Check for updates

Cycloaddition and functionalization reactions involving tropone

Fatemeh Doraghi, [ID] [a] Mohammad Hadi Edareh, [ID] [b] Bagher Larijani[a] and Mohammad Mahdavi [ID] *[a]

Tropones are valuable moieties in the synthesis of natural products and bioactive molecules. Tropones have also emerged as fascinating synthetic partners for various (4 + 2)-, (4 + 6)-, (6 + 3)-, (6 + 4)-, (6 + 6)-, (8 + 2)-, and (8 + 3)-cycloaddition reactions as well as functionalization reactions. This review highlights various cycloaddition and functionalization reactions involving tropone building blocks reported since 2014.

1. Introduction

Tropones are frequently present in numerous natural products,[1–4] as well as agricultural[5] and pharmaceutical[6,7] molecules. (−)-Gweicurculactone (anti-oxidant, antimicrobial, anti-inflammatory),[8] grandirubrine (anticancer),[9] gukulenin B (anticancer),[10] colchicine (antigout),[11] purpurogallin (anti-oxidant),[12] and harringtonolide (anticancer)[13] are representative examples of densely polycyclic scaffolds that include the cycloheptatrienone core (Fig. 1). Tropones have also been widely used in organic synthesis and mechanistic studies to explore the chemistry and reactivity of these important synthons.[14–20] They have been proved to be versatile 4π, 6π, or 8π synthons in (4 + 2)-,[21] (4 + 6)-,[22] (6 + 3)-,[23] (6 + 4)-,[24] (6 + 6)-,[25] (8 + 2)-,[26] and (8 + 3)-cycloadditions.[27] In particular, higher-order cycloadditions exploit their distinctive extended π-conjugation, enabling efficient access to a wide range of bridged and fused cyclic skeletons of biological interest in the synthesis of medicinally important molecules.

From a synthetic perspective, tropones are suitable substrates for a variety of functionalization reactions, retaining the cycloheptatrienone structure.[10] In contrast to conventional aromatic compounds, little attention has been paid to tropones

[a]Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran. E-mail: momahdavi@sina.tums.ac.ir

[b]School of Chemistry, College of Science, University of Tehran, Tehran, Iran

Fatemeh Doraghi received her bachelor and master degrees in organic chemistry from Shahid Chamran University, Ahvaz in 2008 and 2014, respectively. She received her PhD degree in organic chemistry from the University of Tehran, Tehran in 2022. During her PhD research, she focused on the development of new synthetic methodologies via transition metal as well as metal-free oxidative coupling reactions. She is currently employed as a researcher at the Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences, Tehran, Iran.

Fatemeh Doraghi

Mohammad Hadi Edareh is a research assistant at the Endocrine & Metabolism Research Institute, specializing in medicinal organic chemistry. He completed his Master's degree in nano chemistry at the University of Tehran in September 2024, following his Bachelor's degree in medicinal chemistry at Azad University, Tehran Medical Branch in February 202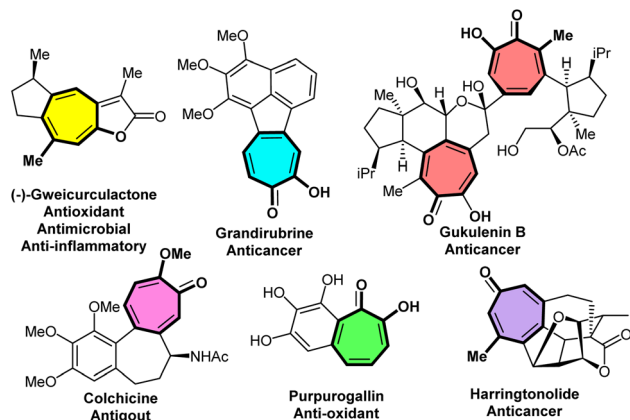1. His master's thesis focused on the design and synthesis of novel thioqunoline derivatives using copper nano-catalysts, with specific investigation of their potential anti-diabetes type 2 properties and comparative inhibition concentration analysis to reference material acarbose. His current research interests encompass organic chemistry synthesis, medicinal chemistry, nanotechnology, and nanocatalysis synthesis.

Mohammad Hadi Edareh

Fig. 1 Representative pharmaceutical molecules containing a tropone motif.

Fig. 2 Primary synthetic methods in the synthesis of tropone derivatives: (i) Nozoe *et al.*, 1953 (ii) Nakamura, 1962 (iii) Noyori, 1975 (iv) Boger, 1995.

concerning direct C(sp²)–H bond functionalization, which constitutes a direct and atom-economical protocol towards structurally diverse substituted tropones. For instance, in 1953, Nozoe and coworkers reported the reaction of 2-phenyltropone with hydrazine hydrate, which led to the access of 2-amino-7-phenyltropone (Fig. 2(i)).[28] Over the years, many research teams have reported the synthesis of tropone derivatives. For example, Nakamura presented total synthesis of colchiceine in 1962,[29] and 1985,[30] respectively (Fig. 2(ii) and (iv)). In 1975, Noyori reported a two-step reaction access to 2-isopropyltropone (Figure 2(iii)),[31] and Boger, in 1995, developed a synthetic strategy for the assembly of granditropone (Fig. 2(v)).[32]

In recent years, the existing portfolio of tropone chemistry has focused on dearomative cycloaddition reactions, the *de novo* construction of seven-membered rings, and investigations into chemical tropone decorations *via* direct C–H bond functionalization.

Considering the notable importance of tropone in medicinal discovery and organic synthesis, numerous studies
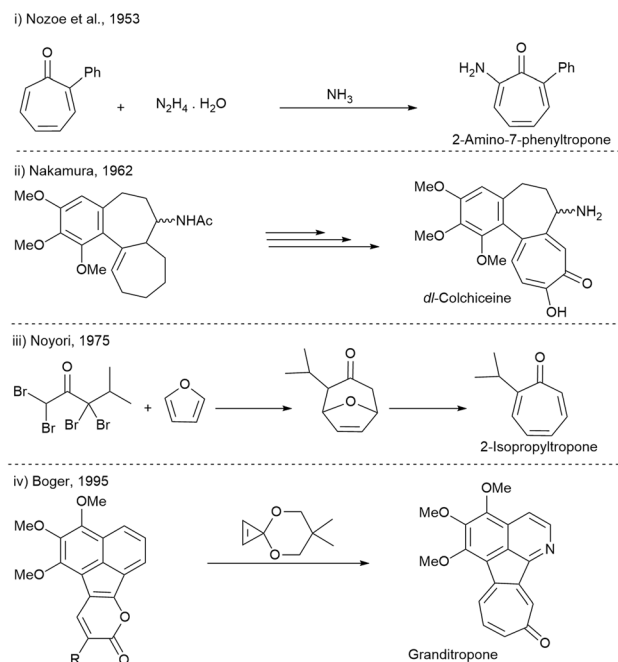
on the chemistry and reactivity of this valuable synthon have been conducted by several research groups. In this review, we highlight various cycloaddition and functionalization reactions involving tropone and its derivatives, which occur in the presence of metal catalysts such as Ag, Ni, Rh, Mg, Au, Pd, Mo, organocatalysts, bases, and under catalyst-free conditions.

Bagher Larijani was born in 1961 in, Iran, He obtained his MD from Tehran University, in 1986. His current research interests focus on diabetes.

Bagher Larijani

Mohammad Mahdavi was born in 1981 in Tehran, Iran. He received his MSc from the University of Tehran in 2008 and his PhD degree in medicinal chemistry from the Tehran University of Medical Science, Tehran, Iran, in 2016. Since August 2017, he has been with the Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences,

Mohammad Mahdavi

Tehran, Iran where he is an Assistant Professor. His current research interests focus on the synthesis of heterocyclic compounds with biological activities.
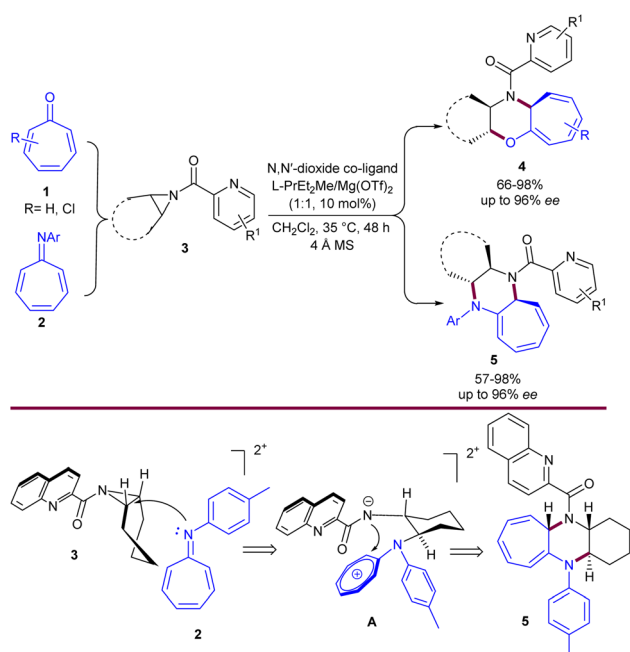
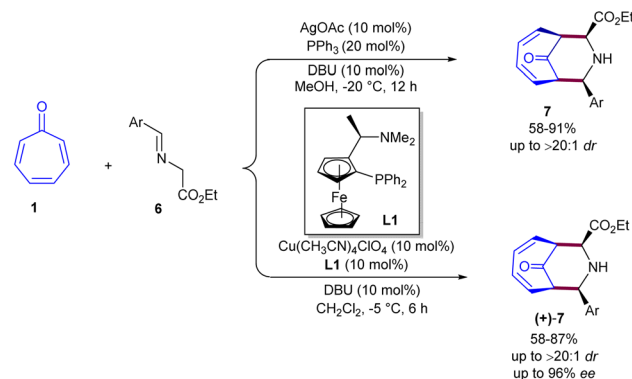# 2. Cycloaddition reactions involving tropone

2.1. Metal-catalyzed cycloaddition reactions involving tropone

2.1.1. Mg-catalyzed cycloaddition reactions involving tropone. A highly enantioselective magnesium-catalyzed system for the (8 + 3)-cycloaddition of tropone **1** or azaheptafulvenes **2** with *meso*-aziridines **3** was developed by Liu, Feng, and coworkers (Scheme 1).[33] This desymmetrization/annulation process proceeded in the presence of chiral *N*,*N*′-dioxide/ Mg(OTf)$_2$ complex (1:1, 10 mol%), in DCM at 35 °C. A new series of tricyclic heterocycles containing a cycloheptatriene motif **4**, **5** was synthesized in up to 98% yield, 96% ee, and >19 : 1 dr. The aziridine **3** bound the Mg with both the pyridine nitrogen and the carbonyl oxygen group. So, the cyclohexenyl ring of aziridine is oriented downwards to have the lowest spatial repulsion with the top-right amide of the ligand. At this time, the nitrogen of the azaheptafulvene **2** attacked from behind the aziridine ring at the outer carbon center, producing *trans*-cyclohexane-1,2-diamino intermediate after ring-opening. Subsequent annulation yielded the final product **5**. Moreover, the synthetic application of this method was demonstrated with the gram-scale synthesis of the final product (1.12 g, 90% yield, 91% ee).

2.1.2. Ag-catalyzed cycloaddition reactions involving tropone. In 2014, Honglei Liu *et al.* reported the first metal-catalyzed (6 + 3)-cycloaddition of tropone **1** with azomethine ylides **6** (Scheme 2).[34] Two metal salts, Ag(I) and Cu(II), were tested in the catalytic cycloaddition of tropone with azomethine ylides towards piperidine-fused bicyclic heterocycles. A silver acetate
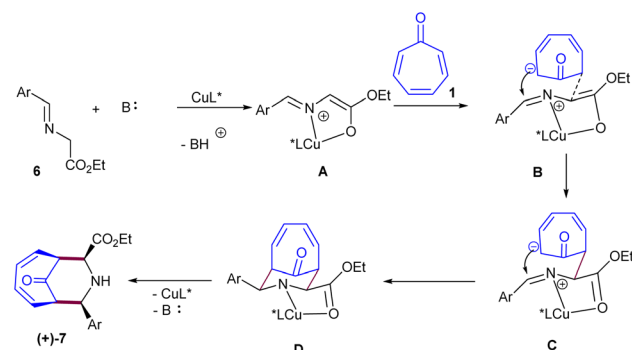

Scheme 2 (6 + 3)-Cycloaddition between tropone and azomethine ylides.
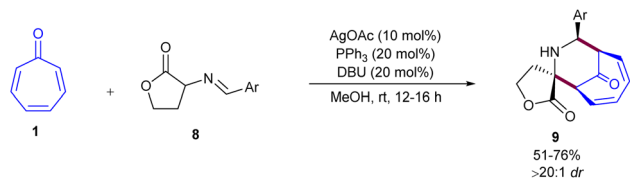
catalyst, in combination with a triphenyl phosphine ligand, can catalyze the diastereoselective (6 + 3)-cycloaddition of tropone with azomethine ylides. The use of a chiral ferrocenylphosphine in the copper-catalysis system enabled the achievement of final products with good to excellent enantioselectivities. The catalytic asymmetric (6 + 3)-cycloaddition reaction was suggested to occur through the formation of carboxyl enolate cuprous salt **A**, resulting from the abstraction of acidic hydrogen by the base under copper catalysis. This active species rapidly underwent nucleophilic addition to tropone towards zwitterion **C** through the transition state **B**. The steric crowding at the front side of **A** guided the approach of tropone from the backside. Subsequent intramolecular nucleophilic addition to the *si* face of the imine gave intermediate **D**, which was protonated to yield product **7** with release of the Cu(I) species and the base for the next catalytic cycle (Scheme 3). Huang's research group reported (6 + 3)-cycloaddition reaction between tropone **1** and azomethine ylides **7** (Scheme 4).[35] Various azomethine ylides prepared from homoserine lactone and aryl aldehydes with both electron-donating and electron-withdrawing substituents smoothly reacted with tropone at room temperature to yield tricyclic spiropiperidines in moderate to excellent yields (51–92%) with excellent diastereoselectivities (>20 : 1 dr). The position of the substituent on the aryl ring in the azomethine ylides had no notable influence on the yield and diastereoselectivity.

Scheme 1 Mg-catalyzed (8 + 3)-cycloaddition of tropone or azaheptafulvenes with *meso*-aziridines.

Scheme 3 Proposed mechanism or asymmetric (6 + 3)-cycloaddition of tropone and azomethine ylides.
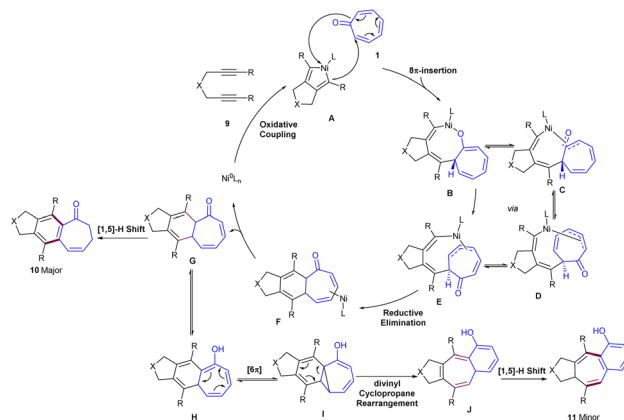
Scheme 4 (6 + 3)-Cycloaddition of tropone and azomethine ylides.

Azomethine ylides prepared from 2-CH$_3$, 4-OCH$_3$, and 2-F substituted benzaldehydes showed moderate reactivity. The 1-naphthyl-substituted azomethine ylide exhibited good reactivity, yielding the corresponding product in 67% yield with excellent diastereoselectivity.
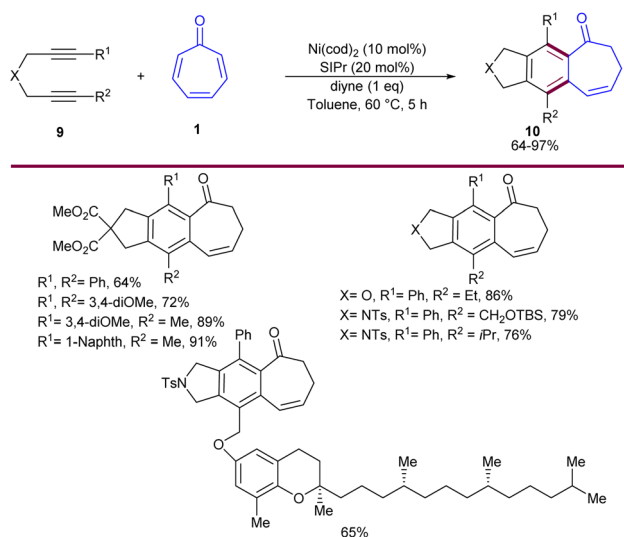
2.1.3. Ni-catalyzed cycloaddition reactions involving tropone. Nickel-catalyzed cycloaddition of tropone **1** with diynes **9** was reported by Louie and co-workers in 2014 (Scheme 5).[36] Various diynes were efficiently coupled with tropone, affording [5-6-7] fused tricyclic products. The reaction had broad substrate scope with respect to diynes, and excellent regioselectivities were observed in the case of unsymmetrical diynes. In the mechanism, nickel can selectively incorporate into the C–C π-bond of tropone, forming both major and minor products. The reaction began by the homo-oxidative coupling of diyne on Ni(0) to obtain Ni(II)-cyclopentadiene **A** that underwent 8π insertion of tropone **1** to generate a seven-membered ring complex **IB**, followed by isomerization to form intermediate **C**. Then, **C** isomerized to intermediate **D**, which in turn isomerized to intermediate **E**, which, upon reductive elimination, gave intermediate **F**. Next, **F** was converted into intermediate **G**, followed by [1,5]-H shift to form major product **10**. On the other hand, **G** can move through another pathway involving tautomerization to form cycloheptatrienol **H**, followed by 6π-electrocyclization to afford bis(divinyl)-cyclopropane **I**. This intermediate can either revert to **H** or irreversibly rearrange to [5-7-6]-fused intermediate **J** through divinyl cyclopropane
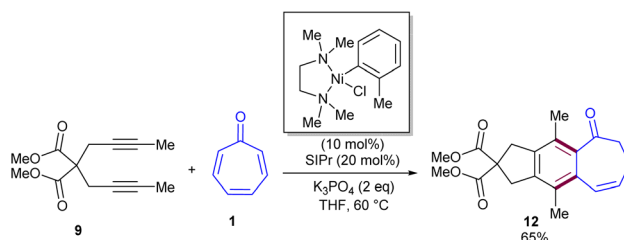

Scheme 5 Ni(NHC)-catalyzed cycloaddition of diynes and tropone.

Scheme 6 Catalytic cycle for Ni(NHC)-catalyzed cycloaddition of diynes and tropone.
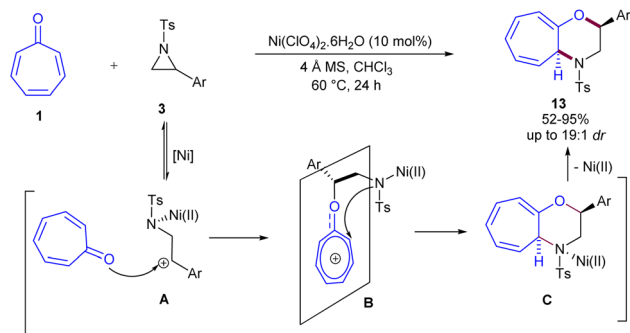
rearrangement. Further sigmatropic shifts in **J** afforded minor product **11** (Scheme 6). The authors mentioned that the presence of a small amount of water could catalyze this sigmatropic shift step *via* the bridging of one or multiple water molecules. A new air-stable, crystalline solid [(TMEDA)Ni(*ortho*-tolyl)Cl] was utilized for the cycloaddition of tropone **1** with diynes **9** (Scheme 7).[37] Preliminary mechanistic studies showed that [(TMEDA)Ni(*ortho*-tolyl)Cl] can be activated by either Ni–C or Ni–Ni transmetalation.

The (8 + 3)-cycloaddition of tropone and 2-aryl-*N*-tosylaziridines can be catalyzed in the presence of a nickel(II) catalyst (Scheme 8).[38] A wide range of aziridines bearing both electron-rich and electron-deficient aryl moieties reacted well with tropone, affording various 4-tosyl-2,3,4,4a-tetrahydrocyclohepta[*b*]-[1,4]oxazines in moderate to excellent yields with good diastereoselectivities. To investigate the mechanism, the authors conducted a reaction of an enantiopure aziridine with tropone, resulting in a racemic product, which confirmed the opening of the aziridine ring during the reaction. Therefore, the mechanism involves a Ni(II)-catalyzed ring opening of aziridine **3**, generating intermediate **A**, followed by a nucleophilic attack of tropone **1** on the carbocation from the top of the tropone plane, as the Ar group blocks the bottom of the tropone. This produced intermediate **B** with good diastereoselectivity. Another nucleophilic attack led to intramolecular cyclization towards intermediate **C**, which, upon removal of the Ni catalyst, resulted in the liberation of the final product **13**. Furthermore, the large-
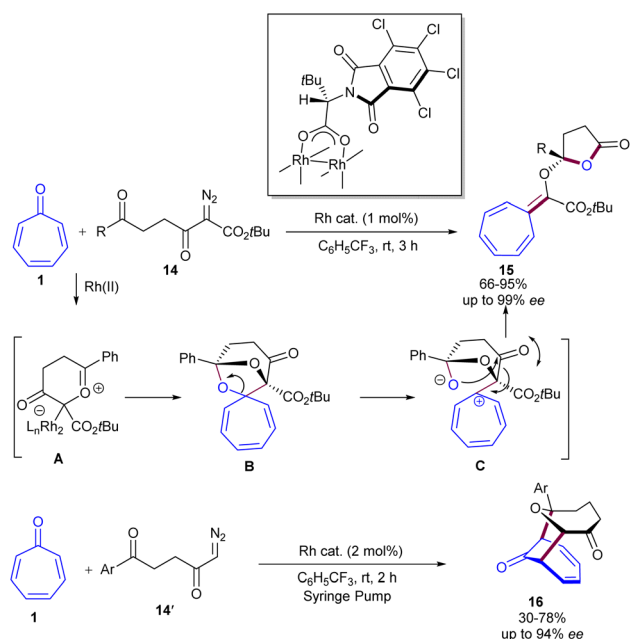

Scheme 7 [(TMEDA)Ni(*o*-tolyl)Cl]-catalyzed cycloaddition of tropone with diynes.

Scheme 8 Ni-catalyzed (8 + 3)-cycloaddition of tropone with 2-aryl-*N*-tosylaziridines.

scale synthesis of the product (1.55 g, 82%, 13 : 1 dr) and the reduction of the tropone ring demonstrated the synthetic utility of this method.

2.1.4. Rh-catalyzed cycloaddition reactions involving tropone. In 2015, Sandip Murarka *et al.* reported Rh-catalyzed enantioselective (3 + 2)-cycloaddition reaction between tropone **1** and α-diazoketone-derived carbonyl ylides **14** (Scheme 9).[39] A chiral rhodium complex was utilized in the reaction of tropone **1** and diazodiketoester **14** to construct lactone **15** with complete diastereoselectivity (>20 : 1 dr) and excellent enantioselectivity (up to 99% ee). Using the same rhodium catalyst, bridged polyheterocyclic compounds **16** were constructed through (6 + 3)-cycloaddition of the conjugated triene system of tropone **1** as electrophile with the carbonylylide derived from α-diazoketone **14′** as dipoles. The reactivity difference arises from the different HOMO/LUMO energy levels of carbonyl ylides derived from diazodiketoesters and α-
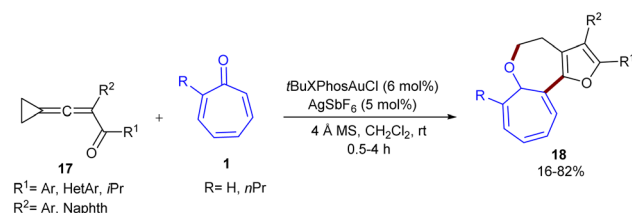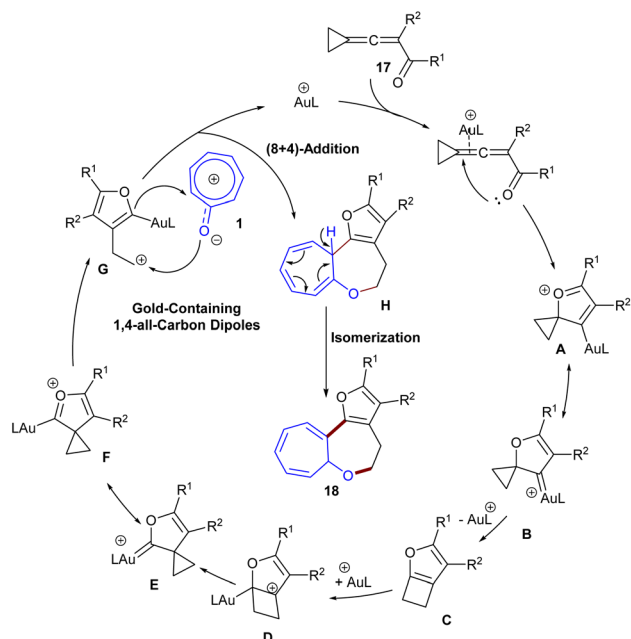
diazoketones. In general, the reaction proceeded through (3 + 2)-cycloaddition of a carbonyl ylide **14** with the keto group of tropone **1** to form spirocyclic intermediate **A**. Then, **A** was converted into zwitterion **B**, followed by intramolecular (3 + 2)-cycloaddition and rearrangement to generate lactone **15**.

2.1.5. Au-catalyzed cycloaddition reactions involving tropone. In 2020, Miao's research team developed a gold catalysis system for the (8 + 4)-annulation reaction between tropone **1** and cyclopropyl-tethered allenyl ketone derivatives **17** (Scheme 10).[40] A gold-containing 1,4-allcarbon dipole derived from allenyl ketone bearing a cyclopropyl moiety was found to be a key intermediate in the high-order (8 + 4)-cycloaddition with tropone, delivering 7,7,5-fused tricyclic frameworks in low to high yields (16–82%) with complete selectivity. According to the mechanism, the reaction begins with the π-activation of allene by the cationic Au(I) catalyst, followed by nucleophilic cyclization to the spirocyclic oxonium ion **A** and its resonance structure, the gold-carbene form **B**. Then, **B** underwent ring-expansion and proto-demetalation to generate the furan-fused cyclobutene **C**. The re-addition of cationic gold species to a highly strained C=C bond of **C** led to the cationic furan **D**. Subsequent ring contraction in **D** resulted in the gold carbene **E** and spirocyclic oxonium ion **F** as resonance species. Ring opening of **F** generated the gold-containing 1,4-all-carbon dipole **G**, which moved through intermolecular (8 + 4)-cycloaddition with tropone **1** *via* either a stepwise or a concerted route to furnish intermediate **H**. The obtained intermediate underwent C=C bond isomerization to deliver product **18** (Scheme 11). The gram-scale synthesis of the product resulted in 1.12 g, 65% yield. The direct reduction of the tropone ring yielded the hydrogenation product in 70% yield, which, after a (4 + 2)-cyclization with *in situ* generated benzyne, provided an *O*-bridged polycyclic compound.
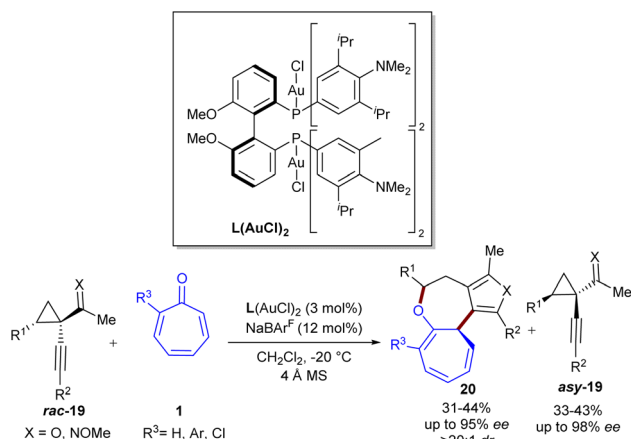
Au-catalyzed regio-, stereo-, and enantioselective (8 + 4)-cycloaddition of tropone 1 with 1-(1-alkynyl)cyclopropyl ketones **19** was reported by Wang *et al.* in 2024 (Scheme 12).[41] A variety of tropone and 2-halo/aryl tropones smoothly participated in the reaction with cyclopropyl ketones bearing aryl/heteroaryl/cyclohexenyl, producing highly functionalized cyclohepta[*b*]furo[3,4-*d*]oxepines **20** in satisfactory yields with >20 : 1 dr, and up to 95% ee. The reaction of oxime-containing substrate **2** with tropone was also successful under this gold catalysis system, yielding chiral [5.5.0] bicyclic product containing a pyrrole moiety in 31% yield and 73% ee. Additionally, a kinetic resolution study using racemic 1-(1-alkynyl)cyclopropyl ketones ***asy-***

Scheme 9 Rh-catalyzed enantioselective 1,3-dipolar cycloaddition of tropone and carbonyl ylides.

Scheme 10 Au-catalyzed reaction of tropone and cyclopropyl-tethered allenyl ketone.
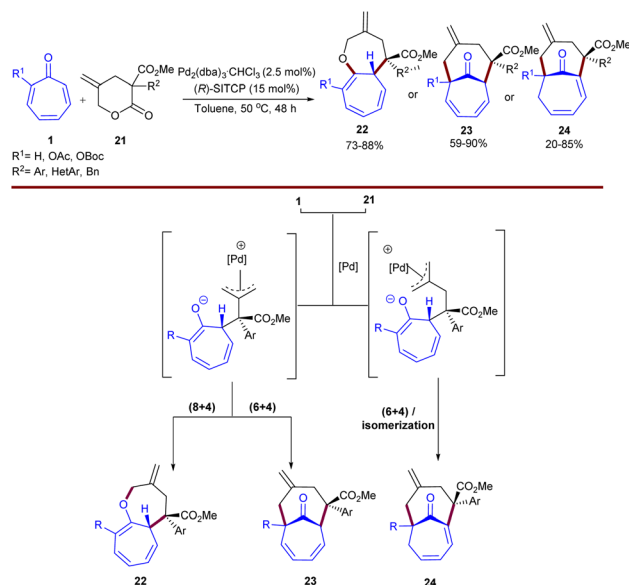
Scheme 11 Catalytic cycle for Au-catalyzed reaction of tropone and cyclopropyl-tethered allenyl ketone.

Scheme 12 Au-catalyzed (8 + 4)-cycloaddition of tropone with 1-(1-alkynyl)cyclopropyl ketones.

Scheme 13 Pd-catalyzed reaction of tropones with γ-methylidene-δ-valerolactones.

the direct synthesis of [5.5.0] and [4.4.1] bicyclic compounds. Mechanistic studies and DFT calculations revealed that two possible key diastereomeric intermediates could be generated, leading to three classes of medium-sized bicyclic compounds. One intermediate can undergo either O- or C-allylation, providing [5.5.0] or [4.4.1] bicyclic compounds **22**, and **23** through (8 + 4)- or (6 + 4)-cycloaddition reaction, respectively. In contrast, another conformation of diastereomer afforded bridgehead alkene-containing bicyclo[4.4.1] compounds **24** *via* (6 + 4)-cycloaddition/unconventional alkene isomerization. By controlling the reaction conditions, the authors were able to increase the yield of each product as the major product.

In 2024, Shi, Wei and co-workers established the (8 + 3)-cycloaddition of tropones **1** or tropsulfimides **2** with vinylidenecyclopropane-diester **25** (Scheme 14).[43] In this reaction system, the nature of tropone derivatives can influence on the product formation; decahydro-1H-cyclohepta[b]pyridines

19 was performed (*s* factor up to 104). The synthetic utility of this method was demonstrated by the gram-scale synthesis of the product (0.76 g, 40% yield, 92% ee), the hydrogenation of the troponyl ring, and the (4 + 2)-cyclization of the furan unit with *in situ* generated benzyne. Additionally, the [1,5]-H shift of some products was performed in the presence of PTSA at room temperature, yielding the corresponding products in 61–71% yields and 80–88% ee.
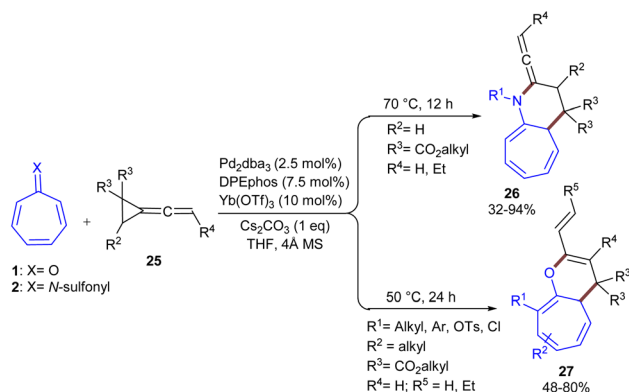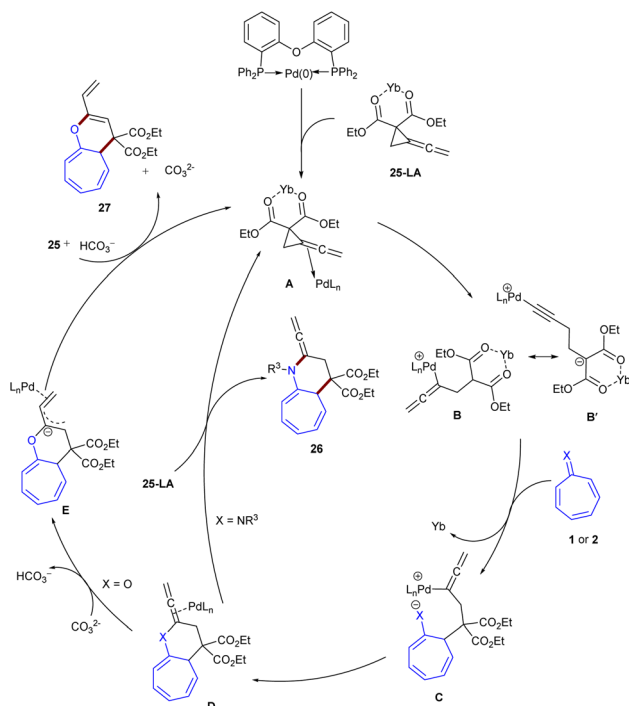
2.1.6. Pd-catalyzed cycloaddition reactions involving tropone. In 2020, Lan's research team reported the first example of Pd-catalyzed cycloaddition reaction of tropones **1** with γ-methylidene-δ-valerolactones **21** (Scheme 13).[42] Merging of a palladium(0) complex with a chiral phosphine ligand can constitute an efficient diastereo- and enantioselective catalytic system for
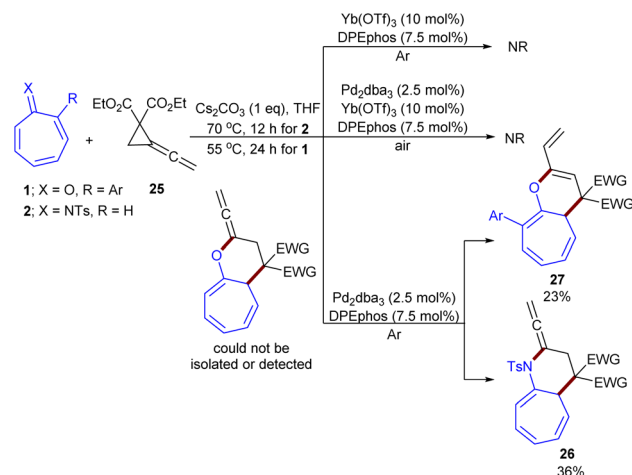

Scheme 14 Pd/Yb-catalyzed reaction of tropones with vinylidene-cyclopropane-diester.

bearing an allene unit **26** were obtained when X = N, whereas decahydro-1*H*-cyclohepta-[*b*]pyrans **27** were the main product when C=O. The structure of zwitterionic propargyl palladium intermediates was confirmed with the help of DFT calculations and HRMS experiment. Thereby, a rational mechanism was suggested for this cycloaddition. First, Pd(0) coordinated to vinylidenecyclopropane-diester **25** to generate complex **A**. This complex underwent oxidative addition at the electron-deficient C–C site of the cyclopropyl motif, yielding intermediate **B**. The isomerization of **B** produced zwitterionic propargyl palladium species **B′**, which underwent (8 + 3)-cycloaddition with trop-sulfimide **25** or tropone **1** to obtain intermediate **C**. Subsequent intramolecular nucleophilic addition yielded intermediate **D**. When X = NSO₂R, ligand exchange by **25** afforded product **26** and regenerated **A**. For X = O, proton transfer driven by the carbonate anion occurred to form allyl anionic intermediate **E**, which underwent protonation of **E** on another side of the allyl anion with the bicarbonate anion, delivering product **27**, and the ligand exchange with **25** regenerated the Pd complex **A** to fulfill the catalytic cycle (Scheme 15). It was found that palladium catalyst, Lewis acid, and the base are all necessary for the reaction to proceed. In another study, this research group investigated the reaction of tropones/tropsulfimides with vinylidenecyclopropane-diester in the presence and absence of the Lewis acid Yb(OTf)₃ to determine the impact of the Lewis acid on the promotion of oxidative addition (Scheme 16).[44] By studying DFT results and HRMS experiments, they could confirm the position of C–C oxidative addition cleavage and the positive impact of the Lewis acid Yb(OTf)₃ in promoting oxidative addition.
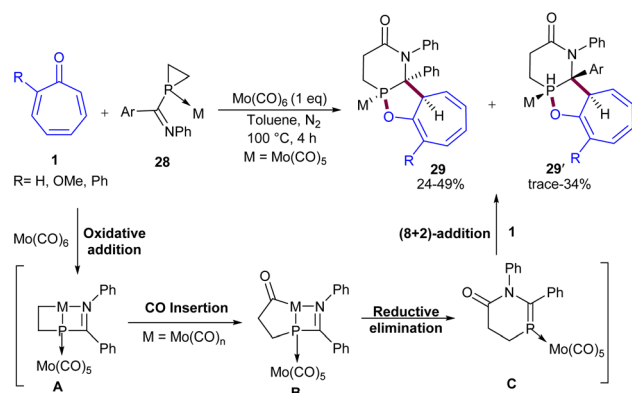

Scheme 16 Pd-catalyzed reaction of tropones with vinylidenecyclopropane-diester.

2.1.7. Mo-catalyzed cycloaddition reactions involving tropone. In 2022, Tian and co-workers disclosed a tandem (5 + 1)/(8 + 2)-cycloaddition reaction between tropones **1** and phosphiranes **28** (Scheme 17).[45] Tropone, 2-phenyl tropone, and 2-methoxy tropone were well incorporated in the reaction with 1-iminylphosphiranes bearing *N*-aryl moieties. The highly reactive C=P bond, derived from the carbonylative ring expansion of 1-iminylphosphirane complexes, enabled high-order (8 + 2)-cycloaddition of tropones, leading to structurally diverse 6,5,7-fused tricyclic scaffolds in satisfactory yields with excellent site selectivity. As shown in the mechanism, the oxidative addition of Mo(0) to the C–P bond of the strained phosphirane complex **B** resulted in the cyclocarbonylation of 1-iminylphosphirane. Sequential CO insertion and reductive elimination resulted in azaphosphacyclohexone complex **C**. The following (8 + 2)-cycloaddition between the C=P bond of **5** and tropone delivered **29** and **29′** as *endo/exo* isomers.
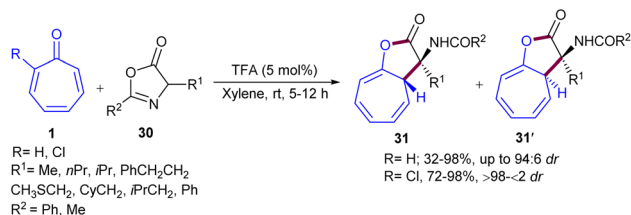
2.2. Metal-free cycloaddition reactions involving tropone

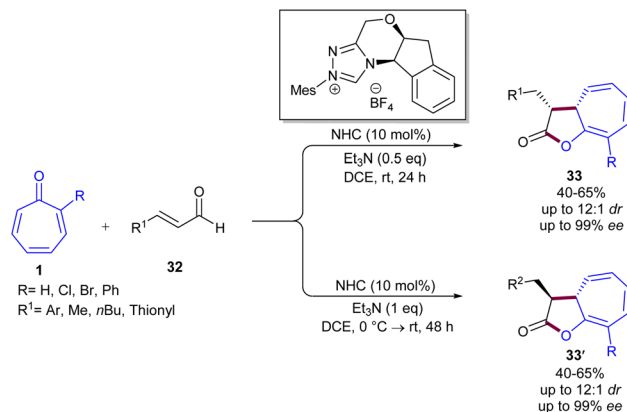**2.2.1. Organocatalyst-catalyzed cycloaddition reactions involving tropone.** A Brønsted acid catalyst was used for

Scheme 15 Catalytic cycle for Pd/Yb-catalyzed reaction of tropones with vinylidenecyclopropane-diester.

Scheme 17 Mo-catalyzed (5 + 1)/(8 + 2)-cycloadditions of phosphiranes and tropones.

Scheme 18 (8 + 2)-Formal cycloaddition reactions of tropones with azlactones.

tropones **1** with azlactones **30** to construct dihydro-2*H*-cyclohepta[*b*]furan skeleton **31** (Scheme 18).[46] In this reaction, both tropone, as an electrophile, and azlactone, as a nucleophile, were activated by the action of a Brønsted acid catalyst. A hydrogen bond was formed between the OH group of the enol and the oxygen atom of the protonated tropone, which could be the origin of the stereoselectivity in the reaction. The authors assumed two transition states (**TS-I** and **TS-II**), differing in the diastereotopic carbon atom (C-α in **TS-I** or C-α in **TS-II**), which were attacked by the enol nucleophile. **TS-I** was less stable compared to **TS-II** due to steric interactions, which could explain the predominance of the *S**,*S** isomer in the reaction mixture. The evolution of the obtained intermediates by intramolecular ring-opening of azlactone liberated products **31** (major) and **31′** (minor) (Scheme 19). It was found that the presence of a substituent at the electrophilic α-carbon of tropone has a significant impact on chemoselectivity because it produced an additional destabilization of **A** (with the Cl/R interaction instead of H/R) without affecting **B**, which favored **31** concerning **31′**. In addition, the presence of the Cl group at the α-carbon of tropone could generate quaternary amino acids with the tropone ring at the α-carbon. Since α-chlorotropone was less reactive than tropone and full conversion occurred after 24 hours, the chemoselectivity could be controlled entirely, affording the diastereomerically pure products from the attack at the unsubstituted α-position. Additionally, further ring-opening of the obtained product in the presence of various
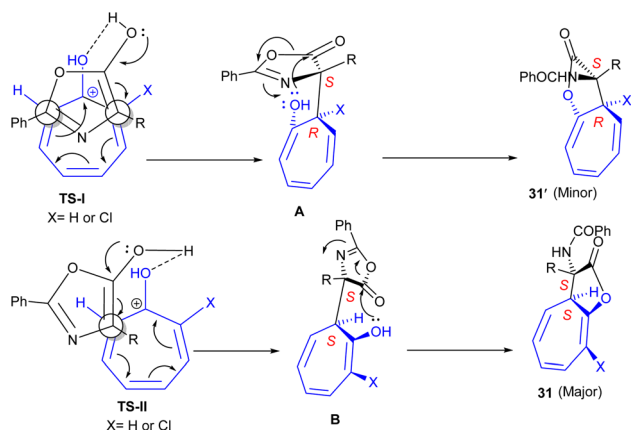

Scheme 19 Possible transition states in the reaction of protonated tropones with azlactones.

Scheme 20 NHC-catalyzed (8 + 2)-cycloaddition of enals with tropones.

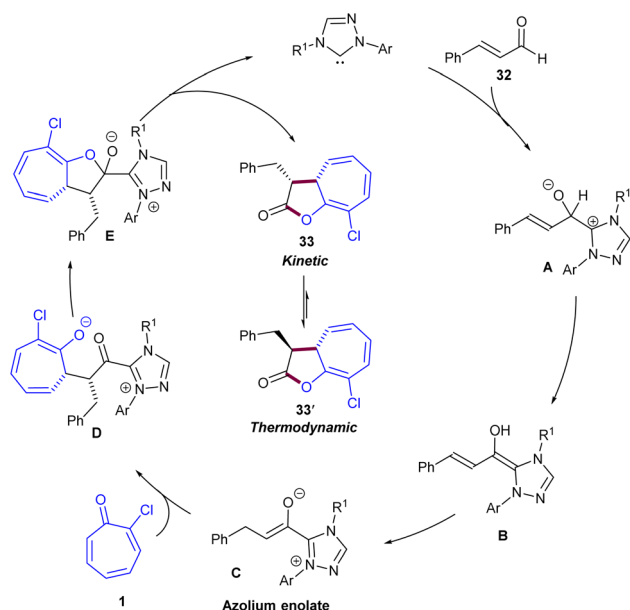nucleophiles can result in the formation of α,α-disubstituted α-amino acid derivatives.

Maseras and his colleagues employed *N*-heterocyclic carbene catalysts for asymmetric (8 + 2)-cycloadditions of tropones **1** with enals **32** (Scheme 20).[47] This is a classic example of using NHC catalysts in (8 + 2)-cycloadditions of tropones, which provides access to a kinetic *cis*-cycloadduct that can be epimerized to its trans analogue by using an excess amount of base and a longer reaction time. Besides, the obtained cycloadducts can be derivatized by hydrogenation or methanolysis. According to DFT calculation results, a credible mechanism was proposed for this transformation, which involved the interaction of NHC with enal **32** to form the Breslow intermediate **A**, followed by the conversion of **A** to azolium anolate **C** *via* **B**. After that, **C** underwent a rapid and irreversible 1,8-addition to tropone **1** through transition state T4 to form **D**, which determined both the enantio- and the diastereoselectivity of the process. Then, **D** converted into **E**, followed by the release of product **4** and the regeneration of the NHC catalyst. The obtained cycloadduct can also undergo NEt₃-catalyzed epimerization, leading to the thermodynamically stable trans diastereomer. Since only the *Z*-enolate in intermediate **C** was energetically available, the cycloaddition only led to the products with (**33**-*R*,**33**-*S*) and (**33**-*R*,**33**-*R*) configurations, depending on the face (*Re* or *Si*, respectively) of the tropone involved in the reaction (Scheme 21). Another example of the use of NHCs in the (8 + 2)-cycloaddition of tropones **1** was reported by Ye and co-workers (Scheme 22).[48] For this purpose, aldehydes **34** served as a reactant in the annulation with tropones to construct cycloheptanefused furanones **35**. A similar mechanism to Maseras' reaction was suggested, involving the formation of the Breslow intermediate, and the enolate intermediate, followed by intramolecular acylation and liberation of the product after aromatization and regeneration of the NHC catalyst. The production of the gram-scale synthesis (1.29 g, 80%) and hydrogenation of the product demonstrated the synthetic application of this method.

Guanidine can act as an efficient organocatalyst in stereoselective (8 + 2)-cycloaddition of tropones **1** with azlactones **30**
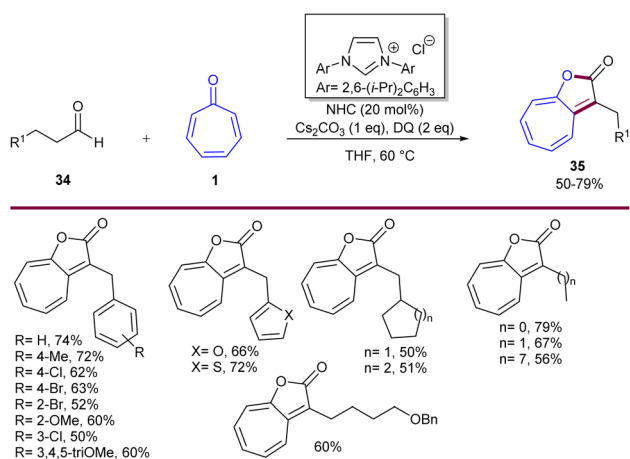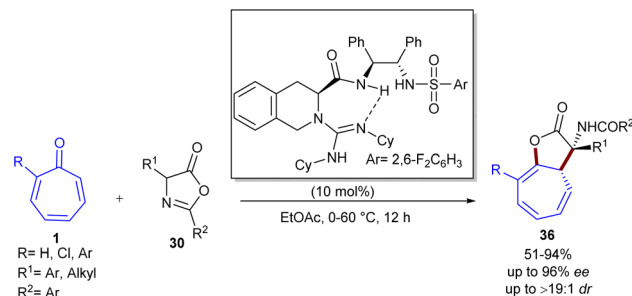
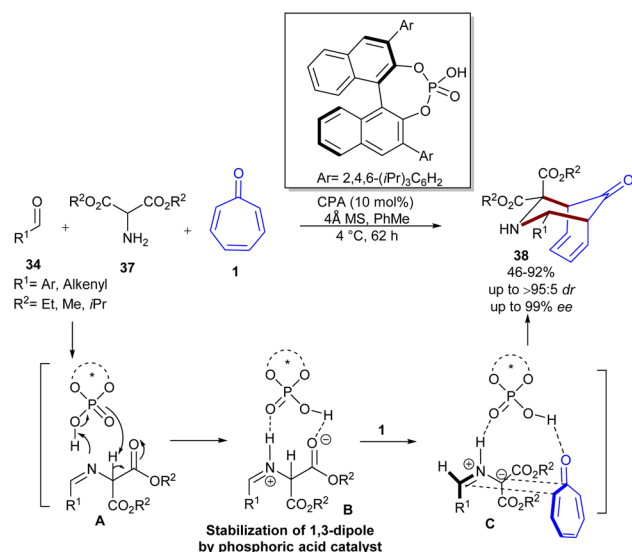**Scheme 21** Credible catalytic cycle for NHC-catalyzed (8 + 2)-cycloaddition of enals with tropones.

Scheme 22 NHC-catalyzed (8 + 2)-cycloaddition of aldehydes with tropones.

(Scheme 23).[49] In this reaction, bifunctional guanidine acted as a hydrogen-bond-mediated catalyst to construct [5.3.0]bicyclic compounds **36** in up to 95% yield, >19 : 1 dr, and 96% ee. The bifunctional property of guanidine with an additional sulfonamide functional group (GS1–GS5) was found to be beneficial to the enantio-induction, while sterically hindered GS6 decreased the enantioselectivity. With the chiral catalyst GS8, the yield, enantioselectivity, and diastereoselectivity of the product significantly increased, making this catalyst the best one. When 2-substituted tropones were used, the cycloaddition occurred at the less substituted position. 2-Aryl tropones exhibited good compatibility with a little electronic effect (86–94% yield and 88–92% ee). For azlactones, 4-alkyl-substituted azlactones showed good compatibility regardless of the steric hindrance.

Scheme 23 Organocatalytic (8 + 2)-cycloaddition of tropones with azlactones.

The electronic feature of the 4-halo substituent on the phenyl ring of phenylalanine-derived azlactones had a slight influence on the enantioselectivity (92–94% ee) but significantly affected the reactivity (51–78% yield). According to the isolated [1,5]-H shift isomer, the X-ray crystal structure of a chiral guanidinium salt, and DFT calculations, the authors were able to explain the origin of enantio- and diastereoselectivity in the reaction. In addition, the synthetic utility of the method was demonstrated by the rapid transformation into enantio-enriched α-amino acid derivatives and the gram-scale synthesis of the product (99% yield, 92% ee). Another use of NHC catalyst was demonstrated in Jørgensen's work (Scheme 24).[50] A stereoselective high-order (6 + 4)-cycloaddition between tropone **1**, aldehydes **34**, and 2-aminomalonates **37** was performed to build a novel series of bridged azabicyclo[4.3.1]decane scaffolds **38** in the presence of a chiral phosphoric acid catalyst. The initial reaction of aldehydes and 2-aminomalonates resulted in the formation of azomethine ylides as key intermediates, followed by a 1,3-dipolar (6 + 4)-addition to tropone, providing the corresponding products in moderate to high yields, with excellent stereoselectivities (>95 : 5 dr and up to 99% ee).
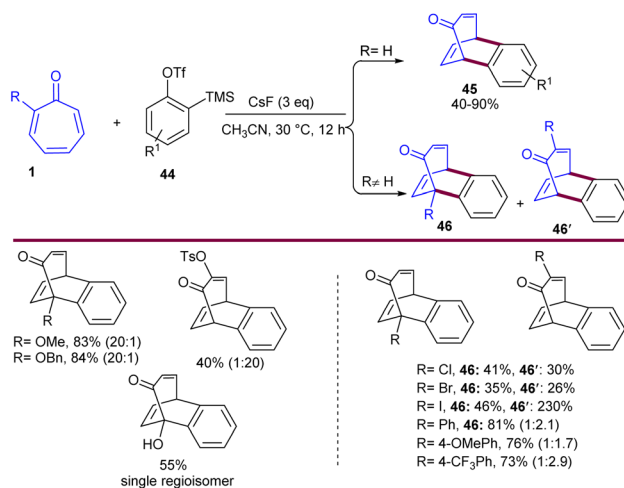

Scheme 24 (6 + 4)-Cycloaddition of tropone, aldehydes, and 2-aminomalonates.

Bifunctional phosphoric acid catalyst can efficiently stabilize *in situ* generated azomethine ylides as a 1,3-dipole *via* hydrogen bonding interactions. The subsequent approach of tropone occurred from the less hindered position, as dictated by the bulky groups of the chiral catalyst. Jørgensen and his colleagues also reported chiral Brønsted base-catalyzed (8 + 3)-cycloaddition of donor–acceptor cyclopropanes **40** with tropone **1** (Scheme 25).[51] Screening of various chiral organocatalysts showed that the organocatalyst **g** is the best choice. DFT calculations demonstrated the important role of the optically active bifunctional Brønsted base **g** in the activation of both the donor–acceptor cyclopropane and tropone through hydrogen-bonding interactions, leading to a stepwise manner with di-astereo- and enantioselective ring-closure. The desired products **42** were constructed in moderate to high yields (21–92%) with excellent enantioselectivities (up to 92% ee). Besides, tropone derivative **41** can also be incorporated in the cycloaddition with cyclopropane **40** in the presence of another chiral organo-catalyst **I**, yielding polycyclic compound **43** in good to high yields with high enantioselectivities.
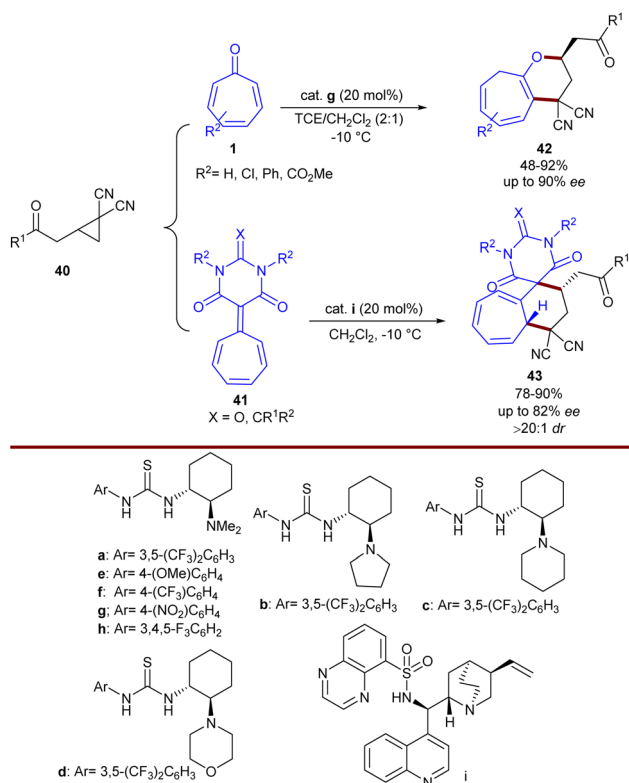
2.2.2. Base-catalyzed cycloaddition reactions involving tropone. Diels–Alder reaction of tropones **1** with 2-(tri-methylsilyl)aryl triflates **44** could be occurred in the presence of CsF as a base (Scheme 26).[52] The base promoted the formation of a benzyne intermediate, which underwent (4 + 2)-cycloaddition with tropone to obtain benzobicyclo[3.2.2]nonatrienone derivatives **45**. Variation of tropones, including electron-
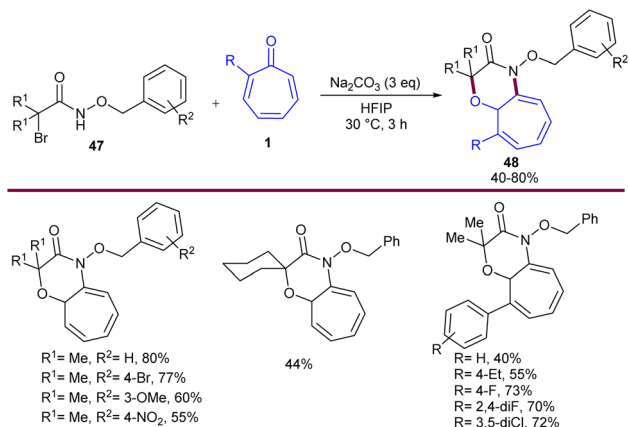
Scheme 26 Diels–Alder reaction of tropones with 2-(trimethylsilyl) aryl triflates.

donating groups (OMe, OTs, OBn), exhibited 20 : 1 regio-selectivity, whereas halogen (Cl, I, Br) and aryl groups resulted in moderate regioselectivity. This reaction was also applicable for tropolone, producing cycloadduct **46** as a single regioisomer in moderate yield (55%). The observation of this single regio-isomer indicated that the Diels–Alder reaction proceeds faster than the aryne O–H insertion. The photophysical properties of some of the final products were investigated, which showed weak fluorescence absorption/emission at 270–290 nm.
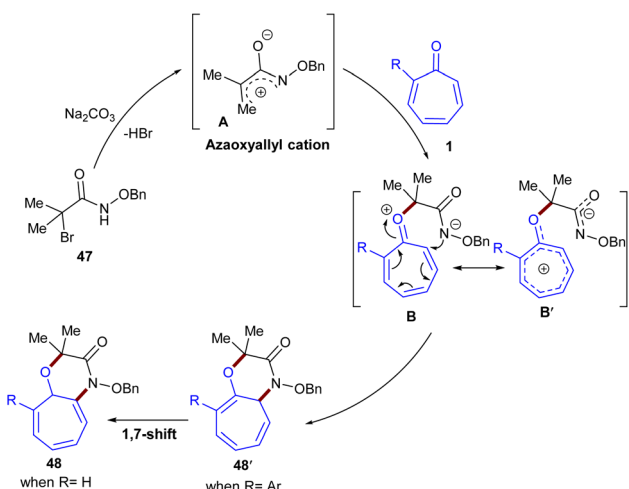
In 2019, Roy *et al.* established base-mediated (8 + 3)-cyclo-addition of tropones **1** with azaoxyallyl cations **47** (Scheme 27).[53] Mechanistically, the reaction proceeded through the formation of the azaoxyallyl cation **A** from the interaction of the base with α-bromo hydroxamate **1**. The nucleophilic addition of **47** to **A** led to the zwitterionic intermediate **B**, which could be in equi-librium with the stable tropylium cation **B′**. Then, **B** or **B′** was subjected to intramolecular cyclization to form (8 + 3)-adduct **48′** when 2-aryl tropone was used. However, for unsubstituted tropone, the initial (8 + 3)-adduct underwent a 1,7-H shift to obtain the desired product **48**. It should be noted that the production of the more substituted olefin is a reason for the stability of the initially formed (8 + 3)-adduct for 2-aryl tropones (Scheme 28). To get information on the kinetics of this (8 + 3)-cycloaddition, the authors performed a competition reaction between tropone **1** and 4-chlorobenzaldehyde, in which (3 + 2)-cycloadduct derived from 4-chlorobenzaldehyde was formed in 42% yield, while (8 + 3)-adduct from tropone had only 3% yield. This result showed that 4-chlorobenzaldehyde can react 14 times faster than tropone in the reaction with azaoxyallyl cations. At the same time, similar (8 + 3)-cycloaddition of tro-pones **1** with azaoxyallyl cations **47** was reported by another group (Scheme 29).[54] This reaction was carried out in the pres-ence of Et₃N as a base in HFPI as a solvent at room temperature. DFT computations demonstrated the origin of selectivity in the reaction and the formation of key spiro intermediate **A** that could undergo ring-expansion to access nitrogen-containing [7,6]-fused bicycles **49**.

Scheme 25 Brønsted base-catalyzed (8 + 3)-cycloaddition of donor–acceptor cyclopropanes with tropone.
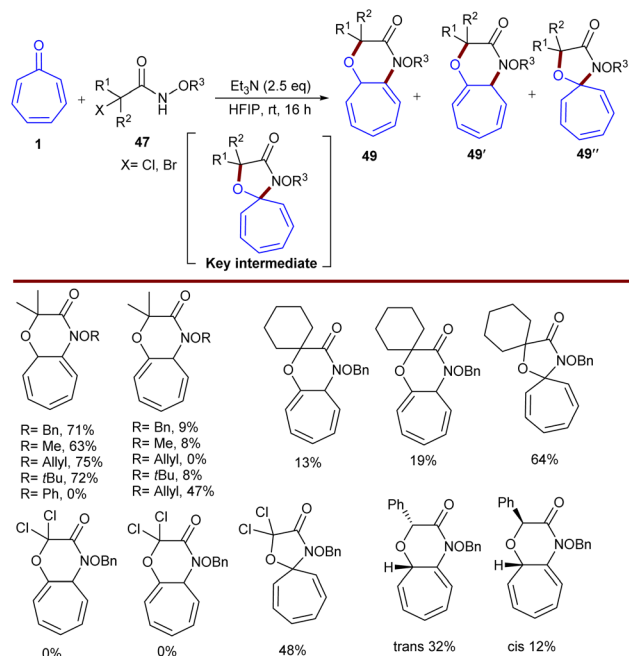
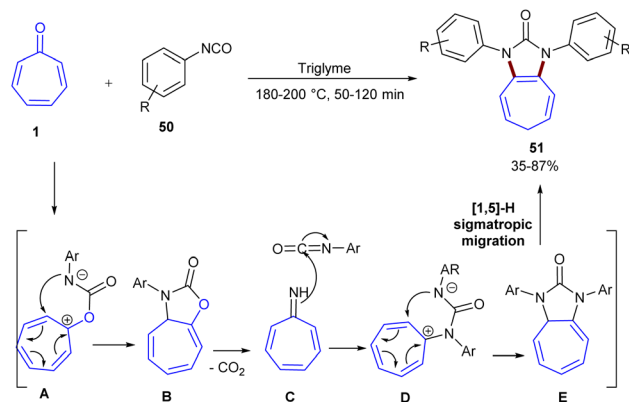**Scheme 27** Na$_2$CO$_3$-promoted (8 + 3)-cycloaddition of tropones with azaoxyallyl cations.

Scheme 28 Plausible mechanism for Na$_2$CO$_3$-promoted (8 + 3)-cycloaddition of tropones with azaoxyallyl cations.

Scheme 29 Et$_3$N-promoted (8 + 3)-cycloaddition of tropones with azaoxyallyl cations.

Scheme 30 Catalyst- and oxidant-free reaction of isocyanates with tropones.

A high atom- and step-economical methodology for assembling troponoid derivatives incorporating imidazolin-2-one motifs **51** was reported by Hu and co-workers in 2020 (Scheme 30).[55] In this regard, tropone reacted with isocyanates under catalyst- and oxidant-free conditions, using only triglyme as the solvent, at 180 °C for 50–120 min. The reaction was also applicable in other solvents, such as DMSO, DMI, tetraglyme, and bis(2-ethylhexyl)adipate, albeit with moderate yields of the product (28–73%). Generally, the cascade reaction involves the *O*-nucleophilic attack of tropone **1** to the carbonyl of isocyanate **50**, followed by an intramolecular S$_N$2′-like reaction. Tandem decarboxylation and *N*-nucleophilic attack on the second isocyanate, followed by sigmatropic [1,5]-hydrogen migration, afforded the desired product **51**.

Biju and co-workers developed a metal-free diastereoselective (6 + 3)-cycloaddition reaction between tropone **1**, imino esters **6**, and arynes **44** to make several bridged azabicyclo[4.3.1]decadiene compounds (Scheme 31).[56] Two
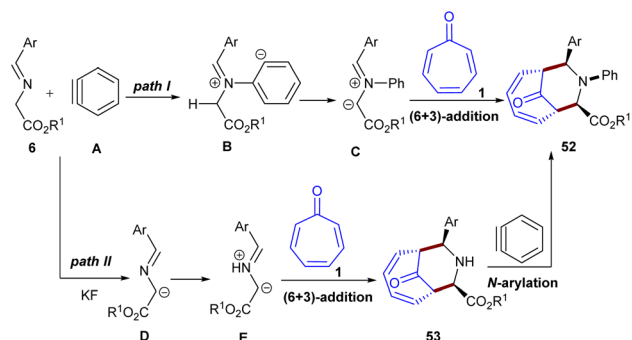
possible pathways were suggested for this transformation (Scheme 32). Path I involved the nucleophilic addition of imino ester **6** to aryne **44**, generating the nitrogen ylide **C** *via* the zwitterion **B**, followed by diastereoselective (6 + 3)-cycloaddition with tropone **1**, affording product **52**. However, in path II, the presence of KF/18-crown-6 allowed the conversion of imino ester into *aza*-allyl anion **E**, which was protonated to form azomethine ylide **F**. Subsequent (6 + 3)-cycloaddition of **F** with tropone **1** delivered adduct **53**, followed by *N*-arylation with aryne **44** to form product **52**. To shed light on the mechanism, the authors performed the reaction in the absence of the aryne precursor, but did not observe the final product. The stop of the standard reaction after 2 hours also did not reveal compound **53**, which ruled out pathway II.
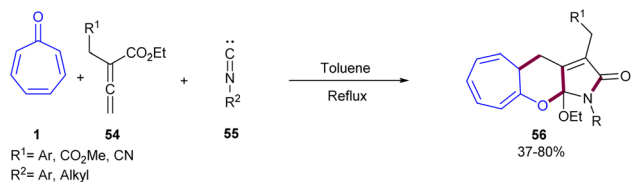
Scheme 31 Metal-free (6 + 3)-cycloaddition of tropone, imino esters, and arynes.
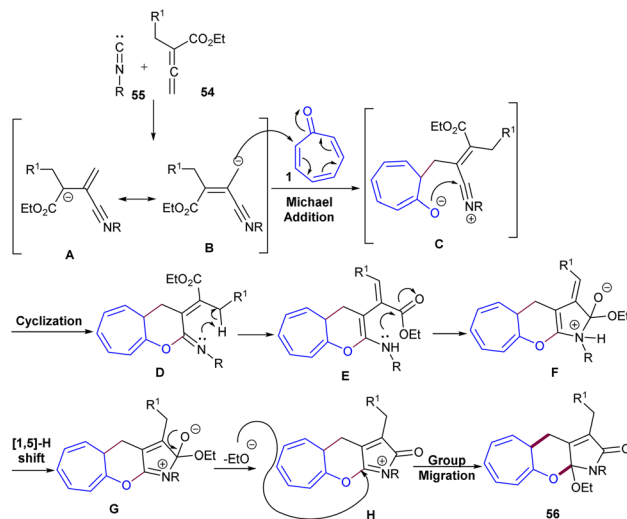

Scheme 32 Mechanism metal-free (6 + 3)-cycloaddition of tropone, imino esters, and arynes.

2.2.3. Catalyst-free cycloaddition reactions involving tropone. A rapid access to a 7,6,5-fused tricyclic framework was suggested by Jia and co-workers in 2014 (Scheme 33).[57] For this purpose, tropone **1**, allenoate **54**, and isocyanide **55** were utilized as feedstock in toluene as a sole solvent under reflux conditions. The cycloaddition reaction was compatible with allenoate bearing electron-deficient and electron-rich aryl groups, as well as aryl and alkyl isocyanide. A plausible mechanism involving cascade (8 + 2 + 1)-cycloaddition, [1,5]-H shift, cyclization, and alkoxy group migration was proposed for the construction of highly unusual tricyclic products. Firstly, resonance-stabilized species **A** ↔ **B** was formed from the reaction of allenoate **54** and isocyanide **55**. Then, the nucleophilic attack of these species on tropone **1** led to intermediate **C**, which underwent a [1,5]-H shift facilitated by an aryl or another electron-withdrawing group. The following cyclization and the second [1,5]-H shift afforded intermediate **G**. Finally, the elimination of the ethoxy group and nucleophilic addition furnished the desired product **56** (Scheme 34).
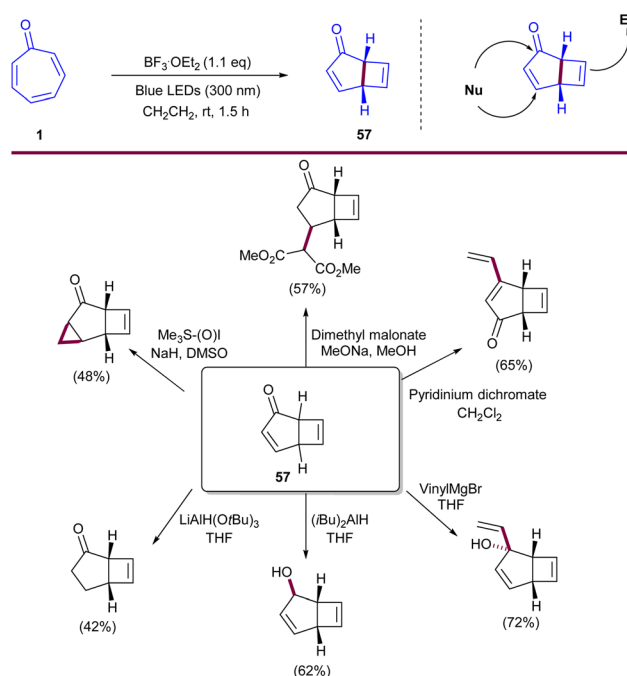
Lewis acid-catalyzed 4π-photocyclization of tropone was reported by Coote and co-workers (Scheme 35).[17] BF$_3$·OEt$_2$ was used as a Lewis acid to promote 4π-photocyclization of tropone **1** under visible light irradiation to form bicyclo[3.2.0]-

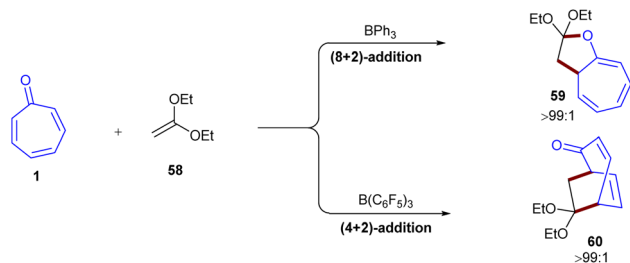**Scheme 33** Multicomponent cascade cycloaddition involving tropone, allenoate, and isocyanide.

Scheme 34 Proposed mechanism for multicomponent cascade cycloaddition involving tropone, allenoate, and isocyanide.

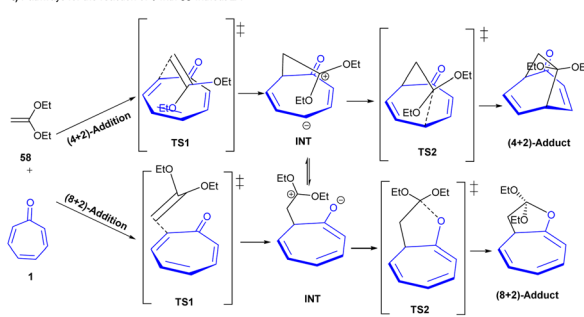**Scheme 35** Lewis acid-catalyzed 4π-photocyclization of tropone.

heptadienone **57**. Notably, the lowest excited state of tropone complexed to a Lewis acid corresponded to a π–π* transition that enabled 4π-photocyclization. In contrast, in the absence of a Lewis acid, the lowest excited state of tropone corresponded to a prohibited n–π* transition from which 4π-photocyclization did not occur. Additionally, a variety of new rigid bicyclic scaffolds can be achieved through nucleophilic and electrophilic reactions of bicyclo[3.2.0]-heptadienone **57**. Another use of Lewis acid catalyst in the cycloaddition of tropone **1** with 1,1-diethoxyethene **58** was observed (Scheme 36).[58] The reaction was investigated in the absence of Lewis acid and in the
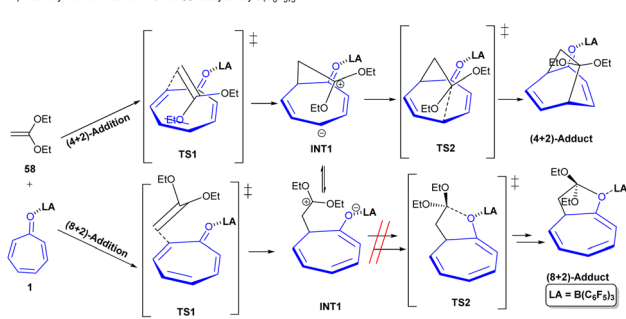
Scheme 36 Lewis acids–catalyzed cycloadditions of tropone with ethene.

presence of two kinds of Lewis acids, $B(C_6F_5)_3$ and BPh_3. In the absence of a Lewis acid, $(8 + 2)$- and $(4 + 2)$-cycloadducts **59** and **60** could be constructed through a stepwise reaction, wherein the C2 atom in tropone is bound with the C2 atom in ethene, and then the C5 atom in the former is bound with the C1 atom in the latter. For $B(C_6F_5)_3$, firstly, the O atom in tropone is attached to the Lewis acid, and secondly, the C5 atom in
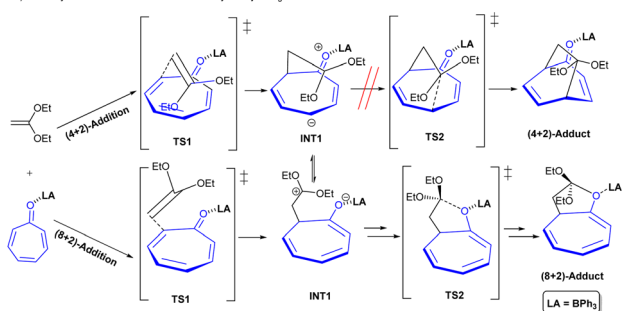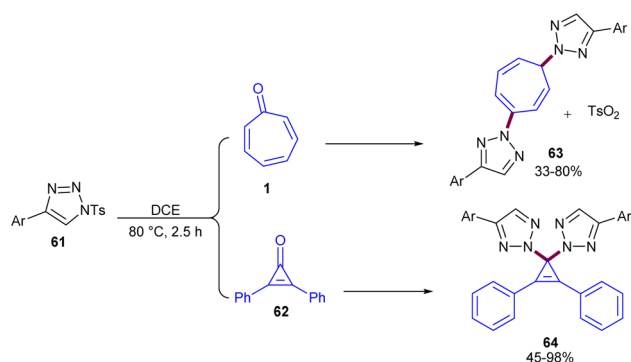

Scheme 37 Lewis acids–catalyzed cycloadditions of tropone with ethene.

tropone is attacked by the C1 atom in ethene. Although it was found that the attack of the O atom in tropone is less likely, favoring the $(4 + 2)$-cycloaddition in this case. In contrast, the attack of the O atom in the BPh_3-attached tropone to the C1 atom in ethene was preferred over the attack of the C5 atom, proving the favorability of $(8 + 2)$-cycloaddition instead of $(4 + 2)$-cycloaddition. The attack of C5 or by O atom in tropone on the C1 atom in ethene both was controlled by the nucleophilicity of σ-lone pair electrons of the carbonyl O atom in the presence of Lewis acids (Scheme 37). Guerra and coworkers conducted a study on the 4-photocyclization mechanism of α-tropone derivatives.[59] For this purpose, they chose tropone, 2-methoxy-tropone, and 2-cyanotropone as substrates and employed *ab initio* methods to investigate the 4π-photocyclization. Energy barrier calculations revealed that substituted α-tropones exhibit high barriers in the excited states, such as S_4, S_3, and S_2. Although the electron-donating groups or the formation of hydroxytropenium ions can notably lower these barriers, thereby making 4π-photocyclization more feasible. It is worth noting that the 4-photocyclization of α-tropone derivatives primarily proceeds *via* low-lying excited states, with substituent effects influencing both reaction pathways and energy barriers. In addition, it was found that acid catalysts and the substitution of tropones with electron-donating groups reduce the energy barriers. Specifically, electron-donating groups on tropones promote degeneracy between S_1 and S_0 electronic states during the return to the ground state.
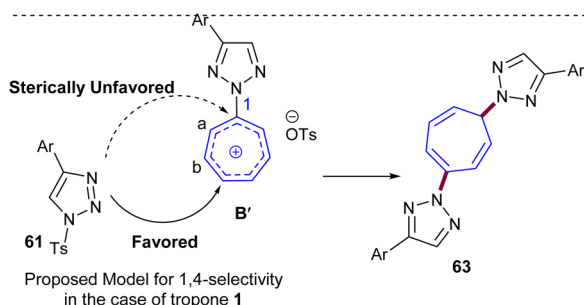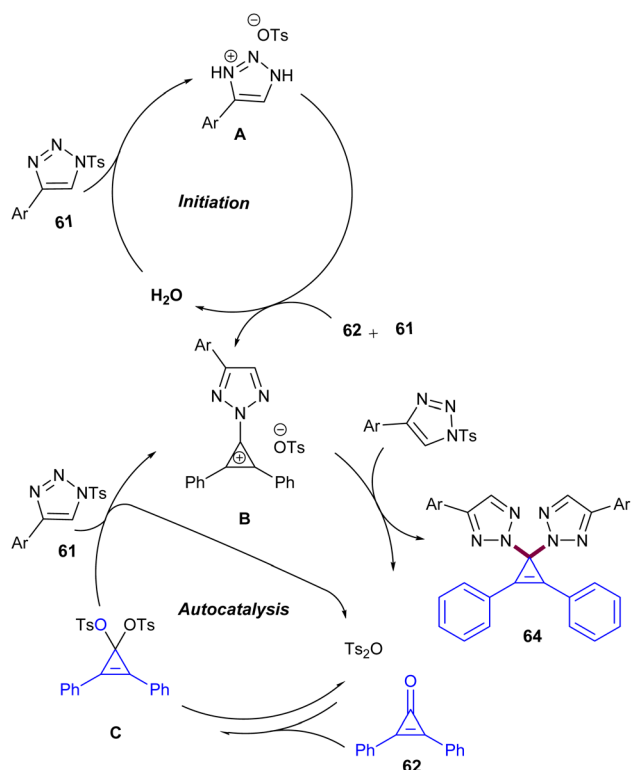
3. Functionalization reactions involving tropone

An unexemplified N^2-selective autocatalytic ditriazolylation reaction between N^1-sulfonyl-1,2,3-triazoles **61** with tropone **1** or cyclopropanones **62** was reported by Hao and co-workers in 2017 (Scheme 38).[60] This protocol provides a simple and one-step transformation for the synthesis of N^2-substituted bis(1,2,3-triazolyl) compounds **63** and **64**. The reaction in the presence of a molecular sieve or at room temperature did not proceed, indicating the vital role of water as a solvent and the importance of heating in this reaction. Following mechanistic investigations, a proposed mechanism involved the hydrolysis of N^1-sulfonyl-1,2,3-triazole **61** to generate intermediate **A**, which could act as an acid catalyst and catalyze the reaction of cyclopropanones **62** with another molecule of **61**, providing intermediate **B**. Then, the remaining **61** acted as a nucleophile and reacted with **B** to form product **64** and Ts_2O. Ts_2O could formally be engaged in the autocatalytic cycle and react with **62** to generate intermediate **C**, which in turn reacts with two molecules of **61** consecutively to yield **64** through 1,4-di-substitution. It should be noted that due to the influence of steric hindrance in tropone, 1,4-disubstitution is more favored compared to 1,1-disubstitution in cyclopropanones. Meanwhile, Ts_2O accumulated continuously until tropone **1** was consumed completely. A similar reaction mechanism was proposed for the reaction of tropone **1** and N^1-sulfonyl-1,2,3-triazoles **61** (Scheme 39).
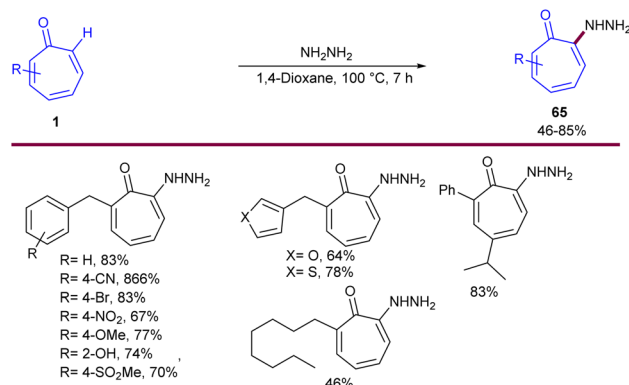
Scheme 38 Ditriazolylation reaction of tropone with N^1-sulfonyl-1,2,3-triazoles.

Scheme 40 Metal-free C(sp^2)–H bond amination of tropone with hydrazine.

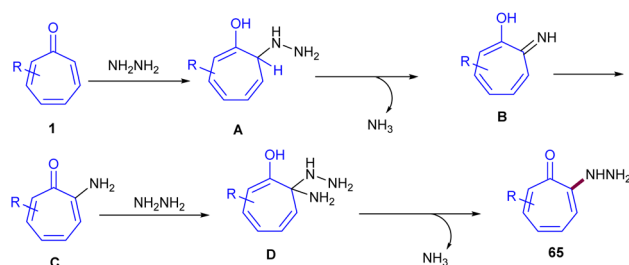Scheme 41 Proposed mechanism for metal-free C(sp^2)–H bond amination of tropone with hydrazine.

Scheme 39 Proposed mechanism for ditriazolylation reaction of tropone with N^1-sulfonyl-1,2,3-triazoles.

In 2024, Zhang and co-workers reported C(sp^2)–H bond functionalization of the tropones **1** using hydrazine (Scheme 40).[61] They introduced a metal-free and simple method
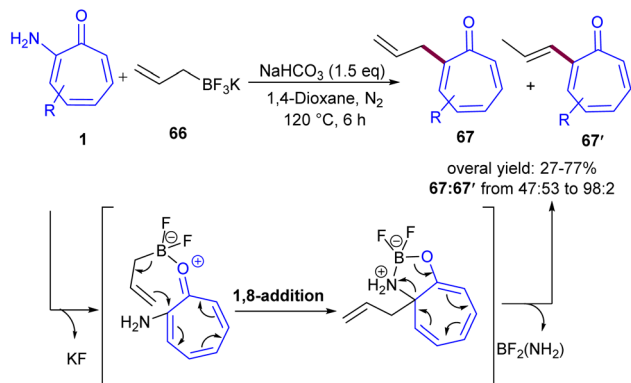
for highly regioselective preparation of 2-hydrazinotropones **65** *via* C–H amination process. By isolating 2-aminotropone intermediate **A**, the authors were able to propose a possible mechanism for this reaction, in which regioselective 1,8-addition of hydrazine to tropone **1** generated intermediate **B**, followed by the elimination of ammonia from to form imine **C**. Subsequent tautomerization afforded 2-aminotropone **A**, which underwent the second regioselective 1,8-addition of hydrazine and elimination of ammonia, producing the target product **65** (Scheme 41). The gram-scale reaction yielded the desired product in 841 mg, corresponding to a 62% yield. Further transformations of 2-hydrazinotropone to 2-chlorotropone, hydrazone-substituted tropone, or hydrazide-substituted tropone were also performed in this work. 2-Aminotropones **1** can undergo allylation reaction with potassium allyltrifluoroborates **66** (Scheme 42).[62] The amino group was directly substituted with potassium allyltrifluoroborates **66** in the presence of a base, producing complex **A**. Then, the allyl group underwent an intramolecular 1,8-addition to tropone, generating intermediate **B**, which subsequently aromatized to the final product **67**. The isomerization of **67** can result in the alkenylation product **67′** as a side product.

Functional groups at the C2-position of tropone can control regioselective conjugate addition (1,8- and 1,4-addition) of difluoroenoxysilanes to tropones (Scheme 43).[63] In particular, 1,8-addition processed in the case of α-H, or α-Ph substituted-tropones **1**, affording 3,5-cycloheptadien-1-ones bearing a *gem*-
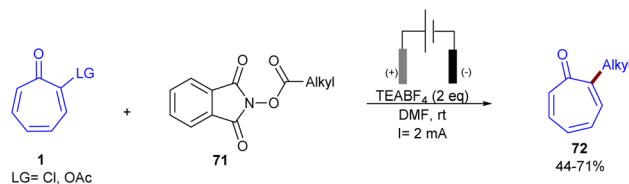
Scheme 42 Metal-free C(sp^2)−H bond allylation of tropone with potassium allyltrifluoroborates.
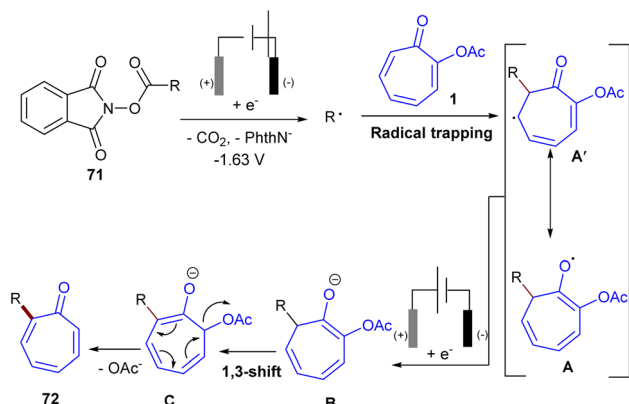

Scheme 43 Bi(OTf)$_3$-promoted reaction of tropone with difluoroenoxysilanes.

Scheme 44 Electrochemical alkylation of tropones with N-hydroxyphthalimide esters.

Scheme 45 Possible mechanism for electrochemical alkylation of tropones with N-hydroxyphthalimide esters.

difluoroketone moiety **69**. For tropones with α-halo, or α-TsO substituents, 1,4-addition adducts were formed as the major products. By studying DFT calculations, the authors found that 2-halo/TsO-substituted tropone has smaller HOMO–LUMO energy gaps relative to tropone, indicating that their electrons are more easily excited from the ground state to the excited state, so that they could undergo greater electron delocalization. And significant changes in their electron density upon excitation caused them to be favored for reaction sites far from the carbonyl of tropone, leading to 1,4-addition. In addition, the LUMO lobes on the C6 of 2-substituted tropones are greater than those of tropone, thereby increasing the tendency of C6 to participate in the 1,4-addition. At last, the synthetic utility of the method was demonstrated by the gram-scale synthesis of 1,8- and 1,4-addition products, yielding 1.20 g, 57%, and 1.42 g, 60%, respectively. Furthermore, the *in vitro* anti-proliferative activity of the obtained products against human colon cancer cells was investigated in this work.

Metal-free electrochemical functionalization of tropone **1** and substituted tropones with N-hydroxyphthalimide esters **71** as a redox-active ester was introduced by Bertuzzi's research lab (Scheme 44).[64] This electro-induced alkylation reaction offers a highly regioselective method for synthesizing mono- and di-alkylated tropones in moderate to high yields under very mild conditions. The steric hindrance of substituents in tropones had a significant impact on the site-selectivity, and alkylation occurred at the less hindered position. A possible mechanism
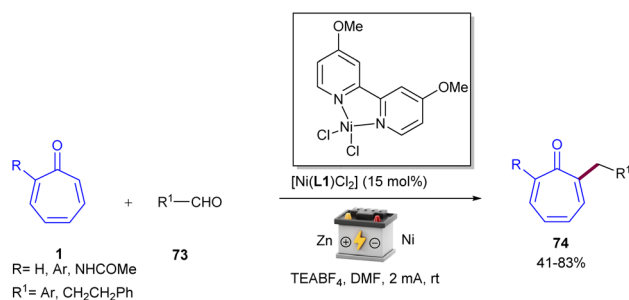
was suggested for this electroreductive transformation, where a monoelectronic cathodic reduction of redox-active ester **71** resulted in the fragmentation of this molecule, delivering a nucleophilic radical species R˙. Then, R˙ was trapped chemoselectively at the α-position of tropone, providing a stable delocalized π-system intermediate **A**. Another cathodic reduction occurred to obtain the enolic form **B**, which underwent a [1,3]-H shift to form isomer **C**. The re-aromatization of **C** *via* elimination of the acetoxy group afforded product **72** (Scheme 45). Moreover, the late-stage functionalization of a bioactive compound (*i.e.*, colchicine analogue) emphasized the synthetic utility of this method. After a year, this research team introduced a nickel catalysis system for the alkylation of tropones under electrochemical conditions (Scheme 46).[65] The reaction was found to proceed through the coordination of Ni
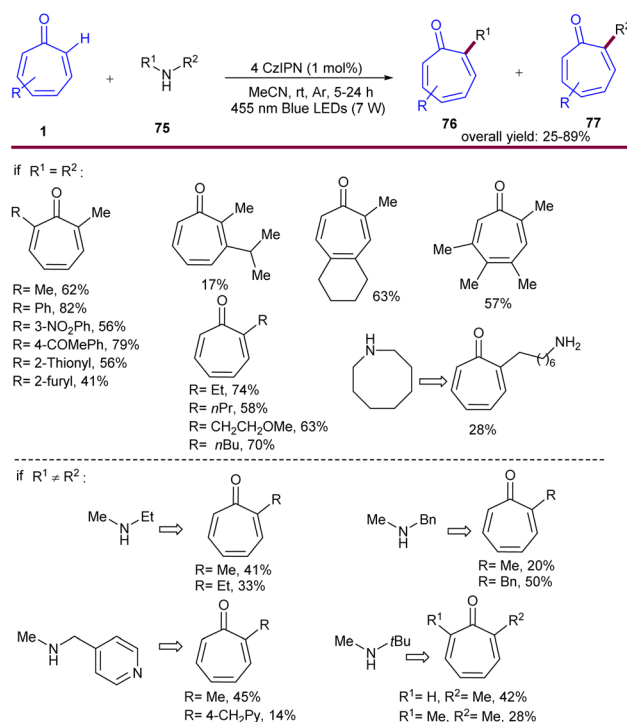

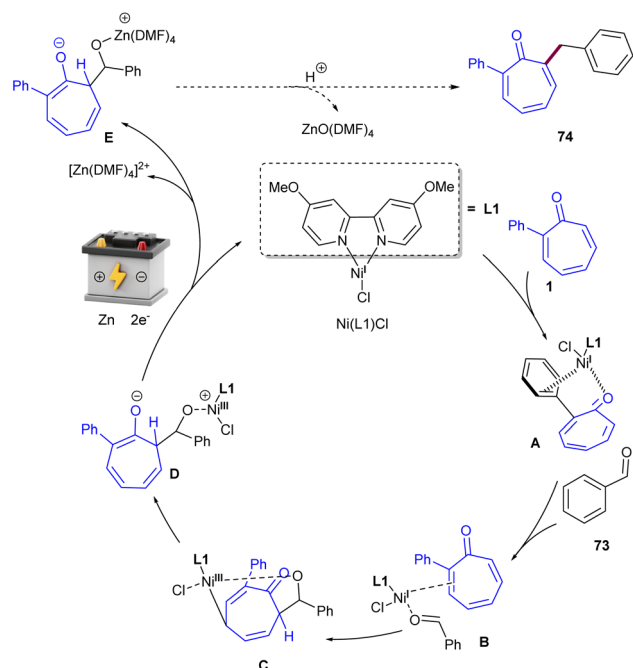**Scheme 46** Ni-catalyzed electrochemical alkylation of tropones with aldehydes.

with tropone **1** to complex **A**. Complex **B** forms after the Ni–O coordination with aldehyde **73**, which results in a net transfer of electron-density from the Ni to the tropone. It should be noted that upon nickel coordination in complex **B**, the tropone moiety carried a negative charge, while the aldehyde was unperturbed. This interaction made the Umpolung of the reactivity of tropone and triggered the nucleophilic condensation to an aldehyde. The consequent C–C bond formation took place exclusively at the α-carbon of tropone, affording the organo-Ni(III) complex **C** with a C(δ)–Ni bond. Then, the weak Ni–C bond broke, and a new Ni(III)–O alkoxide **D** formed. The last electrochemical reduction of Ni(III) to Ni(I) yielded the active species, and a Zn–Ni ion exchange between **C** and the Zn(II) ions released from the sacrificial anode produced the Zn-alkoxide **E** through an exothermic step. Finally, **E** was converted to product **74** either directly or assisted by mild acidic media used during work-up (Scheme 47).
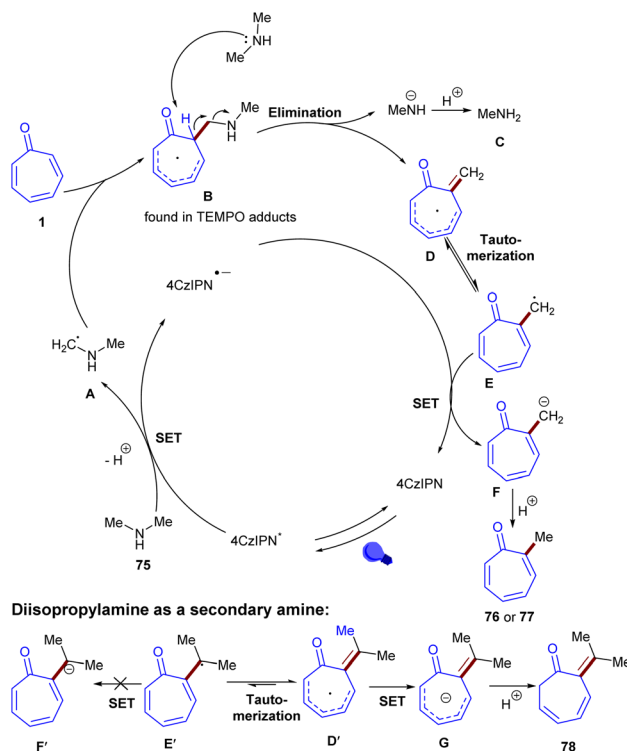
Another example of alkylation of tropone derivatives was catalyzed by 4CzIPN photocatalyst under visible light irradiation (Scheme 48).[66] Screening of other photocatalysts, such as [Ru(bpz)₃](PF₆)₂, thioxanthone, 4DPAIPN, or Eosin Y in this reaction was not successful. The reaction was initiated by photo-mediated excitation of 4CzIPN to the excited state 4CzIPN*, followed by attract of one electron from dimethylamine **75** *via* a SET process, delivering a radical anion 4CzIPN•⁻ and α-aminoalkyl radical **A**. The latter attacked tropone **1** to generate the amine-tropone radical **B** regioselectively. The acidity of the α-C(sp³)–H in the ketone can facilitate the following base-initiated elimination, catalyzed by dimethylamine **75**, leading to the formation of the exocyclic double bond-containing radical **D**, accompanied by the liberation of methylamine **C** as a side product. In the next step, **D** was

Scheme 48 Photocatalytic alkylation of tropones with secondary aliphatic amines.

Scheme 49 Proposed mechanism for photocatalytic alkylation of tropones with secondary aliphatic amines.

Scheme 47 Catalytic cycle for Ni-catalyzed electrochemical alkylation of tropones with aldehydes.

tautomerized to the methylene radical **E**, which subsequently attracted 1e⁻ from 4CzIPN•⁻ *via* a SET process. At the same time, the tropone-methyl anion **F** was generated and protonated

to yield α-methyl tropone **1**. It was realized that the presence of the exocyclic intermediate was substantiated by analysis of the mechanism leading to compound **78** with an exocyclic double bond. Since the inert tertiary carbon radical **E′** was found to be unable to attract $1e^-$ from 4CzIPN·⁻, thereby rendering the tautomerization from **D′** to **E′** unfavorable. As a result, the tropone radical **D′** directly acquired $1e^-$ from 4CzIPN·⁻ to obtain the tropone anion **G**, which protonated to yield **78**. As the secondary amine functions dually as both an alkylation reagent and a base, thereby more than one equivalent of **75** should be suffice (Scheme 49). This protocol was also amenable to late-stage functionalization of some bioactive molecules and the transformation of fortunolide **A** into cephafortunoids **A** and **B**.

4. Conclusions

Over the last decade, attention to tropone synthetic chemistry has grown rapidly, resulting in the publication of elegant total syntheses of tropone-based bioactive molecules. As shown in this review, tropone has served as a 2π component in (2 + 4)-cycloadditions, a 4π component in (4 + 2)- and (4 + 6)-cycloadditions, a 6π component in (6 + 3)- and (6 + 4)-cycloadditions, and an 8π component in (8 + 2)-cycloadditions.

However, the electron-deficient nature of tropones limits Diels–Alder (4 + 2)-cycloadditions. One method for overcoming the low reactivity of tropones is to increase their nucleophilicity, enabling them to be used as dienes in normal electron demand Diels–Alder reactions.

For higher-order cycloadditions of tropones, one challenge is that the reaction often requires harsh conditions (high pressure or temperature) or yields are low, as the reaction requires overcoming the electron-poor nature and $(4n + 2)$ π-aromatic character of the seven-membered ring. Another limitation in conjugate additions involving tropones is regio- and stereo-selectivity, likely due to the challenges in controlling selectivity. Therefore, the development of site- and stereoselective conjugate additions of tropones that are capable of incorporating another pharmacophore to tropone is highly desirable, and important in medicinal chemistry.

For instance, the use of chiral ligands in metal-catalyzed reactions, or chiral organocatalysts, especially NHC catalysts, can provide an efficient and practical, highly stereoselective reaction systems that are desirable, and important in medicinal discovery.

We hope that this review article will help researchers explore the hidden aspects of tropone's nature and reactivity, thereby utilizing this valuable building block in organic transformations.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Notes and references

1 J. Zhao, *Curr. Med. Chem.*, 2007, **14**, 2597–2621.
2 N. Liu, W. Song, C. M. Schienebeck, M. Zhang and W. Tang, *Tetrahedron*, 2014, **70**, 9281–9305.
3 Y. Duan, M. Petzold, R. Saleem-Batcha and R. Teufel, *ChemBioChem*, 2020, **21**, 2384–2407.
4 H. Guo, D. Roman and C. Beemelmanns, *Nat. Prod. Rep.*, 2019, **36**, 1137–1155.
5 M. Saniewski, M. Horbowicz and S. Kanlayanarat, *J. Hortic. Res.*, 2014, **22**, 5–19.
6 D. Pal and P. Lal, *Curr. Drug Targets*, 2023, **24**, 698–717.
7 F. Cao, C. Orth, M. J. Donlin, P. Adegboyega, M. J. Meyers, R. P. Murelli, M. Elagawany, B. Elgendy and J. E. Tavis, *ACS Omega*, 2018, **3**, 15125–15133.
8 E. E. Anagnostaki, V. P. Demertzidou and A. L. Zografos, *Chem. Commun.*, 2015, **51**, 2364–2367.
9 J. C. Lee and J. K. Cha, *J. Am. Chem. Soc.*, 2001, **123**, 3243–3246.
10 K. Nicolaou, R. Yu, Z. Lu and F. G. Alvarez, *J. Am. Chem. Soc.*, 2022, **144**, 5190–5196.
11 T. Graening and H. G. Schmalz, *Angew. Chem., Int. Ed.*, 2004, **43**, 3230–3256.
12 X. Xie, X. Zu, F. Liu, T. Wang, X. Wang, H. Chen, K. Liu, P. Wang, F. Liu and Y. Zheng, *Mol. Carcinog.*, 2019, **58**, 1248–1259.
13 H. J. Zhang, L. Hu, Z. Ma, R. Li, Z. Zhang, C. Tao, B. Cheng, Y. Li, H. Wang and H. Zhai, *Angew. Chem., Int. Ed.*, 2016, **55**, 11638–11641.
14 S. Tan, Q. Chen, P. Lan and M. G. Banwell, *Synlett*, 2022, **33**, 1968–1990.
15 D. J. Lyons, C. Empel, D. P. Pace, A. H. Dinh, B. K. Mai, R. M. Koenigs and T. V. Nguyen, *ACS Catal.*, 2020, **10**, 12596–12606.
16 D. C. Tymann, L. Benedix, L. Iovkova, R. Pallach, S. Henke, D. Tymann and M. Hiersemann, *Chem.–Eur. J.*, 2020, **26**, 11974–11978.
17 J. P. Lowe, N. R. Halcovitch and S. C. Coote, *J. Org. Chem.*, 2023, **88**, 9514–9517.
18 J. Zhang, Z.-X. Luo, X. Wu, C.-F. Gao, P.-Y. Wang, J.-Z. Chai, M. Liu, X.-S. Ye and D.-C. Xiong, *Nat. Commun.*, 2023, **14**, 8025.
19 A. Dastan, H. Kilic and N. Saracoglu, *Beilstein J. Org. Chem.*, 2018, **14**, 1120–1180.
20 S. Frankowski, M. Romaniszyn, A. Skrzyńska and Ł. Albrecht, *Chem.–Eur. J.*, 2020, **26**, 2120–2132.
21 P. Li and H. Yamamoto, *J. Am. Chem. Soc.*, 2009, **131**, 16628–16629.
22 K. Houk, L. Luskus and N. Bhacca, *J. Am. Chem. Soc.*, 1970, **92**, 6392–6394.
23 Y. Du, J. Feng and X. Lu, *Org. Lett.*, 2005, **7**, 1987–1989.
24 R. L. Funk and G. L. Bolton, *J. Am. Chem. Soc.*, 1986, **108**, 4655–4657.
25 T. Mukai, T. Tezuka and Y. Akasaki, *J. Am. Chem. Soc.*, 1966, **88**, 5025–5026.

26 K. Kumar, A. Kapur and M. P. S. Ishar, *Org. Lett.*, 2000, **2**, 787–789.

27 V. Nair, M. Poonoth, S. Vellalath, E. Suresh and R. Thirumalai, *J. Org. Chem.*, 2006, **71**, 8964–8965.

28 T. NozoE, S. Itô and K. Sonobe, *Proc. Jpn. Acad.*, 1953, **29**, 101–106.

29 T. Nakamura, *Chem. Pharm. Bull.*, 1962, **10**, 299–304.

30 D. L. Boger and C. E. Brotherton, *J. Org. Chem.*, 1985, **50**, 3425–3427.

31 R. Noyori, S. Makino, T. Okita and Y. Hayakawa, *J. Org. Chem.*, 1975, **40**, 806–807.

32 D. L. Boger and K. Takahashi, *J. Am. Chem. Soc.*, 1995, **117**, 12452–12459.

33 J. Zhang, W. Xiao, H. Hu, L. Lin, X. Liu and X. Feng, *Chem.–Eur. J.*, 2018, **24**, 13428–13431.

34 H. Liu, Y. Wu, Y. Zhao, Z. Li, L. Zhang, W. Yang, H. Jiang, C. Jing, H. Yu and B. Wang, *J. Am. Chem. Soc.*, 2014, **136**, 2625–2629.

35 Y. Wu, H. Liu, L. Zhang, Z. Sun, Y. Xiao, J. Huang, M. Wang and H. Guo, *RSC Adv.*, 2016, **6**, 73547–73550.

36 P. Kumar, A. Thakur, X. Hong, K. Houk and J. Louie, *J. Am. Chem. Soc.*, 2014, **136**, 17844–17851.

37 J. D. Shields, E. E. Gray and A. G. Doyle, *Org. Lett.*, 2015, **17**, 2166–2169.

38 H. Liu, H. Jia, W. Shi, C. Wang, C. Zhang and H. Guo, *Org. Lett.*, 2018, **20**, 3570–3573.

39 S. Murarka, Z. J. Jia, C. Merten, C. G. Daniliuc, A. P. Antonchick and H. Waldmann, *Angew. Chem.*, 2015, **127**, 7763–7766.

40 S. Zhang, R. Xie, A. Tang, P. Chen, Z. Zhao, M. Miao and H. Ren, *Org. Lett.*, 2020, **22**, 3056–3061.

41 X. Wang, J. Wang and X. Li, *Org. Chem. Front.*, 2025, **12**, 159–166.

42 L.-C. Yang, Y.-N. Wang, R. Liu, Y. Luo, X. Q. Ng, B. Yang, Z.-Q. Rong, Y. Lan, Z. Shao and Y. Zhao, *Nat. Chem.*, 2020, **12**, 860–868.

43 Y.-J. Long, J.-H. Shen, Y. Wei and M. Shi, *J. Org. Chem.*, 2024, **89**, 14831–14850.

44 Y. Long, J. Shen, M. Shi and Y. Wei, *Molecules*, 2024, **30**, 103.

45 M. Cui, J. Li, R. Tian and Z. Duan, *Org. Chem. Front.*, 2022, **9**, 2753–2758.

46 F. Esteban, R. Alfaro, F. Yuste, A. Parra, J. L. G. Ruano and J. Aleman, *Eur. J. Org Chem.*, 2014, **2014**, 1395–1400.

47 S. Wang, C. Rodríguez-Escrich, M. Fianchini, F. Maseras and M. A. Pericàs, *Org. Lett.*, 2019, **21**, 3187–3192.

48 F. Xia, Z. H. Gao, C. L. Zhang and S. Ye, *Adv. Synth. Catal.*, 2019, **361**, 2291–2294.

49 J. Li, Y. Mo, L. Yan, X. Feng, Z. Su and X. Liu, *CCS Chem.*, 2022, **4**, 650–659.

50 G. Bertuzzi, D. McLeod, L. M. Mohr and K. A. Jørgensen, *Chem.–Eur. J.*, 2020, **26**, 15491–15496.

51 D. A. McLeod, M. K. Thøgersen, C. L. Barløse, M. L. Skipper, E. B. Obregón and K. A. Jørgensen, *Angew. Chem.*, 2022, **134**, e202206096.

52 M. Thangaraj, S. S. Bhojgude, R. H. Bisht, R. G. Gonnade and A. T. Biju, *J. Org. Chem.*, 2014, **79**, 4757–4762.

53 T. Roy, A. Jacob, S. Bhattacharjee and A. T. Biju, *Chem.–Asian J.*, 2019, **14**, 4748–4753.

54 G. Force, A. Pérot, R. Guillot, V. Gandon and D. Leboeuf, *Synthesis*, 2020, **52**, 553–564.

55 J. Yu, X. Chen, Y. Liu, B. Wu, H. Li, Y. Hu, L. Wang and S. Zhang, *Synthesis*, 2020, **52**, 1847–1854.

56 A. Guin, R. N. Gaykar, S. Deswal and A. T. Biju, *Org. Lett.*, 2021, **23**, 7456–7461.

57 S. Jia, S. Su, C. Li, X. Jia and J. Li, *Org. Lett.*, 2014, **16**, 5604–5607.

58 K. Sakata, S. Suzuki, T. Sugimoto and T. Yoshikawa, *ACS Omega*, 2023, **8**, 30410–30420.

59 C. Guerra, Y. A. Rodríguez-Núñez, M. E. Taborda-Martínez, M. Bacho, R. Miranda-Pastrana and A. E. Ensuncho, *New J. Chem.*, 2024, **48**, 17633–17640.

60 L. H. Li, Y. Jiang, J. Hao, Y. Wei and M. Shi, *Adv. Synth. Catal.*, 2017, **359**, 3304–3310.

61 Y. Wang, M. Zhang and S.-K. Tian, *J. Org. Chem.*, 2024, **89**, 17853–17859.

62 Q. Q. Wu, Y. Wang, M. Zhang and S. K. Tian, *Asian J. Org. Chem.*, 2024, **13**, e202400386.

63 X. Y. Wang, Y. Z. Guo, S. Shi, S. Li, J. S. Yu, S. Z. Dong, Y. J. Hao and J. Zhou, *Adv. Synth. Catal.*, 2024, **366**, 3585–3590.

64 A. Brunetti, M. Garbini, N. Gino Kub, M. Monari, R. Pedrazzani, C. Zanardi, G. Bertuzzi and M. Bandini, *Adv. Synth. Catal.*, 2024, **366**, 1965–1971.

65 A. Brunetti, S. Kiriakidi, M. Garbini, G. Monda, C. Zanardi, C. S. López, G. Bertuzzi and M. Bandini, *ACS Catal.*, 2025, **15**, 3184–3190.

66 Q.-X. Zeng, C.-Y. Zheng, Z.-P. Ge, J.-X. Zhao and J.-M. Yue, *Chem. Sci.*, 2025, **16**, 8836–8844.