds, such as 2-azabicyclo[3.1.0]hex-3-ene and 5-azatricyclo[4.1.0.0^{2,4}]heptane, are much less studied due to their limited synthetic methods, although these scaffolds may also have broad pharmacological effects for the related scaffolds. As an example, our group recently discovered that incorporation of a further nitrogen into the 2-azabicyclo[3.1.0]hexane scaffold also enabled the resulted 2-diazabicyclo[3.1.0]hexanes with promising anti-proliferative activities [8].

Despite of its significance, available practical synthetic strategies toward construction of such scaffolds usually feature long steps, low overall efficiency and lack of diversity. Retrosynthetic analysis of the 2-azabicyclo[3.1.0]hexane scaffold typically relies on two fundamental strategies (Fig. 1B). The first strategy is to construct the cyclopropane ring on the existing pyrrole/pyrrolidine core [9–11], and the second one features simultaneous formulation of both rings in one operation [12, 13]. A notable example of the second strategy is the straightforward access to 2-azabicyclo[3.1.0]hexane via Cu-catalyzed *intra*-molecular reductive isocyanide-alkene (1 + 2) cycloaddition [13]. While the latter seems more straightforward, lacking of versatility in substrate preparation places limitations on its application in compound library construction. Cyclopropanation of indole and their derivatives with metal carbenoids holds promise as an effective strategy for constructing the benzo 2-azabicyclo[3.1.0]hexane skeleton. However, direct cyclopropanation of 2,3-non-substituted indoles with diazo compounds under the catalysis of various transition metals usually faces competitive formal C_{sp2}-H bond alkylation besides the desired cyclopropanation process. In 2019, Sen and coworkers

✉ Jinbo Zhao
zhaojinbo@ccut.edu.cn

[1] College of Chemistry and Life Sciences, Changchun University of Technology, Changchun, Jilin 130012, P. R. China

[2] INSA Rennes, CNRS, lSCR (Institut des Sciences Chimiques de Rennes)-UMR 6226, Univ Rennes, F-35000 Rennes, France

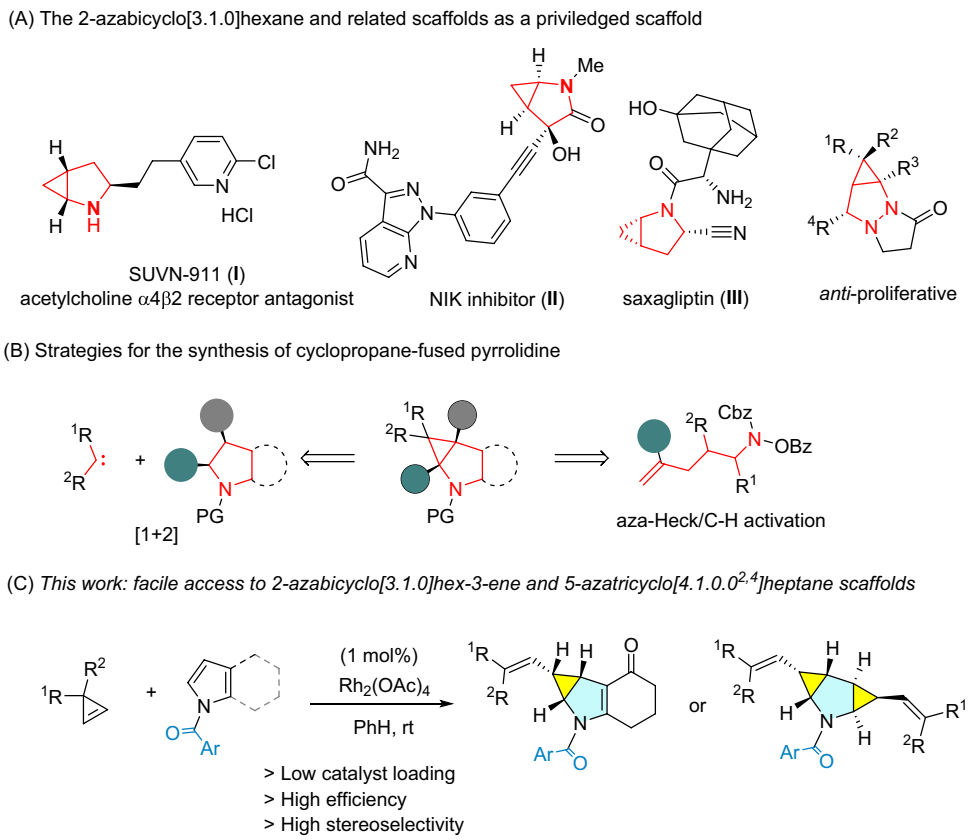


Fig. 1 Research background (**A**, **B**) and this work (**C**).

reported the first example of selective cyclopropanation of *N*-acylindole using aryl diazo esters as metal donor–acceptor carbenes with Mn-based catalyst, but only moderate diastereoselectivities were achieved with no indication of the relative configuration of the major isomer [14]. In the following year, Lautens group expanded this work by exploring the use of cyclopropene as an alternative to diazo compounds for the cyclopropanation of indoles, benzofurans, and related compounds [11]. In the meantime, Jiang and Loh reported in-depth investigation into cyclopropanation of indoles, revealing the critical role of *N*-protecting group in the control of *E*/*Z* selectivity of the olefin moiety in the product [15]. Although the cyclopropanation reaction has progressed from acceptor carbenes to donor/donor carbenes, the selectivity issue of these studies remains un-solved, and importantly, studies on pyrrole and its derivatives, which is electronically distinct from indole, remains unexplored. Extension of the reaction to pyrrole derivatives expands the chemical space to related scaffolds such as 2-azabicyclo[3.1.0]hex-3-ene and 5-azatricyclo[4.1.0.$0^{2,4}$]heptane scaffolds which are also significant yet under-explored.

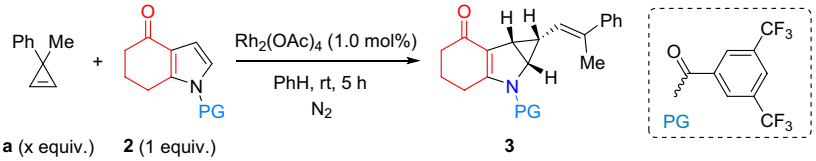
Our long interest in cyclopropene chemistry [16–22], especially the transition-metal catalyzed carbenoid chemistry involving cyclopropene as precursors [21, 22] motivated to address the above limitations in cyclopropanation of pyrrole to synthesize the 2-azabicyclo[3.1.0]hex-3-ene and 5-azatricyclo[4.1.0.$0^{2,4}$]heptane scaffolds. Transition metal catalyzed cyclopropanation reactions with cyclopropene as precursor are mainly limited to alkenes [23], while limited studies have been disclosed to electron-rich alkenes or arenes. Bearing this in mind, we first evaluated the reactivity of some representative *N*-protective groups on the pyrrole, aiming to obtain optimal *Z*/*E* selectivity and diastereoselectivity by reducing the reactivity of pyrrole while improving the selectivity. As formation of bis-cyclopropane structures at both ends of the pyrrole ring complicates the stereoselectivity of the resulting spiro compounds, making it challenging to control, we elected to start with pyrrole derivatives with one side being blocked to achieve better stereoselectivity. After some screening, we found the cyclohexanone fused pyrrole derivative, 1-(3,5-bis(trifluoromethyl) phenyl)−1,5,6,7-tetrahydro-4H-indol-4-one (**2a**), to be a good candidate, which reacted with cyclopropene **1a** with $Rh_2(OAc)_4$ as the catalyst in benzene as solvent to yield the *E*-configured product **3aa** in 91% yield (Table 1, entry 1). We attempted to reduce the amount of cyclopropene, the yield decreased because the substrate **2a** could not be fully converted (entries 2 and 3). Subsequently, we investigated the reaction of 3-phenyl-3-methylcyclopropene **1a** with a series of *N*-protected pyrroles **2**. We initially used methyl group or *N*-benzyl group, no obvious product was observed (entries 4 & 5). We then gradually increased the

electron-withdrawing ability of the *N*-protecting group. When *tert*-butoxycarbonyl was used as a substituent, the yield was 45% (entry 6). Replacing this with a benzoyl group significantly increased the yield to 84% (entry 7). However, when a strong electron-donating group is present at the position opposite to the benzoyl group, the yield decreases to 74% (entry 8). The substrate protected by the bulky 2,4,6-triisopropylbenzenesulfonyl (TPS) group affords only trace amounts of product (entry 9).The evaluation of solvent effect was also performed, and the reactions in toluene, DCM, PhCl, THF, and MeCN led to dramatically lower yields or trace products (entries 10 ~ 13). It is noted that under all conditions examined, high dr and *E*/*Z* values of > 25/1 was observed. Finally, *N*−3,5-ditrifluoromethylbenzoyl group was used as the *N*-protecting and modulating group as it provided the best 91% yield.

We set out to examine the scope of the reaction with respect to the cyclopropene (Fig. 2). First, variation of the substituents on the aryl rings as R^1 was attempted. Gratifyingly, both strong electron-withdrawing (4-CF_3) and strong electron-donating (4-OMe) groups were well tolerated to afford the corresponding cyclopropanation products in excellent yields (**3b** and **3c**). When an *i*-Bu group is located at the *para*-position of the benzene ring, the reaction can proceed efficiently (**3d**). Halogen atoms, such as (Cl, Br), on the *para*-position of the aromatic ring of cyclopropanes were also tolerated and provided the corresponding compounds in good yields and excellent *E*/*Z* ratios (**3e**, **3f**). Naphthyl group is also tolerated (**3g**). The reaction is sensitive to the position of the substituents on the aromatic ring: while the corresponding *meta*-methyl (**3h**) and *meta*-Cl (**3i**) analogues was obtained in a comparable yield, the *ortho*- analogues were obtained in significantly decreased yields and decreased *E*/*Z* values (**3j** and **3k**). Cyclopropenes bearing other alkyl groups beyond methyl as the R^2 are also tolerated and provided the corresponding products in excellent yields and high *E*/*Z* ratios (**3 l** − **3n**, 72 ~ 96%). 3,3-Dialkyl substitution is also nicely tolerated, although a low *E*/*Z* ratio (52:48) was observed for the case where the two alkyl groups are of similar steric hindrance (**3o**).

Subsequently, the reaction between *N*-protected indole derivatives and cyclopropene was performed. After probing of the effect of the protecting groups, 4-methoxybenzoyl was eventually determined to be the most suitable one (see Table S1 for details). Under the optimized conditions, the reaction between *N*-PMB indole and cyclopropene **1a** reached 63% conversion after 24 h, and the corresponding product **3p** was obtained in 85% yield (brsm) with 40:60 *E*/*Z* ratio. This comparison highlights the distinct electronic requirement of indole and pyrrole in the reaction. An

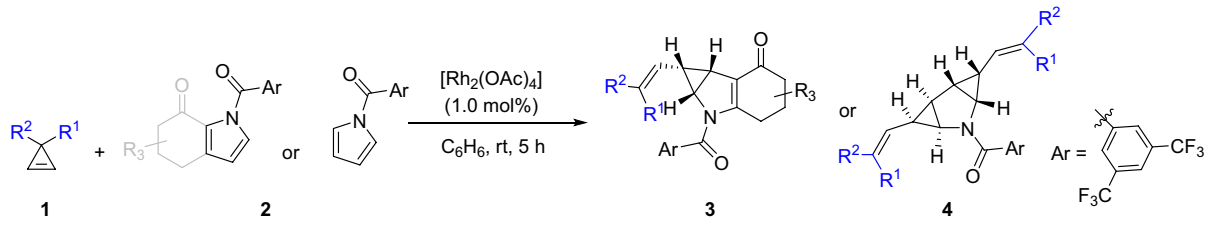
Table 1 Optimization of the reaction conditions[a]



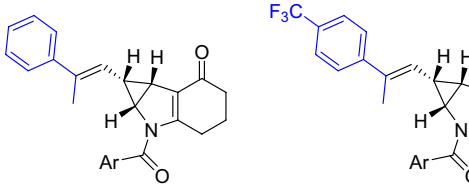
1a (x equiv.) **2** (1 equiv.) **3**

Entry	Deviations from the above conditions	Yield/%[b,c]
1	none	91
2	x = 4	77
3	x = 3	72
4	PG = Me	<10
5	PG = Bn	<10
6	PG = Boc	45
7	PG = Bz	84
8	PG = 4-CF_3Bz	74
9	PG = 2,4,6-(*i*-Pr)$_3C_6H_2$-	trace
10	DCM	80
11	PhCl	68
12	THF	<10
13	MeCN	trace

[a]Reaction conditions:**1a** (5 equiv.), **2a** (0.10 mmol), $Rh_2(OAc)_4$ (1 mol%), solvent (2 mL), N_2, rt, 5 h. [b]Isolated yield. [c] dr and *E*/*Z* values of > 25/1 was observed in all cases

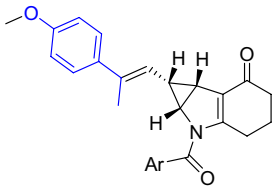


1 2 3 4

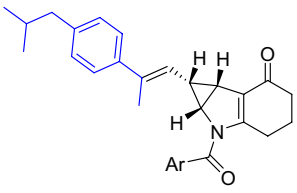


3a, 91 %

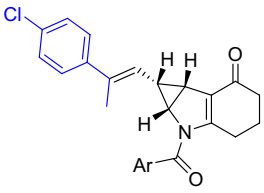
3b, 79 %



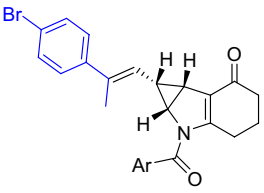
3c, 98 %



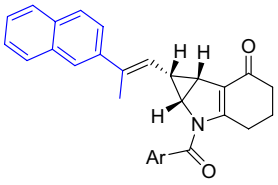
3d, 88%



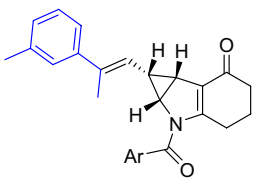
3e, 90 %



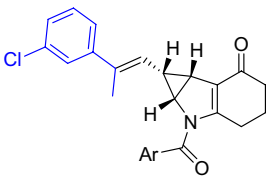
3f, 88%
E/*Z* = 94/6



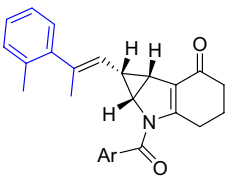
3g, 57 %



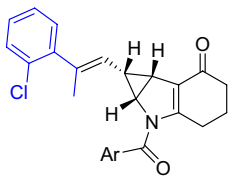
3h, 75 %



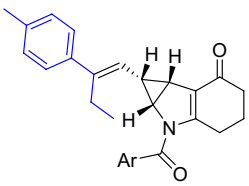
3i, 86 %



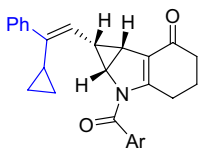
3j, 20 %
E/*Z* = 53:47



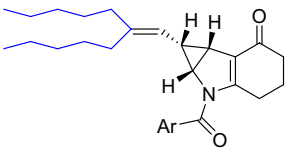
3k, 27 %
E/*Z* = 66:34



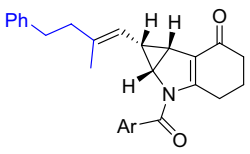
3l, 96 %



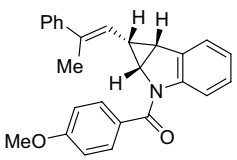
3m, 87%



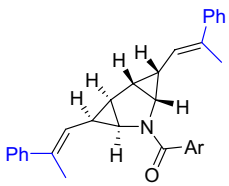
3n, 72 %



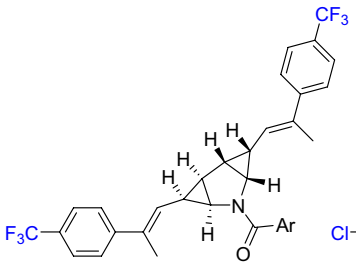
3o, 42 %
E/*Z* = 52:48



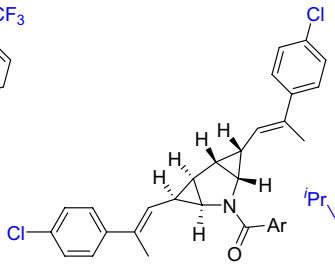
3p, 85 % (BRSM)
E/*Z* = 40:60



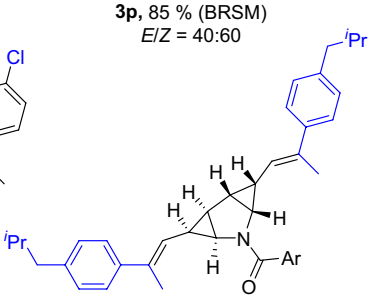
4a[b], 43 %, >25/1 *dr*



4b[b], 45 %, >25/1 *dr*



4c[b], 47 %, >25/1 *dr*



4d[b], 47 %, 4.3/8.4/4.8/1 *dr*

Reaction conditions:**1a** (5 equiv.), **2a** (0.10 mmol), $Rh_2(OAc)_4$ (1 mol%), PhH (2 mL), N_2, rt, 5h. Isolated yield.*dr* value of >25/1 was observed in all cases.[b]**1a**(3 equiv.) was used.

Fig. 2 Substrate scope studies

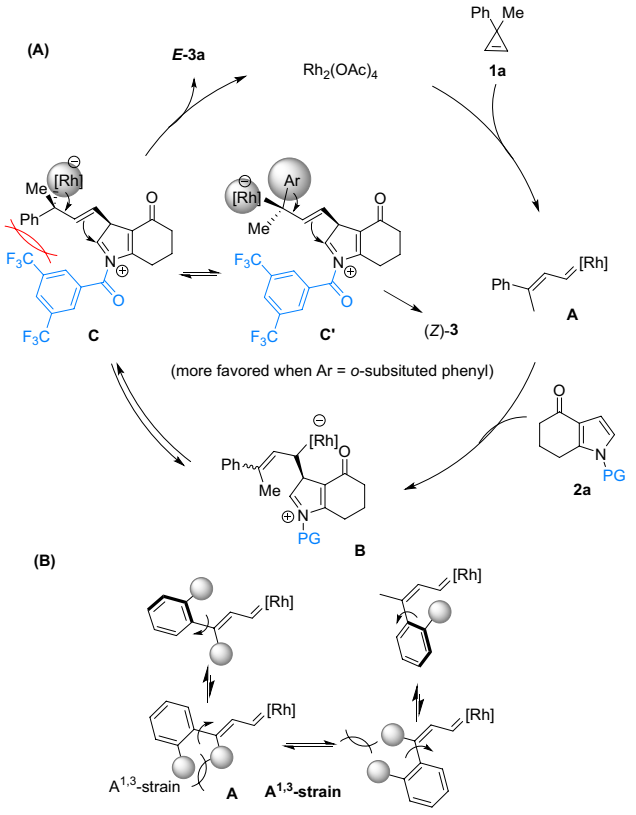


Fig. 3 (**A**) a plausible mechanism; (**B**) the issue of *ortho*-aryl substitution

ester group substituent at the 2-position of the indole ring inhibited the reactivity (Scheme S1). Finally, when pyrrole derivatives are subjected to the optimized conditions, the reactions produced the biscyclopropanated polycyclic compounds **4a**~**4d** in moderate to good yields and high diastereoselectivities (Fig. 2).

A plausible mechanism is proposed to account for the formation of the products (Fig. 3A). The reaction initiates with the ring opening of cyclopropene **1a** catalyzed by $Rh_2(OAc)_4$, leading to the formation of a vinyl rhodium carbene complex **A**. This complex then undergoes nucleophilic attack by the pyrrole derivative **2a**, resulting in the formation of a zwitterionic complex **B**. Since controlling the stereoselectivity during carbene formation is challenging, we hypothesize that the high *E*/*Z* stereoselectivity is primarily governed by the equilibrium between the rhodium propyl complex **B** and complex **C**. Finally, following rhodium migration and C−C bond rotation, the thermodynamically favored *E*-isomer **3aa** was produced, completing the reaction. It is noted that for cyclopropene with 3-aryl being *ortho*-substituted phenyl group (**3j** and **3k**), the $A^{1,3}$-strain in the carbenoid intermediate (Fig. 3B) and the subsequently formed adduct intermediate **C** may hinder effective cyclization to generate the final product, leading to compromised yields. The *Z*/*E* selectivity, which is generated in the cyclization step, may also be significantly reduced, as the sterically demanding *ortho*-substituted aryl may cause C−C bond rotation of the allylic Rh moiety (via **C'**) to avoid clashing with the *N*-aroyl before cyclization, resulting in increased *Z*-form formation. As an alkenyl carbenoid species is always generated starting from cyclopropene, a comparative reaction involving ethyl diazoacetate was performed but led to no product formation, making it difficult to estimate if the alkenyl moiety is responsible for the high diastereoselectivity. Despite of this observation, the use of cyclopropene generates an extra alkene moiety in the product that could be further functionalized if required, increasing the potential utility of the protocol.

In summary, we developed a protocol for straightforward access to 2-azabicyclo[3.1.0]hex-3-ene and 5-azatricyclo[4.1.0.$0^{2,4}$]heptane scaffolds by Rh(II)-catalyzed stereoselective cyclopropanation of pyrrole derivatives with cyclopropene by electronic tuning with *N*-aroyl moiety. The electronic tuning turned out to be key for the improved reactivity, while the diaselectivities are generally not affected by different *N*-protecting groups. The reaction is characterized by simple operation, mild conditions, low catalyst loading, and high yield and stereoselectivities. The good compatibility of variation on both the cyclopropene and pyrrole substrates enables quick library construction and downstream biological and reactivity studies. Further expanding the application of the reaction is currently underway.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s44442-026-00075-9.

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Author contributions D.J. and C.Z. performed condition optimization and substrate scope studies. B. L. helped with starting material preparation. J.M. and S.C. performed compound characterization and data processing. C. Z. and J. Z. wrote the manuscript with feedback from all authors. J. Z. directed the project.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

References

1. Li DS (2025) The roles of fused-cyclopropanes in medicinal chemistry: insights from the past decade. Eur J Med Chem 297:117951. https://doi.org/10.1016/j.ejmech.2025.117951
2. Feng J, Guo H, Ding A (2025) Visible-light-induced dehydrogenation of indolines. Tetrahedron Lett 169:155753. https://doi.org/10.1016/j.tetlet.2025.155753
3. Feng C, Wang J, Guo H et al (2025) Highly selective 1,4-hydrogenation of conjugated dienes by photoinduced electron transfer and proton transfer. Cell Rep Phys Sci 6:102561. https://doi.org/10.1016/j.xcrp.2025.102561
4. Feng J, Tang H, Guo H et al (2025) Visible light-induced dehydrogenation of dihydroquinolinones via the combination of energy transfer and hydrogen atom transfers. Org Chem Front 12:1183–1188. https://doi.org/10.1039/d4qo01902d
5. Nirogi R, Mohammed AR, Shinde AK et al (2020) Discovery and development of 3-(6-chloropyridine-3-yloxymethyl)-2-azabicyclo[3.1.0]hexane hydrochloride (SUVN-911): a novel, potent, selective, and orally active neuronal nicotinic acetylcholine α4β2 receptor antagonist for the treatment of depression. J Med Chem 63:2833–2853. https://doi.org/10.1021/acs.jmedchem.9b00790
6. Crawford JJ, Liao D, Kolesnikov A et al (2020) Synthesis of an azabicyclo[3.1.0]hexanone-containing inhibitor of NF-κB inducing kinase via catalytic C–H activation. Synthesis 52:3420–3426
7. Augeri DJ, Robl JA, Betebenner DA et al (2005) Discovery and preclinical profile of saxagliptin (BMS-477118): a highly potent, long-acting, orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. J Med Chem 48:5025–5037. https://doi.org/10.1021/jm050261p
8. Ding M-G, Gao WY, Zhao C et al (2026) Dipolar cycloaddition of cyclopropene with *N*,N-cyclic azomethine imine: a straightforward protocol for diazabicyclo[3.1.0]hexane scaffold with promising in vitro anti-proliferative activities. J Org Chem 91:3697–3704. https://doi.org/10.1021/acs.joc.5c02983
9. Fu J, Wurzer N, Lehner V et al (2019) Rh(II)-catalyzed monocyclopropanation of pyrroles and its application to the synthesis pharmaceutically relevant compounds. Org Lett 21:6102–6106. https://doi.org/10.1021/acs.orglett.9b02250
10. Huang XL, Cheng YZ, You SL (2022) Visible-light enabled synthesis of cyclopropane-fused indolines via dearomatization of indoles. Org Lett 9:5463–5468. https://doi.org/10.1039/D2QO01174C
11. Ross RJ, Jeyaseelan R, Lautens M (2020) Rhodium-catalyzed intermolecular cyclopropanation of benzofurans, indoles, and alkenes via cyclopropene ring opening. Org Lett 22:4838–4843. https://doi.org/10.1021/acs.orglett.0c01655
12. Du W, Gu QS, Li ZL, Yang D (2015) Palladium(II)-catalyzed intramolecular tandem aminoalkylation via divergent C(sp3)–H functionalization. J Am Chem Soc 137:1130–1135. https://doi.org/10.1021/ja5102739
13. Cheng SD, Yu T, Li J et al (2024) Copper/chiral phosphoric-acid-catalyzed intramolecular reductive isocyanide-alkene (1 + 2) cycloaddition: enantioselective construction of 2-azabicyclo[3.1.0]hexanes. J Am Chem Soc 146:7956–7962. https://doi.org/10.1021/jacs.4c00989
14. Dutta PK, Chauhan J, Ravva MK et al (2019) Directing-group-assisted manganese-catalyzed cyclopropanation of indoles. Org Lett 21:2025–2028. https://doi.org/10.1021/acs.orglett.9b00150
15. Guo P, Sun W, Liu Y et al (2020) Stereoselective synthesis of vinylcyclopropa[b]indolines via a Rh-migration strategy. Org Lett 22:5978–5983. https://doi.org/10.1021/acs.orglett.0c02071
16. Li ZY, Zhao JB, Sun BZ et al (2017) Asymmetric nitrone synthesis via ligand-enabled copper-catalyzed cope-type hydroamination of cyclopropene with oxime. J Am Chem Soc 139:11702–11705. https://doi.org/10.1021/jacs.7b06523
17. Li ZY, Zhang MR, Zhang Y et al (2019) Multicomponent cyclopropane synthesis enabled by Cu-catalyzed cyclopropene carbometalation with organoboron reagent: enantioselective modular access to polysubstituted 2-arylcyclopropylamines. Org Lett 21:5432–5437. https://doi.org/10.1021/acs.orglett.9b01650
18. Liu BW, Wang L, Qin YF et al (2022) Synthesis of trisubstituted chromanes by Lewis-base-catalyzed three-component electrophilic thiofunctionalization of cyclopropene with phenols via a formal [3 + 3] annulation. Org Lett 21:5432–5437. https://doi.org/10.1021/acs.orglett.2c02072
19. Gao WY, He MB, Yang XR et al (2025) Strategic leverage of β-OH elimination for catalytic assembly of alkylidenecyclopropanes. Org Lett 27:9698–9704. https://doi.org/10.1021/acs.orglett.5c02882
20. Huang JH, Li JH, Liu SL et al (2025) Ring opening of donor-acceptor-type cyclopropene unveils electrophilic ketene with vinylogous [4C + n] periselective cyclization mode. Nat Commun 16:4019. https://doi.org/10.1038/s41467-025-59048-y
21. Li ZY, Peng GC, Zhao JB et al (2016) Catalytically generated allyl Cu(I) intermediate via cyclopropene ring-opening coupling en route to allylphosphonates. Org Lett 18:4840–4843. https://doi.org/10.1021/acs.orglett.6b02307
22. Zhang MR, Li HX, Zhao JB, Li Y, Zhang Q (2021) Copper-catalyzed [3 + 1] cyclization of cyclopropenes/diazo compounds and bromodifluoroacetamides: facile synthesis of α,α-difluoro-β-lactam derivatives. Chem Sci 12:11805–11809. https://doi.org/10.1039/D1SC02930D
23. Archambeau A, Miege F, Meyer C, Cossy J (2015) Intramolecular cyclopropanation and C-H insertion reactions with metal carbenoids generated from cyclopropenes. Acc Chem Res 48:1021–1031. https://doi.org/10.1021/acs.accounts.5b00016