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Review

Roles of Guanidines in Recent Cycloaddition Reactions

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Abstract

Guanidines are structurally unique, highly basic, nitrogen-containing organic compounds with strong hydrogen-bonding ability and biological activity, providing valuable functionality in medicinal chemistry, organocatalysis, and materials science. Among modern strategies for assembling guanidine-containing molecules, cycloaddition reactions have emerged as powerful tools due to their efficiency, stereoselectivity, and ability to rapidly build molecular complexity. Recent innovations have expanded cycloaddition methodologies for generating guanidine functionalities, incorporating guanidine-containing substrates, and using guanidine-based catalysts. This review summarizes these advances and highlights the current trends in guanidine-related cycloaddition chemistry.

Keywords: guanidine; cycloaddition reactions; Diels–Alder; [3+2] cycloaddition; [2+2] cycloaddition

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1. Introduction

Guanidines are a structurally unique and functionally versatile class of nitrogen organic compounds with a planar structure, featuring two amino groups ($-NH_2$) and one imino group (=NH) attached to the central carbon atom [1]. Guanidines can be described as equilibrium among three tautomeric forms (Figure 1) [2].

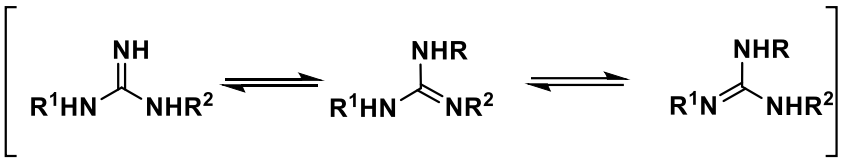


Figure 1. Tautomeric forms of guanidine [2].

Guanidines possess very interesting physicochemical properties [3], such as high basicity, hydrogen bonding capability, and biological activity, providing valuable functionality for applications in medicinal chemistry [4,5], organocatalysis [6], and materials science [7]. In natural biological systems, guanidine-containing molecules such as arginine play crucial roles in protein structure and enzymatic processes. Synthetic guanidines have been extensively studied for their antimicrobial, anticancer, and antiviral activities, and their incorporation into molecular frameworks often enhances binding affinity and pharmacokinetic profiles. The development of new methodologies to construct guanidine motifs with high selectivity and functional group tolerance remains an area of active research.

Among the various strategies for constructing complex nitrogen-containing heterocycles, cycloaddition reactions have proven especially powerful due to their atom economy, stereoselectivity, and ability to rapidly increase molecular complexity. They have long been

key synthetic transformations in natural product synthesis and drug development [8–10]. Diels–Alder [4+2] and [3+2] cycloadditions are typically single-step processes that efficiently preserve stereochemical information, while thermal [2+2] and [4+3] cycloadditions are symmetry-forbidden as single-step reactions and usually proceed through stepwise pathways with reduced stereocontrol. These mechanistic distinctions and their effects on reactivity and stereocontrol have been comprehensively discussed in several reviews [11–15]. In recent years, researchers have adapted these reactions to generate guanidine-containing frameworks through innovative cycloaddition approaches.

Several book chapters and review articles already cover various aspects of guanidine chemistry, including stereoselective organic transformations catalyzed by guanidine-based organocatalysts [6,16], organic reactions mediated by transition metal–guanidine complexes [17], and the cycloaddition of carbon dioxide to epoxides catalyzed by guanidine-based systems [18]. In our previous book chapter, Cycloadditions of Guanidines [19], we summarized earlier developments in cycloaddition reactions involving guanidines and cycloaddition reactions employed in the synthesis of cyclic guanidines.

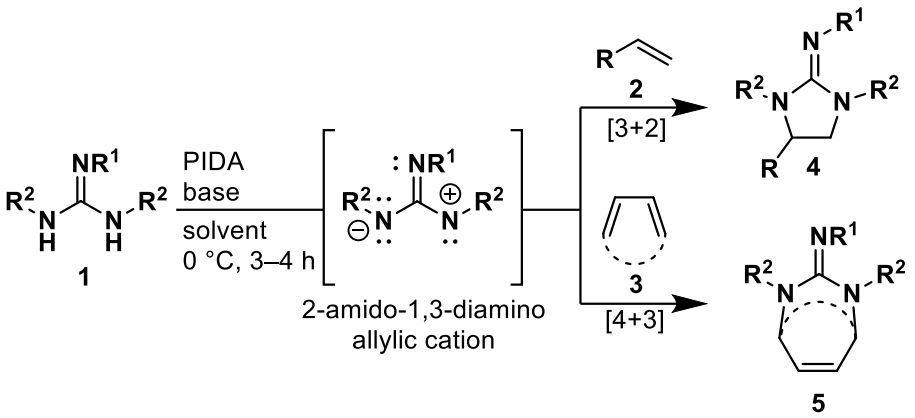
As mentioned above, guanidines are distinguished by their exceptionally high basicity, planar structure, charge delocalization, and strong hydrogen-bond donor and acceptor capabilities. These physicochemical features play a decisive role in cycloaddition chemistry, where guanidines can act as polarized π-systems or cationic intermediates, modulate reactivity through protonation state and counterion effects, or function as bifunctional organocatalysts enabling cooperative substrate activation. As a result, guanidines participate in cycloaddition chemistry in multiple, conceptually connected roles. This review highlights how these intrinsic properties underpin recent advances in (1) the generation of guanidine functionality by cycloaddition reactions, (2) cycloaddition reactions of guanidine-containing substrates, and (3) guanidine-catalyzed cycloaddition processes.

2. Generation of Guanidine Functionality by Cycloaddition Reactions

Recent advances in cycloaddition chemistry have enabled the efficient synthesis of cyclic guanidines and guanidinium-containing heterocycles using both metal-catalyzed and metal-free methods. The following examples highlight various approaches for constructing complex frameworks under mild conditions.

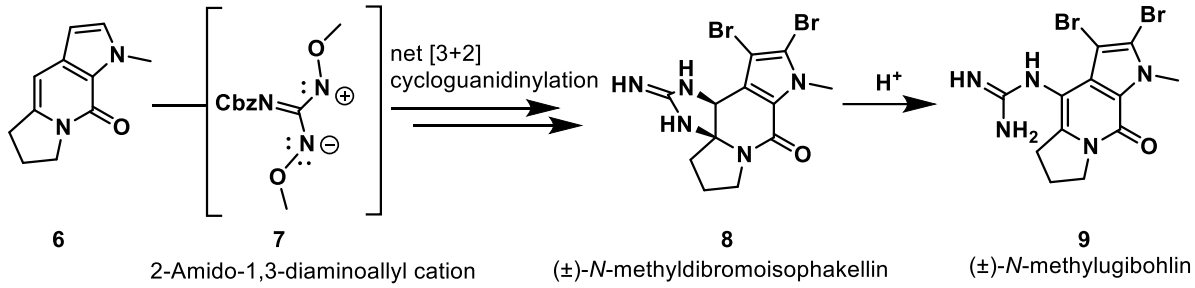
Romo et al. developed a novel method for the direct synthesis of cyclic guanidines via the generation of 2-amido-1,3-diaminoallyl cations [20]. The authors show that these reactive intermediates, formed under oxidative conditions, can undergo both formal [3+2] and [4+3] cycloadditions with alkene **2** and diene **3**, respectively (Scheme 1). They demonstrate that treating a suitably functionalized guanidine precursor with phenyliodine diacetate (PIDA) and a mild base such as sodium carbonate cleanly generates the target allylic cation. This reactive species efficiently engages with electron-rich alkenes, particularly 1,3-disubstituted indoles, to afford tricyclic 2-aminoimidazolines in high yields. The substrate scope has been explored, revealing tolerance for various substituents, including sterically demanding groups. The data support a stepwise ionic mechanism for these formal cycloadditions, involving the nucleophilic attack of indole at C-3 on the allylic cation to form an iminium intermediate. C3-unsubstituted indoles can rearomatize by elimination, leading to side products, while C3-substituted indoles block this pathway and favor higher yields of formal [3+2] cycloadducts. These reactions initially produce mixtures of oximes and cycloadducts, with the oximes converting to the more stable cycloadducts under mild acidic conditions. Extending the reactivity of this 2-amido-1,3-diaminoallyl cation, the authors also report its participation in formal [4+3] cycloadditions with dienes, including furans and cyclopentadienes, to produce

bridged guanidine frameworks. The method demonstrates functional group compatibility, as shown by its successful application to a dihydroxyfuran substrate.



Scheme 1. Formal [3+2] and [4+3] cycloaddition products of 2-amido-1,3-diamino allylic cations with alkenes and dienes [20].

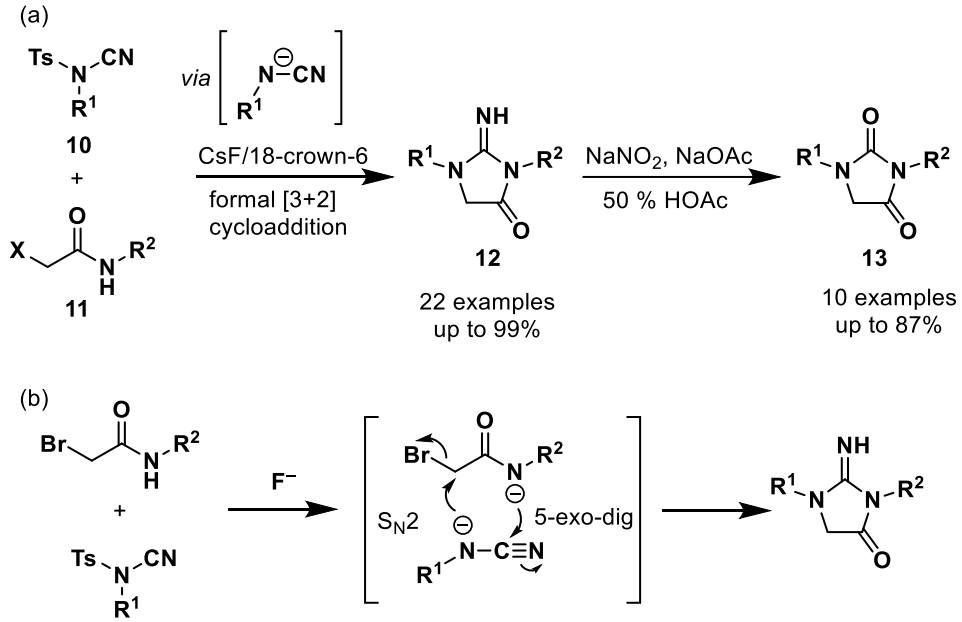
Furthermore, Romo et al. applied this net [3+2] cycloguanidinylation strategy, employing 2-amido-1,3-diaminoallyl cation **7**, for the total synthesis of (±)-*N*-methyldibromoisophakellin **8** and *N*-methylugibohlin **9** (Scheme 2) [21]. The work uses the oxidative generation of the 2-amido-1,3-diaminoallyl cation to annulate a cyclic guanidine onto alkene-containing substrates derived from brominated pyrrole frameworks, providing access to monomeric pyrrole–aminoimidazole alkaloids. Although the core guanidine ring forms in a single step under hypervalent iodine oxidation, the reaction outcome is sensitive to substrate electronics and protecting groups. Using a bis-methoxy, Cbz-protected guanidinylating reagent suppresses competing oxidation pathways and allows the isolation of isomeric cyclic guanidines, whose divergent downstream reactivity enables the completion of the isophakellin synthesis and, via acid-mediated ring cleavage, the formation of *N*-methylugibohlin **9**, suggesting the latter arises as an isolation artefact. Overall, the study illustrates the utility and limitations of 2-amido-1,3-diaminoallyl cations in cyclic guanidine construction and clarifies the mechanistic features relevant to the synthesis of pyrrole–aminoimidazole alkaloids.



Scheme 2. 2-Amido-1,3-diaminoallyl cation in the net [3+2] cycloguanidinylation reaction in the total synthesis of (±)-*N*-methyldibromoisophakellin and *N*-methylugibohlin [21].

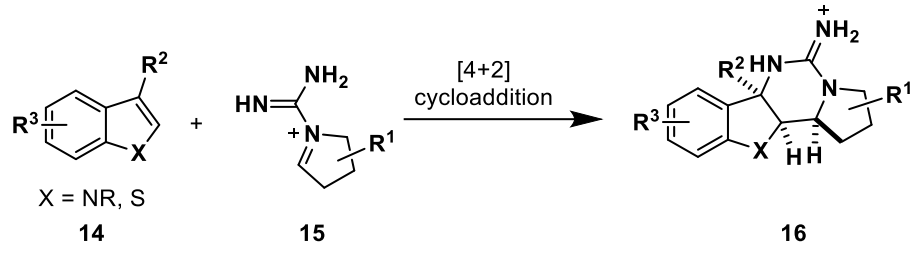
In 2021, Chen et al. reported a mild, metal-free cascade [3+2] cycloaddition for synthesizing five-membered cyclic guanidines using *N*-tosyl-*N*-aryl cyanamide **10** and *α*-haloamide **11** with CsF/18-crown-6 (Scheme 3a) [22]. The process is initiated by fluoride-induced desulfonylation, which generates a cyanamide anion that then attacks the *α*-haloamide in an intermolecular S_N2 step, followed by an intramolecular 5-exo-dig cyclization to yield the cyclic guanidine scaffold (Scheme 3b). This one-pot process forms two C–N bonds without N2 protection, affording five-membered cyclic guanidine **12** in high yields. The reaction shows broad functional group compatibility, accommodating both

electron-donating and electron-withdrawing substituents on the aryl cyanamide, as well as various *N*-alkoxy and *N*-alkyl *α*-haloamides (22 examples, up to 99% yield). The reaction is scalable to gram quantities, and the products can be converted into pharmacologically relevant hydantoin **13** (10 examples, up to 87%), highlighting the method's synthetic utility.



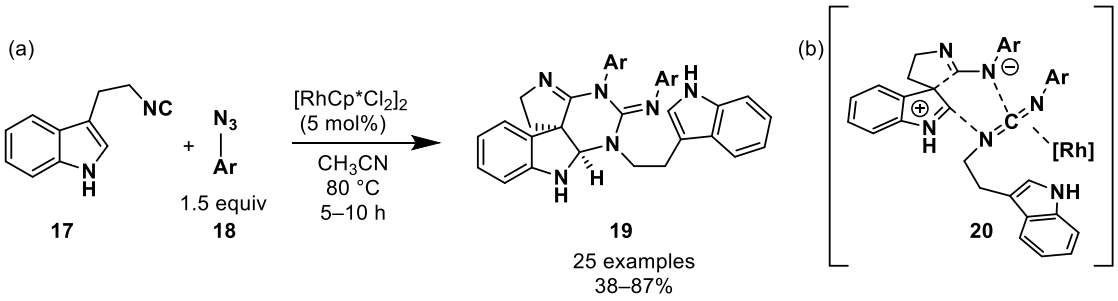
Scheme 3. (**a**) Formal [3+2] cycloaddition for synthesis of five-membered cyclic guanidines; (**b**) mechanism of reaction [22].

Houk, Overman et al. report a regio- and stereoselective [4+2] cycloaddition of *N*-amidinyliminium ion **15** with indoles and benzothiophene **14** to form saturated guanidinium heterocycle **16** (Scheme 4) [23]. This work highlights the underexplored role of *N*-amidinyliminium ions as cationic 1,3-diaza-dienes, enabling rapid access to polycyclic guanidinium frameworks featuring dihydroindole motifs. The reaction proceeds efficiently with three-substituted, *N*-protected indoles and tolerates substitution on the aromatic ring, although steric bulk at C-3 reduces reactivity. Benzothiophene is also a viable partner, indicating that the transformation is not limited to indole substrates. The authors prepared 21 different cycloadducts with good yields (34–87%). Products are formed with high diastereoselectivity, but isolation is challenging due to the polarity of the guanidinium salts. The authors contrast this behavior with *N*-acyliminium ions, which do not undergo analogous cycloadditions, attributing the difference to the unique electronic structure of amidinyliminium ions. Density functional theory (DFT) studies at the B3LYP level of theory with the def2-SVP14 basis set support a single-step, asynchronous mechanism and rationalize the observed regio- and stereoselectivity. Frontier molecular orbital analysis indicates that regioselectivity arises from the interaction of the indole HOMO with the iminium ion LUMO, while endoselectivity is associated with secondary orbital and electrostatic interactions.



Scheme 4. [4+2] cycloadditions of *N*-amidinyliminium ions with indoles and benzothiophene [23].

Liu et al. describe a rhodium-catalyzed cascade reaction between 3-(2-isocyanoethyl)indole **17** and aromatic azide **18** that yields polycyclic spiroindolines bearing a pentasubstituted guanidine moiety **19** (Scheme 5a) [24]. The transformation proceeds through a sequence proposed to involve initial cross-coupling to generate an indole-derived carbodiimide intermediate, followed by intramolecular spirocyclization and a formal [4+2] cycloaddition with a second carbodiimide molecule (Scheme 5b). Using $[RhCp^*Cl_2]_2$ in acetonitrile at 80 °C, the products are obtained as single diastereomers in 38–87% yield. The reaction shows broad scope for aromatic azides, including electron-rich, electron-poor, heteroaryl, alkenyl, and alkynyl variants, while alkyl azides are unreactive. Substituted tryptamine-derived isocyanides are generally tolerated, except for C2-substituted indoles. Gram-scale synthesis and post-functionalization via aza-Michael addition with methyl propiolate, selectively modifying the indole NH group, demonstrate the method's practicality. Mechanistic studies, supported by DFT calculations conducted on the M06-L functional with the basis set 6-31G(d), indicate that the reaction initiates with the rhodium-mediated decomposition of the azide to form a nitrene species, which inserts into the isocyanide to generate the key carbodiimide intermediate. The subsequent spirocyclization and dimerization are calculated to occur in a single step or in a highly coupled manner, with the observed regioselectivity determined by the relative stability of the transition states and the conjugative stabilization of the developing guanidine core.



Scheme 5. (**a**) A rhodium-catalyzed reaction between 3-(2-isocyanoethyl)indoles and aromatic azides; (**b**) favored transition state of the reaction. [24].

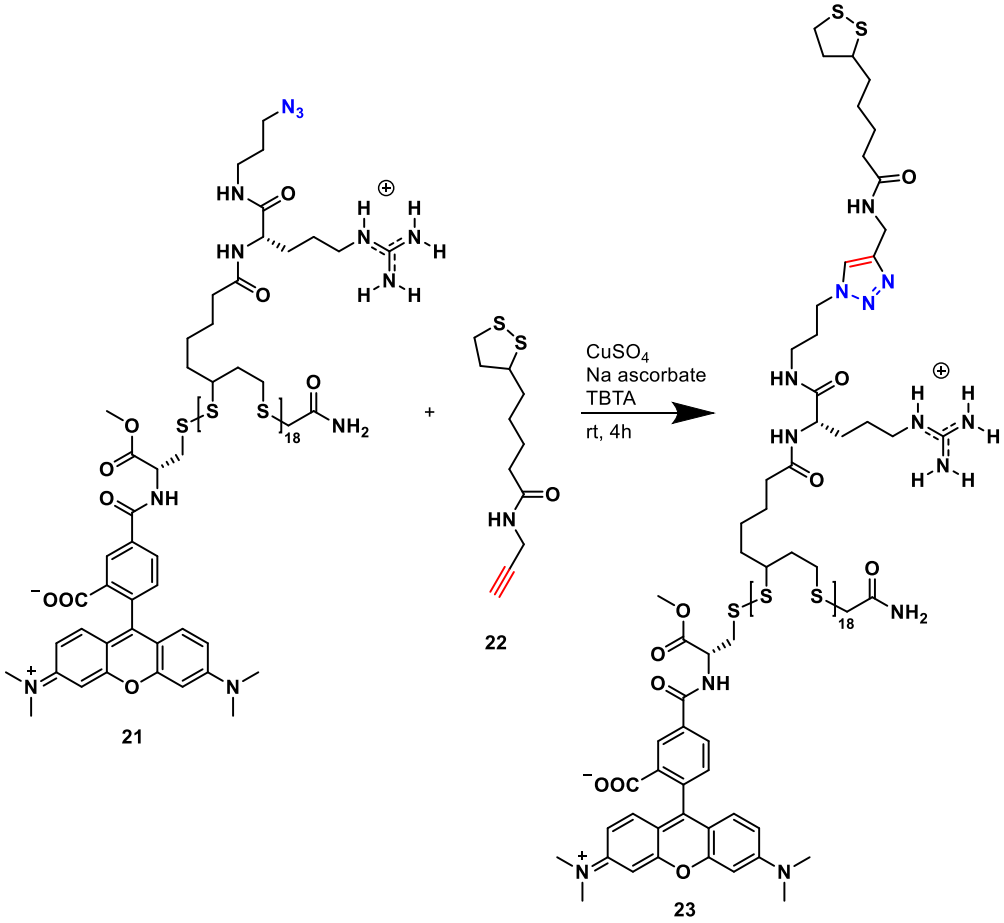
In summary, cycloaddition reactions offer efficient and versatile entry points to cyclic guanidines and guanidinium-containing heterocycles, enabling rapid construction of molecular complexity under mild conditions. The success of these transformations is closely linked to the intrinsic physicochemical properties of guanidines, most notably their high basicity, charge delocalization, and ability to stabilize cationic or highly polarized intermediates. Activation through protonation, oxidation, or iminium formation transforms otherwise inert C=N units into highly reactive cycloaddition partners, underscoring how the controlled modulation of guanidine electronics governs reactivity and selectivity in these processes.

3. Cycloaddition Reactions of Guanidine-Containing Substrates

Building on cycloaddition strategies, recent studies have extended 1,3-dipolar cycloaddition and Diels–Alder reactions to the post-functionalization of polymers, biomolecules, and guanidine-rich materials, enabling applications in chemical biology, materials science, and green synthesis.

Morelli and Matile used copper-catalyzed azide–alkyne cycloaddition (CuAAC) to incorporate strained cyclic disulfides and guanidinium cations into cell-penetrating poly(disulfide)s (CPDs) [25]. Under standard conditions, with copper(II) sulfate, sodium ascorbate, and tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) at room temperature for 4 h, the CuAAC reaction between azide-functionalized CPD **21** and alkyne **22** produced sidechain-modified CPD **23** (Scheme 6). The same procedure was used to modify additional CPDs, either by increasing tension in the sidechain or with different numbers of

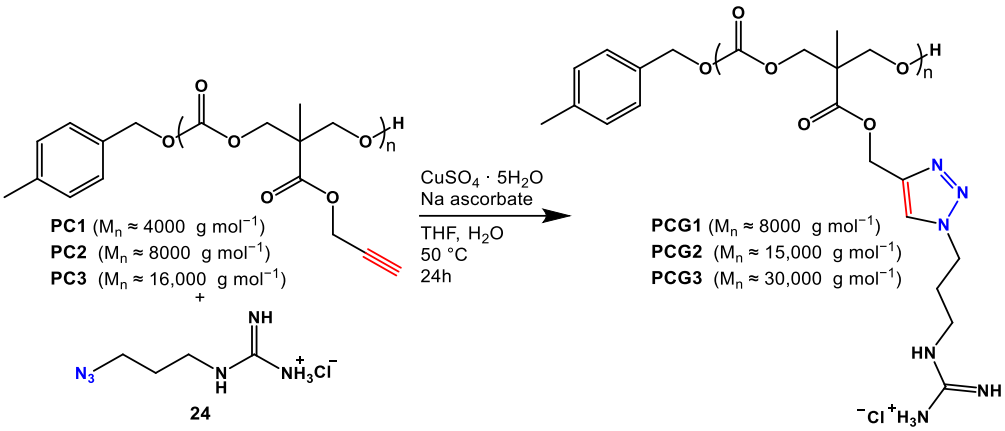
arginine residues in their sidechains, where the strained disulfide was replaced with another guanidinium cation or a more hydrophobic triphenylphosphonium cation. The reaction yields were estimated to be 80–90% by reversed-phase high-performance liquid chromatography (RP-HPLC) analysis after the reductive depolymerization of the described CPDs.



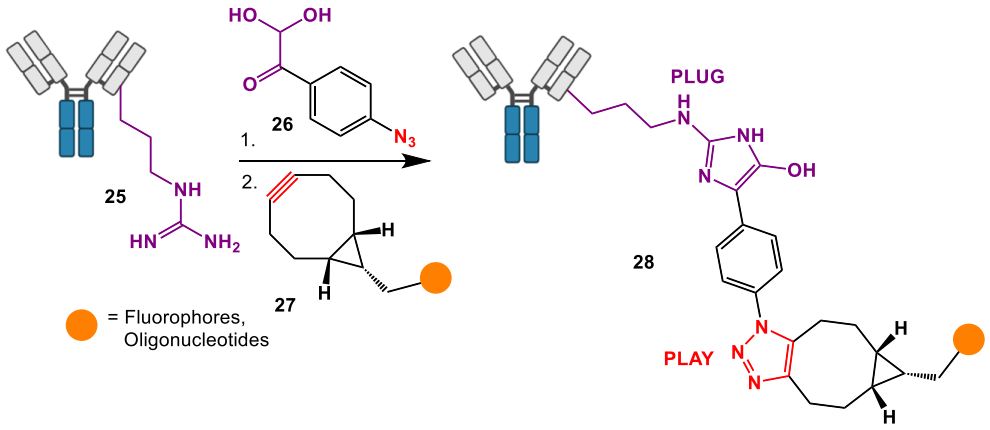
Scheme 6. CuAAC reaction of azide-functionalized CPD and alkyne [25].

Soon after, Swift, Jin et al. also used CuAAC for the post-polymerization modification of aliphatic polycarbonates **PCs**, introducing guanidinium groups in a controlled manner [26]. A set of biodegradable polycarbonates containing guanidine functionality **PCG** were synthesized with molecular weights ranging from 8000 to 30,000 g mol^{-1} (Scheme 7), with isolated yields around 60%. Similarly, another product set containing both guanidine functionality and a passive diluting group was synthesized. In this case, the first CuAAC reaction was performed between **PC** and the diluting group, and afterwards, the polymer with the diluting group was clicked with guanidine azide. The designed series of guanidine-functionalized aliphatic biodegradable polycarbonates were used to investigate the effects of molecular weight and charge density on antimicrobial performance.

In a different context, Wagner et al. used strain-promoted azide–alkyne cycloaddition (SPAAC) in a "plug-and-play" approach to antibody functionalization [27]. Guanidine groups of arginine residues **25** were selectively modified with 4-azidophenyl glyoxal **26** (plug stage), and the introduced azide handles underwent SPAAC with strained alkyne **27** to produce fluorophore- and oligonucleotide-antibody conjugate **28** (play stage) (Scheme 8). Mass spectrometry and peptide mapping confirmed the efficient and selective modification of the arginine residues, with degrees of conjugation depending on the reagent stoichiometry and buffer conditions. This bio-orthogonal strategy generated homogeneous, plasma-stable conjugates with preserved antigen recognition.

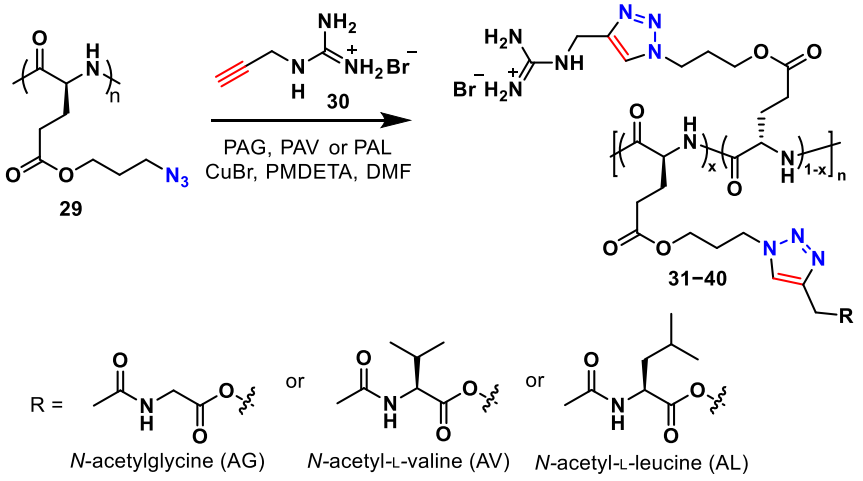


Scheme 7. CuAAC reaction of alkyne precursor polycarbonates and guanidine azide **24** [26].



Scheme 8. Arginine-selective "plug-and-play" functionalization of antibodies [27].

Yin, Tang et al. developed a new class of guanidine-rich helical polypeptides with hydrophobic amino acid pendants for non-viral gene delivery [28]. These polymers were synthesized through a 1,3-dipolar cycloaddition between azido-functionalized polypeptide **29**, propargyl-substituted guanidinium **30**, and propargyl-functionalized *N*-acetyl amino acids (Scheme 9, Table 1), achieving yields of 60–70%. Circular dichroism spectroscopy confirmed that the resulting materials adopted stable α-helical conformations in aqueous solution (Table 1).



Scheme 9. 1,3-Dipolar cycloaddition of azido-functionalized polypeptides, propargyl-substituted guanidinium, and propargyl-functionalized *N*-acetyl amino acids [28].

Table 1. Structural parameters of polypeptides [28].

Polypeptide	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**
x [a]	0	0.05	0.1	0.15	0.05	0.1	0.15	0.05	0.1	0.15
R	N/A	AG	AG	AG	AL	AL	AL	AV	AV	AV
f_H [b] (%)	43	56	44	50	76	40	60	65	42	50

[a] Molar content of hydrophobic amino acid residues. [b] Helicity determined by CD.

Our research group conducted a detailed DFT investigation at the SMD(chloroform)//B3LYP/6-311+G(2d,p) level of theory on the mechanistic landscape of the 1,3-dipolar cycloaddition reaction between azide **41** and guanidine **42** (Figure 2) [29]. The study examined the cycloaddition reactivity of the guanidine imine bond, the regioselectivity of tetrazole formation, and the stability of possible reaction products. The formation of two regioisomeric tetrazoles was modeled: one in which the carbon in the guanidine bound to the azide's N3, and another in which its imino nitrogen interacted with the azide's N1. Both pathways are highly endothermic, with substantial activation barriers exceeding 50 kcal mol^{-1} for the thermodynamically preferred route in which the guanidine carbon binds the terminal azide nitrogen. Although the alternative regioisomer is kinetically more accessible, its progression depends on external activation (e.g., photochemical release of N_2 or deamination), indicating that uncatalyzed cycloaddition requires extreme forcing conditions. In both regioisomeric pathways, the initially formed tetrazoles are predicted to be unstable, undergoing nitrogen expulsion or ammonia loss to yield aziridines or open-chain guanidine products, mirroring the rearrangement processes observed in analogous azide cycloadditions to alkenes and nitriles. Substituent effects on azide reactivity were also examined, revealing that benzyl and perfluorophenyl groups significantly lower activation barriers and thus enhance cycloaddition feasibility.

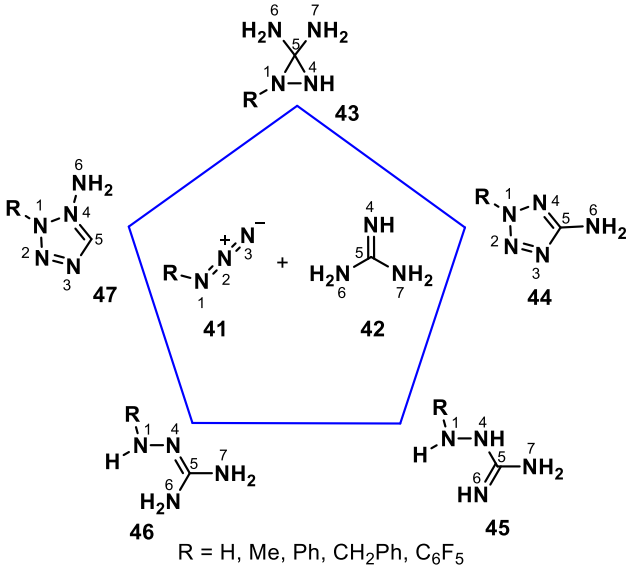
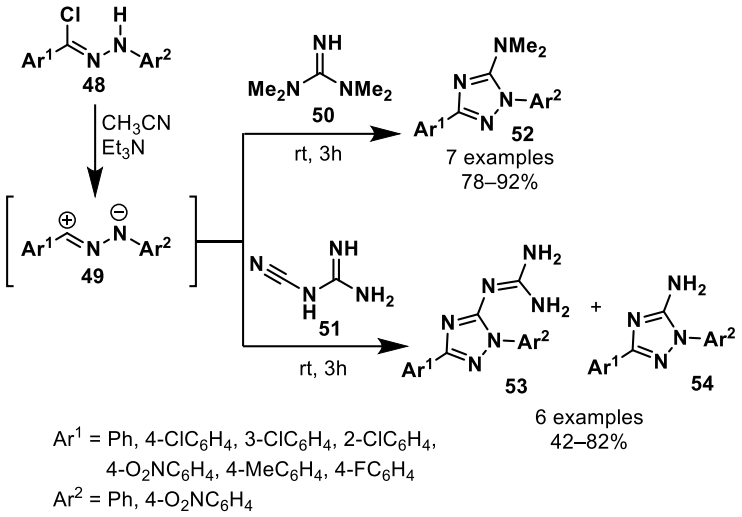


Figure 2. Studied 1,3-dipolar cycloadditions between azides and guanidines and their possible products [29].

Yavari et al. developed an efficient and regioselective strategy for synthesizing trisubstituted 1,2,4-triazoles via 1,3-dipolar cycloaddition reactions of nitrile imines with guanidine derivatives under mild, ambient conditions (Scheme 10) [30]. Optimization studies identified acetonitrile (CH_3CN) and triethylamine (Et_3N) as the most effective, enabling high yields and excellent selectivity. The methodology exhibits broad substrate scope, allowing the use of various hydrazonoyl chlorides **48** that efficiently generate nitrile imine **49** in situ, which undergo [3+2] cycloaddition with tetramethylguanidine **50** or cyanoguani-

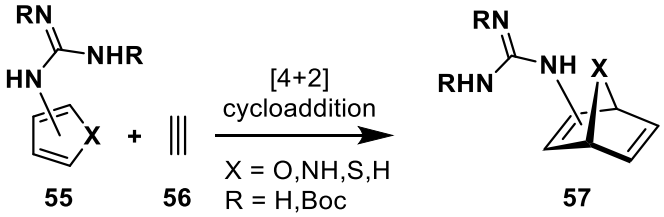
dine **51**. The nitrile imine intermediate **49** reacts with tetramethylguanidine **50,** and the subsequent loss of dimethylamine gives product **52**. In the reaction with cyanoguanidine **51**, two products, **53** and **54,** are observed. Intermediate **49** can react with the cyano group of compound **51** to form product **53**. Alternatively, a 1,3-dipolar cycloaddition occurs at the imino double bond of **51** to produce an intermediate, which then eliminates cyanamide to yield product **54**. This work provides a practical, one-step synthesis route to structurally diverse triazoles, offering valuable insight into triazole chemistry and expanding access to heterocycles with significant relevance in medicinal and materials science.



Scheme 10. Synthesis of trisubstituted 1,2,4-triazoles [30].

Our group has systematically investigated the reactivity of guanidine-functionalized dienes in Diels–Alder reactions through combined computational and experimental studies.

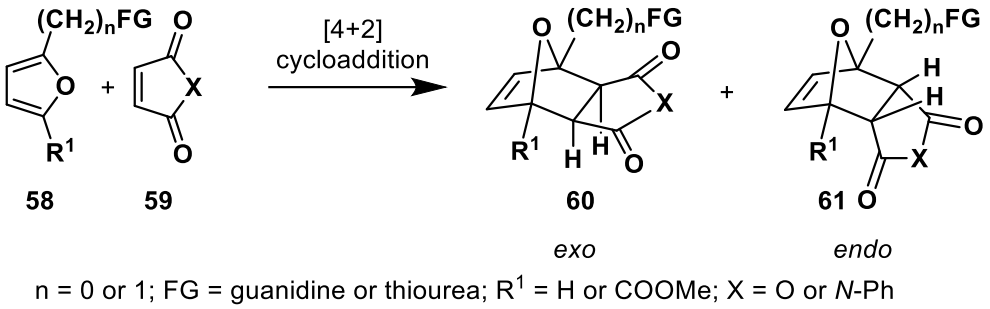
The computational analysis focused on how guanidine substitution affects the reactivity of cyclic heterodienes in Diels–Alder cycloadditions [31]. Using DFT calculations at the (B3LYP/6-31G(d)) level, we examined pyrrole, furan, thiophene, isoindole, and 1,3-butadiene derivatives bearing guanidine groups. Transition-state calculations for the reaction of the studied dienes **55** with acetylene **56** (Scheme 11) show that guanidine substitution has a modest effect (~4 kcal mol^{-1} increase) on the reaction barriers. However, the position of the guanidine substituent on the diene significantly impacts reactivity, and the protonation of the nitrogen-containing substituents generally enhances the reactivity of the dienes.



Scheme 11. [4+2] cycloaddition reaction of the studied dienes with acetylene [31].

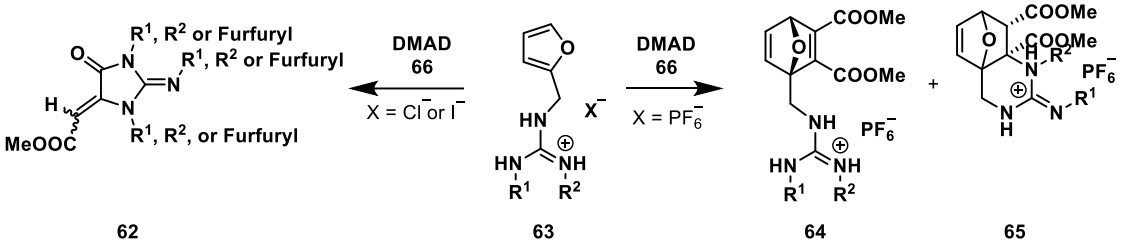
In a comparative study of green synthetic methodologies, the cycloaddition reactions of thiourea- and guanidine-functionalized furans **58** with dienophiles **59**, *N*-phenylmaleimide and maleic anhydride were evaluated under microwave-assisted (MW), high-pressure (HP), high-speed vibrational milling (HSVM), and ultrasound (US) conditions (Scheme 12) [32]. The reactions produced functionalized 7-oxanorbornene derivatives **60/61** with varying *endo/exo* selectivities and yields. Among the tested conditions, HP and HSVM provided the highest conversions and product yields, confirming their suitability for solvent-minimized

green synthesis. Interestingly, when unprotected guanidines were used, competitive aza-Michael addition pathways were observed, which were suppressed by protonation.



Scheme 12. Studied [4+2] cycloaddition reaction of thiourea- and guanidine-functionalized furans with *N*-phenylmaleimide or maleic anhydride [32].

Furthermore, we developed an anion-controlled cycloaddition strategy for synthesizing novel guanidine-substituted oxanorbornanes [33]. The outcome of reactions between furfuryl guanidines **63** and dimethyl acetylenedicarboxylate (DMAD) **66** depends critically on the counterion nucleophilicity and the guanidine structure (Scheme 13). Guanidinium halides favored aza-Michael addition, whereas non-nucleophilic hexafluorophosphate salts enabled clean Diels–Alder cycloadditions to yield oxanorbornadiene products **64**, which could further undergo intramolecular cyclization to form unique polycyclic guanidine **65**. Microwave heating efficiently promoted Diels–Alder cycloadditions, yielding product **64**, while high pressure favored tandem cycloaddition and an intramolecular cyclized product **65**.

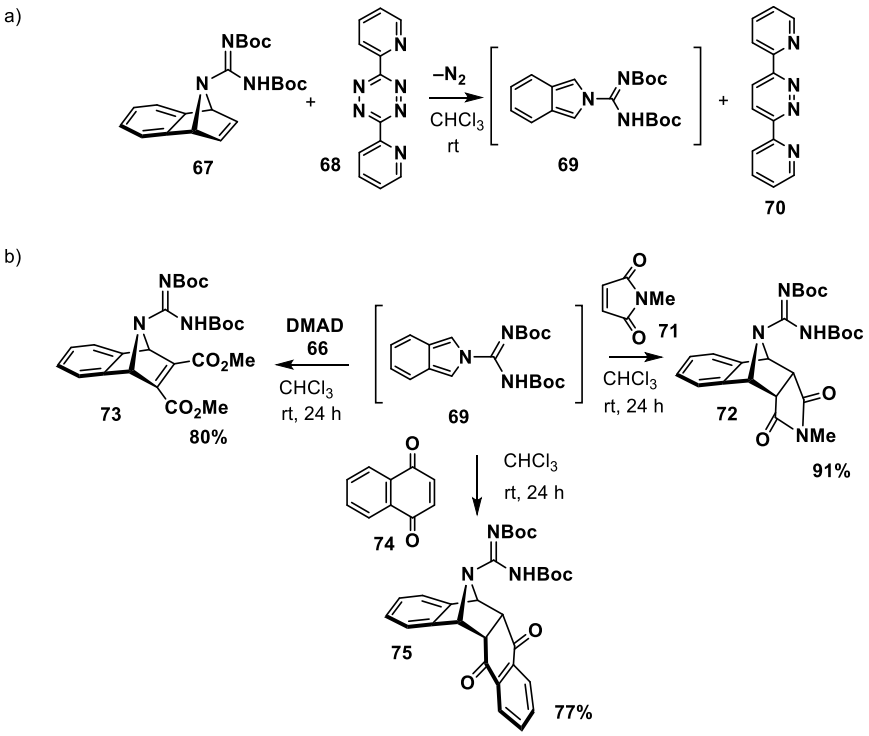


Scheme 13. Reactivity of guanidines and their salts with DMAD [33].

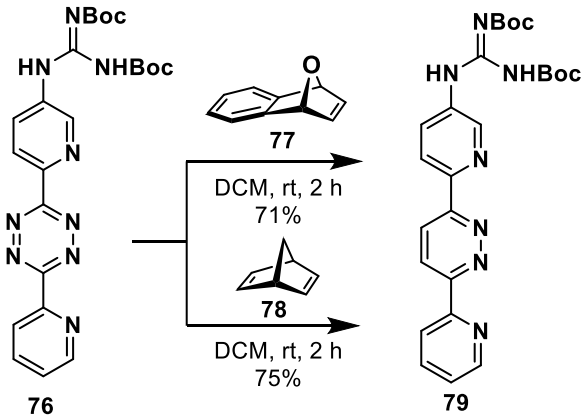
Further progress was achieved with the synthesis of *N*,*N*′-di-Boc-2*H*-isoindole-2-carboxamidine **69**, the first isoindole substituted with a guanidine functionality [34]. The compound was designed as a novel Diels-Alder heterodiene for introducing guanidine moieties into polycyclic systems. It was generated using the tetrazine method (Scheme 14a) [34]. Comparison with the corresponding pyrrole-2-carboxamidine derivative showed that the isoindole framework has enhanced cycloaddition reactivity, producing *endo*-selective adducts **72**, **73** and **75** in reactions with common dienophiles such as *N*-methylmaleimide **71**, DMAD **66**, and benzoquinone **74** (Scheme 14b) [34]. Substitution with fluorine or the relocation of the guanidine group had minimal effects on reactivity, consistent with the DFT-predicted (B3LYP/6-31G(d) level) activation energies. These results demonstrate that isoindole carboxamidine reagents are efficient guanidine delivery systems for constructing functionalized bicyclic frameworks through Diels–Alder cycloadditions and highlight the potential of isoindoles as versatile heterodienes in heterocyclic synthesis.

Complementary studies expanded this concept to guanidine-functionalized *sym*-tetrazines, bis-(4′-pyridyl)-1,2,4,5-tetrazines, which were synthesized as reactive dienes for inverse electron-demand Diels–Alder (IEDDA) reactions [35]. Experimental and DFT analyses with the M06-2X/6-31G(d) level showed that guanidine and amino substituents slightly decreased tetrazine reactivity by raising LUMO energy levels, although Boc-protected

derivatives remained sufficiently reactive toward strained alkenes such as norbornenes. Cycloadditions of tetrazine **76** with alkenes **77** and **78** yielded bispyridylpyridazine **79** (Scheme 15), confirming synthetic potential in bio-orthogonal applications, while reactions with C_{60} fullerene were less efficient due to its lower reactivity. Computational screening of 29 tetrazines further clarified substituents' effects on cycloaddition barriers, identifying *tert*-butyl amino tetrazine as a promising high-reactivity candidate for future guanidine-based functionalization chemistry.



Scheme 14. (**a**) Generation of *N*,*N*′-di-Boc-2*H*-isoindole-2-carboxamidine; (**b**) its cycloaddition reactions with *N*-methylmaleimide, DMAD, and benzoquinone [34].

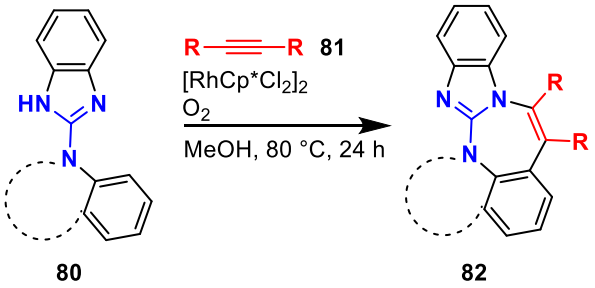


Scheme 15. Diels–Alder reactions of tetrazine **76** with alkenes **77** and **78** [35].

On the other hand, 1- and 2-anthracenyl Boc-protected guanidines do not undergo thermal Diels–Alder reaction, but thermal rearrangement of guanidine led to 6π-diazaelectrocyclization with the formation of Boc-2-amino-quinazolin-4(3*H*)-ones [36].

Saá et al. described a novel Rh(III)-catalyzed [5+2] oxidative annulation strategy for synthesizing 1,3-benzodiazepines **82** from cyclic arylguanidines **80** and alkynes **81** (Scheme 16) [37]. The process employs molecular oxygen as the oxidant, providing a more sustainable alternative to traditional silver-based oxidants. The reaction proceeds

through the formation of an eight-membered rhodacycle intermediate, as indicated by DFT calculations at the BP86 level. This pathway enables the efficient construction of the seven-membered benzodiazepine framework incorporating the guanidine moiety. The methodology produces a range of 1,3-benzodiazepines in good yields under relatively mild conditions, broadening the structural diversity accessible within this important class of heterocycles. Given the established pharmacological relevance of benzodiazepines, this oxidative annulation approach is a valuable addition to the synthetic toolbox for medicinal chemistry.



Scheme 16. [5+2] oxidative annulation of cyclic arylguanidines with alkynes [37].

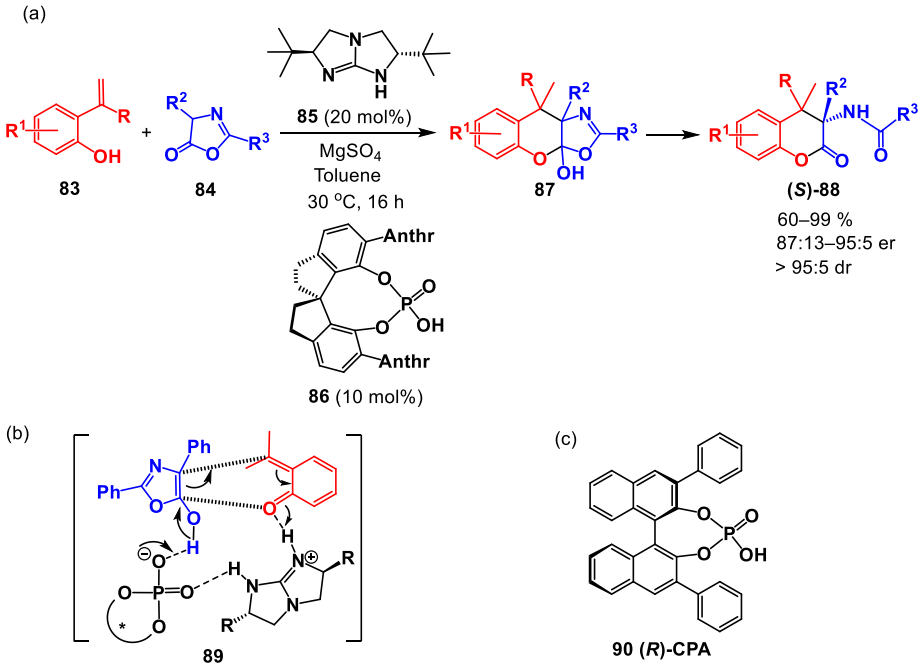
Overall, the cycloaddition reactions of guanidine-containing substrates show how guanidine functionalities can be incorporated into complex molecular and macromolecular architectures without compromising structural integrity or functional performance. The strong hydrogen-bonding ability, persistent positive charge, and tunable protonation state of guanidines play key roles in determining regioselectivity, competing reaction pathways, and ensuring post-cycloaddition stability. These properties allow guanidine-modified substrates to participate in cycloaddition chemistry across small molecules, polymers, and biomolecules, highlighting their adaptability in both synthesis and applied contexts.

4. Guanidine-Catalyzed Cycloaddition Reactions

As noted in the Introduction, several comprehensive reviews have already surveyed the organic reactions catalyzed by guanidine-based systems. These include stereoselective organic transformations mediated by guanidine organocatalysts [6,16], reactions catalyzed by transition-metal–guanidine complexes [17], and the cycloaddition of carbon dioxide to epoxides promoted by guanidine-based catalysts [18]. In this review, we focus exclusively on the employment of guanidine catalysts in cycloaddition reactions. Consequently, only a limited number of such reactions have been reported to date, with most recent studies concentrating on enantioselective variants.

Shi et al. observed efficient cooperative catalysis in an enantioselective [4+2] cycloaddition reaction of *o*-hydroxystyrene **83** with azlactone **84** (Scheme 17a) [38]. The initially formed cycloadduct **87** underwent facile ring opening under the reaction conditions, yielding dihydrocoumarin derivative **88** in a highly enantioselective manner. The cooperative effect of a chiral Brønsted acid (chiral phosphoric acid) **86** and a base (chiral guanidine) **85** was proposed as the source of the observed reactivity and high enantioselectivities. Shi proposed that in the transition state of the [4+2] cycloaddition, a ternary complex forms with guanidine bonded to azlactone and phosphoric acid is bonded to *o*-hydroxystyrene through several hydrogen bonds. Guanidine deprotonates hydroxystyrene, forming an exocyclic diene, while phosphoric acid protonates azlactone and promotes enol formation, which acts as the dienophile in the cycloaddition reaction. More recently, Boonyarattanakalin et al. conducted a computational study of this reaction at the M06-2X/6-31+G(d,p)//M06-2X/6-31G(d):3-21G level of theory using model reactants, chiral BINOL-phosphoric acid (CPA) **90** (Scheme 17c), and chiral guanidine (TBO), revealing details on the origin of

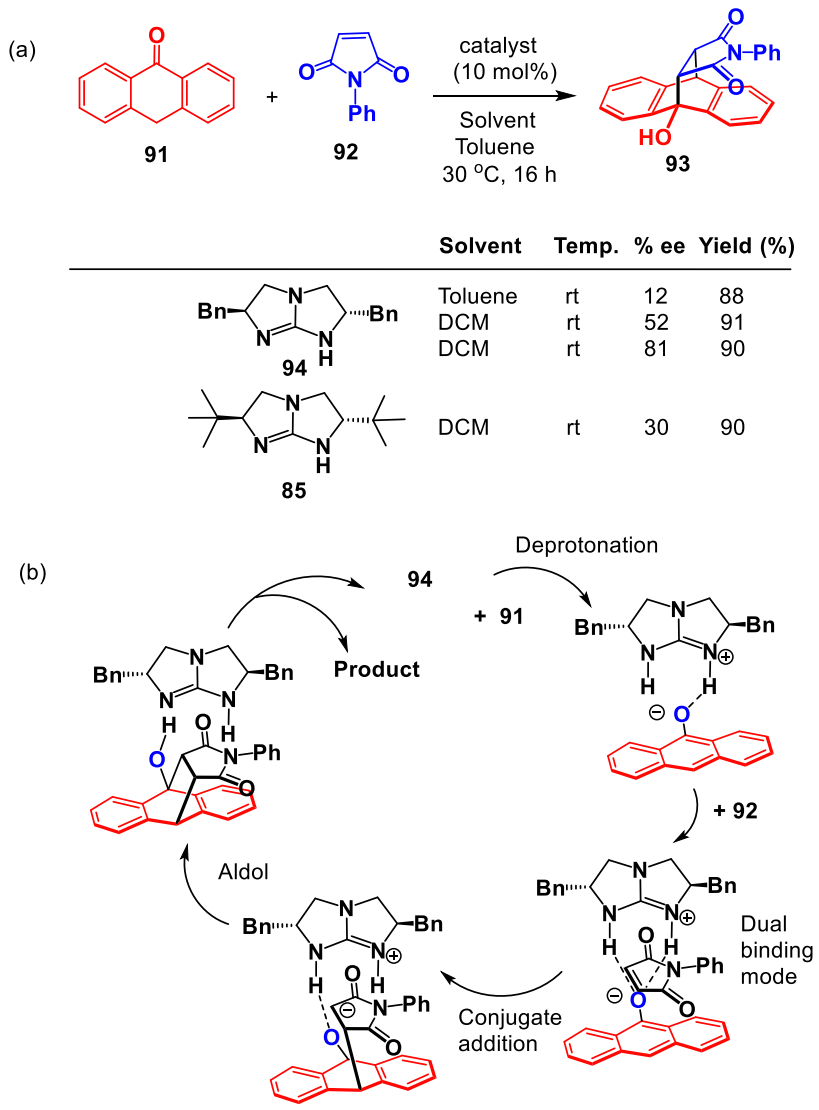
the enantioselectivity in the reaction mechanism [39]. The computational results revealed that the structure of the ternary complex **89** (Scheme 17b) is in the opposite direction to that proposed by Shi et al., with an energetically preferred structure where guanidine binds to hydroxystyrene, and phosphoric acid binds to azlactone.



Scheme 17. (**a**) Enantioselective [4+2] cycloaddition reaction of *o*-hydroxystyrenes with azlactones; (**b**) the ternary complex **89**; (**c**) chiral BINOL-phosphoric acid (CPA) **90** [38,39].

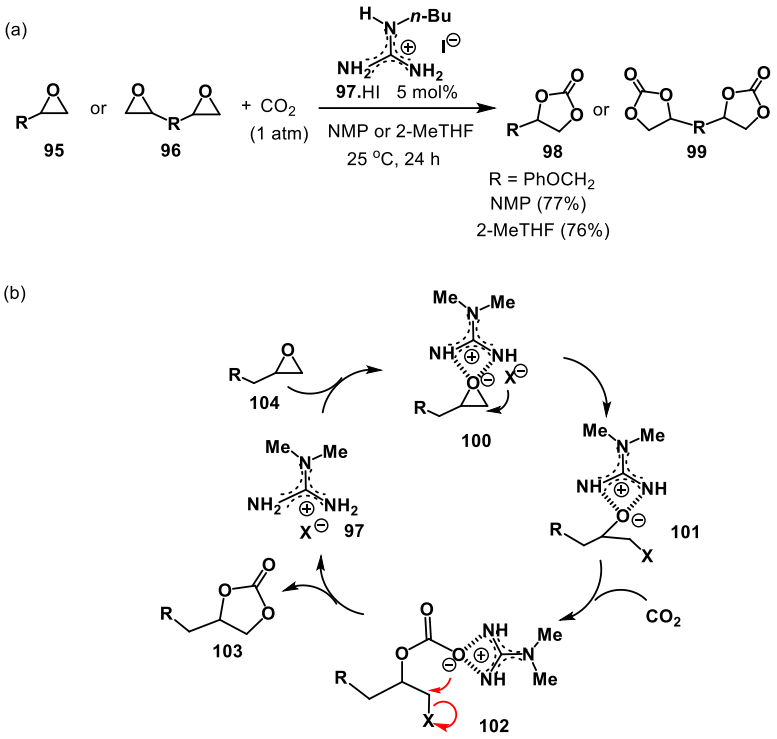
Kee et al. [40] conducted a computational study of previously reported experimental work by Tan et al. [41] on the enantioselective [4+2] cycloaddition reactions of anthrones **91** catalyzed by chiral [5.5]bicyclic guanidines **94/85** (Scheme 18a). The results obtained at the PCM(DCM)/M06HF/6-311++G(2d,2p) level based on CPCM(CCl_3)/M06-2X/6-311G-(d,p)-optimized geometries indicate that the most energetically favorable pathway is a stepwise conjugate addition-aldol mechanism via dual hydrogen-bond bonding with guanidine catalyst **94** (Scheme 18b). This stepwise conjugate addition-aldol mechanism divides the Diels–Alder step into two, i.e., to a formal [4+2] cycloaddition. The catalyst acts through a dual binding mode in which both substrates bind to the guanidinium catalyst primarily via strong ionic hydrogen bonding. Additionally, secondary non-covalent interactions, such as C−H···O and aryl-aryl interactions, are responsible for achieving the experimentally observed high enantioselectivity.

Endo et al. successfully used guanidinium iodides as catalysts for the synthesis of cyclic carbonates **98** and **99** via the formal cycloaddition of carbon dioxide to epoxides **95** and **96** at moderate temperatures (Scheme 19a) [42]. Among the guanidinium salts screened, iodides were the most efficient. The choice of solvent was crucial, with the highest yields obtained in 1-methylpyrrolidin-2-one (NMP) and 2-methyltetrahydrofuran (2-MeTHF). A proposed reaction mechanism is shown in Scheme 19b. In the initial step, a guanidinium salt activates the epoxide ring through hydrogen bonds and the formation of complex **100**. The nucleophilic attack of the anion (X^-) of the catalyst on the activated epoxide ring in the next step leads to ring opening to intermediate **101**. A subsequent nucleophilic attack on CO_2 produces the alkylcarbonate anion **102**. The reaction mechanism concludes with the formation of cyclic carbonate **103** by ring closure via the elimination of the iodide anion (X^-).

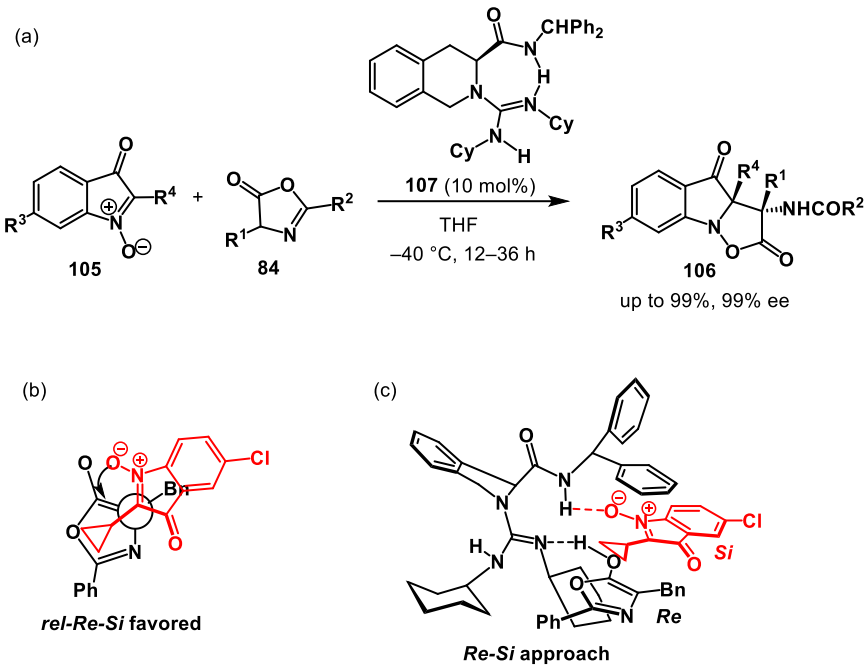


Scheme 18. (**a**) Enantioselective [4+2] cycloaddition reactions of anthrones; (**b**) the mechanism of the reaction. [40,41].

Liu et al. have shown that the use of a chiral guanidine catalyst **107** is essential for achieving the high diastereo- and enantioselectivity observed (up to 19:1 dr, 99% ee) in the catalytic asymmetric formal [3+2] dipolar cycloaddition of isatogens **105** with azlactones **84** (Scheme 20a) [43]. The fused indolin-3-one derivatives **106** were obtained in moderate to good yields (up to 99%).



Scheme 19. (**a**) Guanidinium iodides as catalysts in the synthesis of cyclic carbonates; (**b**) a proposed reaction mechanism. [42].

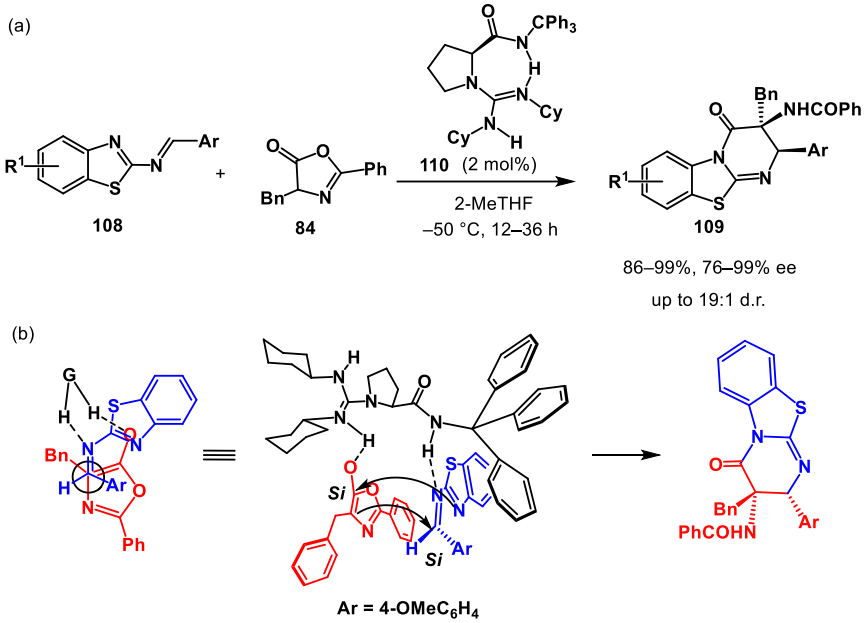


Scheme 20. (**a**) Catalytic asymmetric formal [3+2] dipolar cycloaddition of isatogens with azlactones; (**b**) *rel-Re-Si* favored arrangement of isatogen and azlactone; (**c**) *Re-Si* approach. [43].

It was proposed that the enantioselectivity of this reaction results from a bifunctional activation mode of the catalyst, in which the amide functionality forms a hydrogen bond with the oxygen atom of the isatogen's N−O group (Scheme 20b). Additionally, the basic guanidine moiety facilitates enolization of azlactone **84** by the second hydrogen bond with the formed enolate intermediate. In such a geometrical arrangement, the rotation of the two H-bonded species is slower, as being blocked by the amide substituent and the guanidine *N*-substituent. There, the *Si*-face of the isatogen approaches the *Re*-face of the enolate intermediate and forms

the first C−C bond (Scheme 20c). This process is followed by a second C−C bond formation that takes place between the oxyanion and the carbon atom of acetylide carbon. As a result, a five-membered *N*,*O*-heterocycle with (*S*,*S*) configuration is generated.

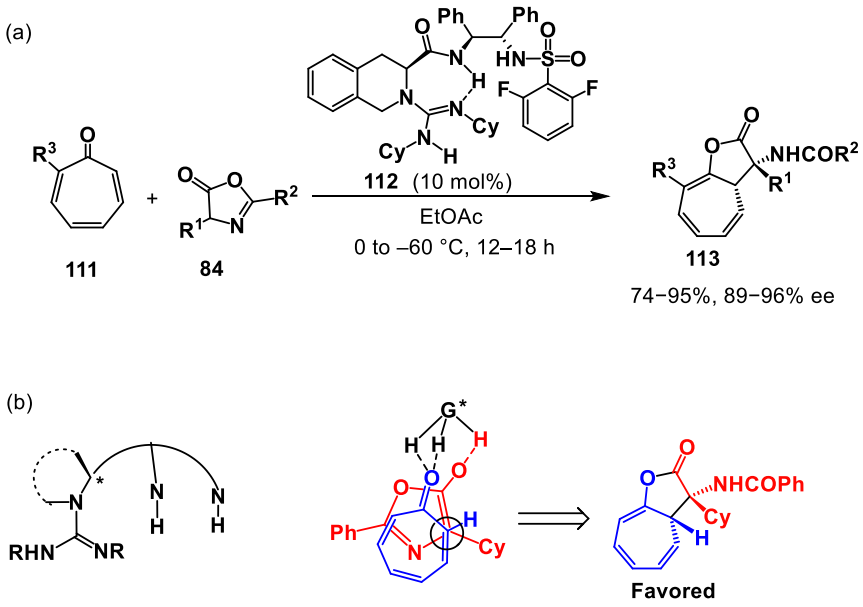
In the follow-up paper, Liu et al. applied a similar chiral guanidine amido catalyst for the asymmetric [4+2] cycloaddition reaction of azlactone **84** with 2-benzothiazolimine **108** (Scheme 21a) [44]. The mechanistic rationale for the high enantioselectivities is the multiple hydrogen-bonding role of the guanidinium catalyst, combined with the steric confinement provided by bulky substituents on the catalyst (Scheme 21b).



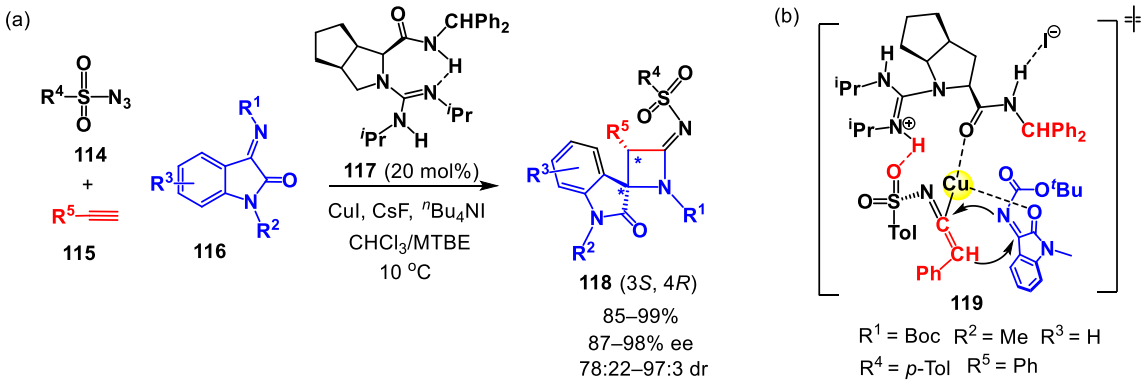
Scheme 21. (**a**) [4+2] cycloaddition reaction of azlactones with 2-benzothiazolimines; (**b**) multiple hydrogen-bonding of the guanidinium catalyst [44].

A guanidine chiral catalyst, similar to **107**, was used by Liu et al. in the organocatalytic stereoselective [8+2] cycloaddition of tropone **111** with azlactone **84** (Scheme 22a) [45]. High yields (up to 95%) and stereoselectivities (up to 96% ee) were achieved at sub-zero temperatures. This was presumably due to the bifunctional action of the guanidine organocatalyst **112**, which forms a triple hydrogen-bonded association intermediate (Scheme 22b). Here, two amide hydrogens bond to the oxygen of tropone **111**, while the third hydrogen bond forms with the oxygen of the azlactone enolate (Scheme 22b). The enolate intermediate then attacks tropone in a 1,8-conjugate addition, determining the stereochemical outcome. In the next reaction step, the oxygen anion of tropone attacks the carbonyl group of azlactone, affording lactone product **113**.

Liu et al. developed an efficient chiral guanidine-catalyzed asymmetric reaction of azide **114**, alkyne **115**, and isatin-derived ketimine **116** [46]. This [2+2] cycloaddition reaction led to the formation of the product, with two *S*-stereocenters formed in spiroazetidinimine oxindole **118** (Scheme 23a).



Scheme 22. (**a**) [8+2] cycloaddition of tropones with azlactones; (**b**) a triple hydrogen-bonded association intermediate. [45].

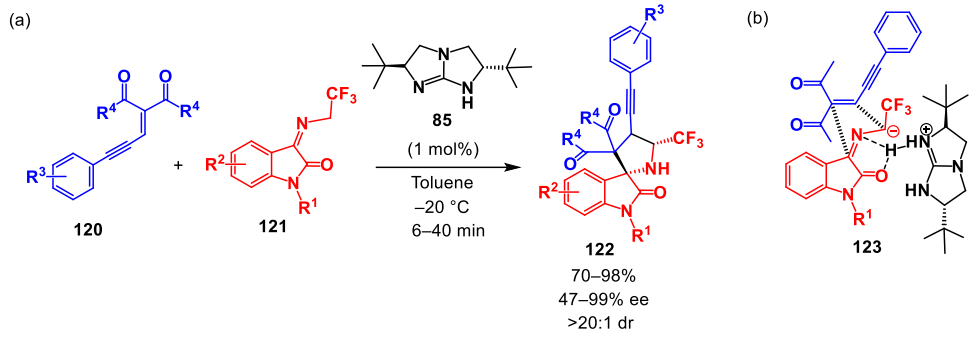


Scheme 23. (**a**) Asymmetric reaction of azides, alkynes, and isatin-derived ketimines; (**b**) the coordination complex **119**. [46,47].

DFT calculations at the BP86-D3(BJ)/def2-SVP level were carried out by Su et al. to elucidate the mechanism of this copper-catalyzed azide–alkyne cycloaddition (CuAAC)/stereoselective guanidine-catalyzed [2+2] cycloaddition cascade reaction [47]. The calculations indicate that, for the catalytic [2+2] cycloaddition reaction step that determines the stereochemical outcome, the most favorable orientation of the assembly of copper, tosyl ketenimine, and ketimine **116** with chiral guanidine catalyst **117** is depicted as **119** (Scheme 23b): the tosylate oxygen is hydrogen-bonded to guanidine, and the carbonyl group of the catalyst coordinates with the copper atom. This coordination complex, supported by the steric hindrance of the $CHPh_2$ group, plays a crucial role in controlling the stereoselectivity of the reaction toward the *SS* configuration.

A series of spiro[indoline-3,2′-pyrrolidine]s **122** were prepared by Yan et al. via an organocatalytic cycloaddition reaction of enynone unsaturated compound **120** and trifluoroethyl ketoimine **121** (Scheme 24a) [48]. At sub-zero temperatures, chiral spiro product **122** was prepared in high yields and with high stereoselectivity when chiral bicyclic guanidinium catalyst **85** was used at low loading (1%). The asymmetric synthesis of trifluoromethyl-containing products is presumably enhanced by the action of the guanidine base, which initially deprotonates the ketoimine and forms a hydrogen-bonded complex **123** (Scheme 24b). The in situ generated azomethine ylide, stabilized by the catalyst, then

undergoes a [3+2] dipolar cycloaddition with the enynone, forming the new pyrrolidine ring. The process occurs through *Si*-face addition, which is governed by the chiral catalyst.



Scheme 24. (**a**) Cycloaddition of enynone unsaturated compounds and trifluoroethyl ketoimines; (**b**) a hydrogen-bonded complex **123** [48].

Taken together, guanidine-catalyzed cycloaddition reactions demonstrate the unique ability of guanidines to serve as highly effective bifunctional organocatalysts. Their exceptional basicity, combined with multidentate hydrogen-bonding capability and conformational rigidity, enables the simultaneous activation and precise spatial organization of the reaction partners in the transition state. These physicochemical features are central to the high levels of stereocontrol observed in both single-step and stepwise cycloaddition pathways and continue to establish guanidines as promising motifs for the development of enantioselective cycloaddition catalysis.

5. Conclusions

Guanidines are a highly versatile class of compounds whose unique structural, electronic, and hydrogen-bonding properties support their broad utility in synthesis, catalysis, biology, and materials science. Recent advances demonstrate that cycloaddition chemistry provides a powerful and unifying strategy for both constructing guanidine-containing heterocycles and employing guanidines as reactive partners or catalysts.

Although the guanidine C=N unit is intrinsically resistant to cycloaddition due to strong N–C–N charge delocalization, appropriate activation through protonation, oxidation, or cation formation can transform guanidines into highly effective cycloaddition partners, heterodienes, or reactive synthons. In this context, the protonation state, counterion identity, and substitution pattern are decisive factors that determine whether cycloaddition pathways are favored or diverted toward competing stepwise processes such as aza-Michael addition or cascade reactions.

Equally important is the role of guanidines as organocatalysts, where their high basicity combined with multidentate, hydrogen bonding enables precise transition-state organization and high stereocontrol in cycloadditions. While many of the reviewed methodologies exhibit impressive scope and selectivity, limitations related to substrate class, protection requirements, and reaction conditions remain. Overall, a deeper understanding of how guanidine structure controls cycloaddition behavior provides a rational foundation for further methodological development and the design of new guanidine-containing systems in synthesis, catalysis, and materials science.

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Data Availability Statement: The data presented in this study is available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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