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# Formal Cycloadditions Driven by the Homolytic Opening of Strained, Saturated Ring Systems

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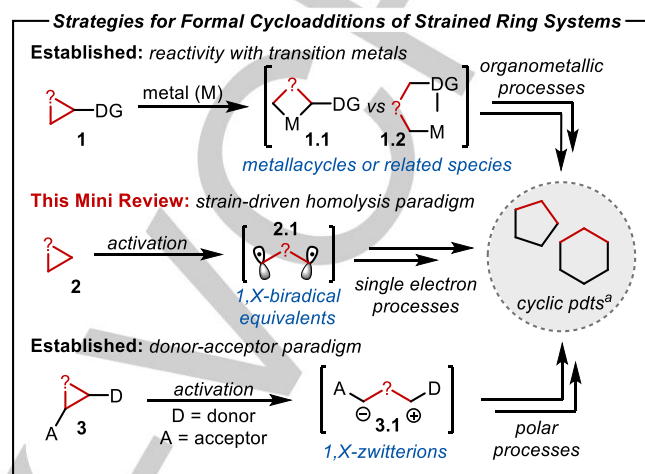
**Abstract:** The field of strain-driven, radical formal cycloadditions is experiencing a surge in activity motivated by a renaissance in free radical chemistry and growing demand for  $sp^3$ -rich ring systems. The former has been driven in large part by the rise of photoredox catalysis, and the latter by adoption of the “Escape from Flatland” concept in medicinal chemistry. In the years since these broader trends emerged, dozens of formal cycloadditions, including catalytic, asymmetric variants, have been developed that operate via radical mechanisms. While cyclopropanes have been studied most extensively, a variety of strained ring systems are amenable to the design of analogous reactions. Many of these processes generate lucrative, functionally decorated  $sp^3$ -rich ring systems that are difficult to access by other means. Herein, we summarize recent efforts in this area and analyze the state of the field.

## 1. Introduction

Cycloadditions (CAs) are an ideally convergent approach to the *de novo* synthesis of rings. While the concerted nature of pericyclic (i.e., “true”) CAs provides unrivaled stereo-control, stepwise “formal” cycloadditions (FCAs) find their worth in the complementary chemical space accessible through such mechanisms. For example, many FCAs lead to saturated carbocyclic systems, such as cyclopentanes, which are poorly accessible by pericyclic processes. These  $sp^3$ -rich motifs have in recent years drawn increased attention from medicinal chemists as they seek to “Escape from [the pharmacokinetic liabilities associated with  $sp^2$ -rich] Flatland.”<sup>[1]</sup>

FCAs typically proceed through the generation of a reactive intermediate from one of two otherwise inert functional groups. This species can engage the other to produce an adduct that ultimately cyclizes. Strain-release of small, saturated ring systems is an established strategy for accessing such intermediates (Figure 1). Reaction with transition metals, for instance, can yield metallacycles capable of FCA.<sup>[2]</sup> Heterolytic activation, exemplified by “donor-acceptor” cyclopropanes, generates zwitterions that tend to undergo FCA with polarized  $\pi$  systems.<sup>[3]</sup>

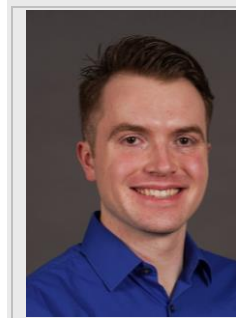
In contrast, strained species within the scope of this minireview behave as formal 1,*n*-biradical equivalents – arguably the most intuitive bond disconnection of a strained ring. However, until the turn of the 21<sup>st</sup> century, few homolytic ring openings had been exploited for FCA, perhaps due to the challenges associated with developing redox-neutral single-electron processes. Indeed, most earlier examples of these reactions from the mid-20th century featured the harsh thermal homolysis of esoteric, highly strained systems.<sup>[4]</sup> The invention of milder methods of radical generation has since allowed strain-driven radical FCA to mature into a synthetically valuable approach.



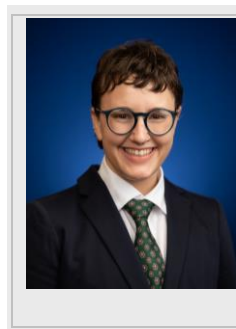
**Figure 1.** Scope of minireview; <sup>a</sup>ptds = products

In this minireview, we aim to succinctly examine the current scope of ring systems employed in FCA across a broad range of radical-generation strategies and identify opportunities for the development of new and useful methodology.<sup>[5, 6]</sup>

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Bec J. Roldan was born in Patterson, NJ, USA, in 1997 and raised in rural Louisiana. They received their BS (Chemistry with Honors) from Rhodes College in 2019, where they performed research in the lab of Dr Larry Peterson. They are currently a 4<sup>th</sup> year PhD candidate in Professor Corey Stephenson's lab. Bec's research interests include leveraging radical chemistry in the synthesis of complex molecules and strained ring systems.



Corey Stephenson, born in Collingwood, Ontario, Canada, received his undergraduate degree from the University of Waterloo in 1998. He completed graduate studies under the direction of Professor Peter Wipf at the University of Pittsburgh before joining the lab of Professor Erick M. Carreira at ETH Zürich. In 2007, he joined the Department of Chemistry at Boston University and was promoted to Associate Professor in February 2013. In July 2013, he moved the lab to the University of Michigan, where in September 2015, he was promoted to Full Professor.



## 2. The $\beta$ -scission approach

Most modern, strain-driven, radical FCAs proceed through the initial generation of radical character adjacent to the strained ring.  $\beta$ -scission yields a species containing a radical moiety that is easily engaged by  $\pi$  bonds of the appropriate radicophilicity to produce radical adducts (Figure 2A). These adducts cyclize onto their remaining  $\pi$  bond or open-shell atom.

This strategy is rife with inherent selectivity challenges. Depending on the symmetry of the strained substrate employed, up to 3 (typically reversible) inequivalent  $\beta$ -scission events can occur (Figure 2B). Any existing stereocenters at the termini of the scissile bond are ablated. The radical addition leads to loss of  $\pi$  bond geometry and can produce regioisomeric mixtures. As an added complication, the radical addition and cyclization often generate new stereocenters. While catalyst control and condition optimization can address some aspects of selectivity, thoughtful substrate choice remains the most common strategy to avoid complex mixtures. The methods discussed in this section are organized firstly by the atom of the activating functional group directly attached to the strained ring, and secondly by the specific activating functionality. Though this minireview emphasizes recent developments, earlier seminal examples are noted.

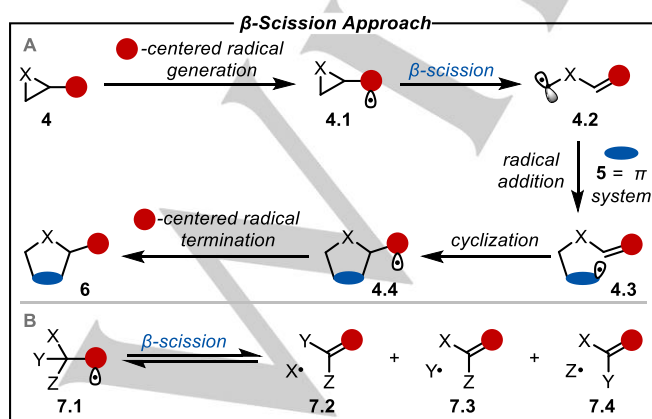


Figure 2. Mechanistic aspects of  $\beta$ -scission FCA strategy

### 2.1. Sulfur

In an early example of an oxidatively-driven strained-ring FCA, Iwata and coworkers reported an intramolecular reaction of cyclopropyl sulfides with tethered alkenes promoted by substoichiometric amounts of the oxidant Magic Blue (Figure 3A).<sup>[7]</sup> To explain the “catalysis” by the oxidant, the authors proposed a chain mechanism wherein the product radical cation oxidizes another molecule of cyclopropyl sulfide. Following Iwata’s work, Itoh, Nakamura, and coworkers reported analogous reactivity with cyclopropenone thioetals (Figure 3B).<sup>[8]</sup> However, diminished yields in the absence of the sacrificial reductant suggested an inefficient chain propagation. Since these two publications, the attention of FCA developers has shifted away from sulfur-substituted strained rings. However, many common features of these early methods are shared by oxidatively-driven FCAs of N-substituted strained rings.

### 2.2. Nitrogen: anilines

Like cyclopropyl sulfides and dithianes, cyclopropylanilines are easily oxidized to give unstable radical cations. Early FCAs of cyclopropylanilines focused on reaction with  $O_2$  to generate 1,2-dioxolanes.<sup>[9]</sup> The charge towards carbocycle synthesis was led by Zheng and coworkers, who in 2012 reported a photocatalytic (3+2) approach to cyclopentylanilines (Figure 4).<sup>[10]</sup> Activated alkenes such as styrenes gave high yields, but modest diastereoselectivities in most cases. Later experiments established that the reaction proceeds to some extent via a chain mechanism.<sup>[11]</sup>

Zheng has also shown that activated alkynes react similarly, albeit more slowly than the corresponding alkenes.<sup>[12]</sup> Enynes and diynes are likewise tolerated (Figure 4).<sup>[13]</sup> Waser expanded the scope of cyclopropylaniline FCAs to include cyclopropenes (Figure 5).<sup>[14]</sup> Cyclobutylanilines, too, react with activated alkenes and alkynes via F-(4+2)-CA.<sup>[15]</sup> Benzocyclobutylanilines open regioselectivity to give benzylic radicals, which react with alkynes to achieve FCA. However, the cycloadducts generated are unstable 1,4-dihydronaphthalenes, which eliminate aniline to form naphthalenes.<sup>[16]</sup>

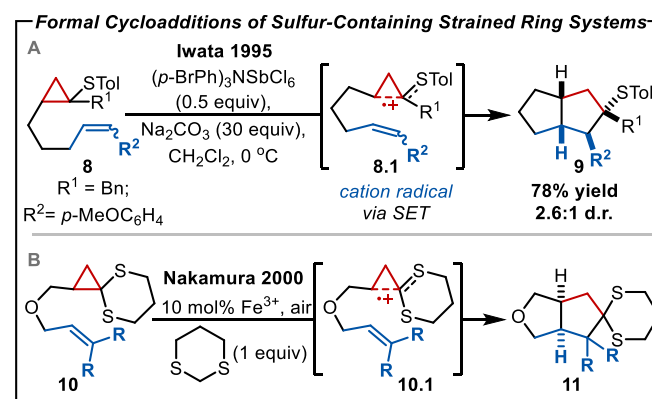
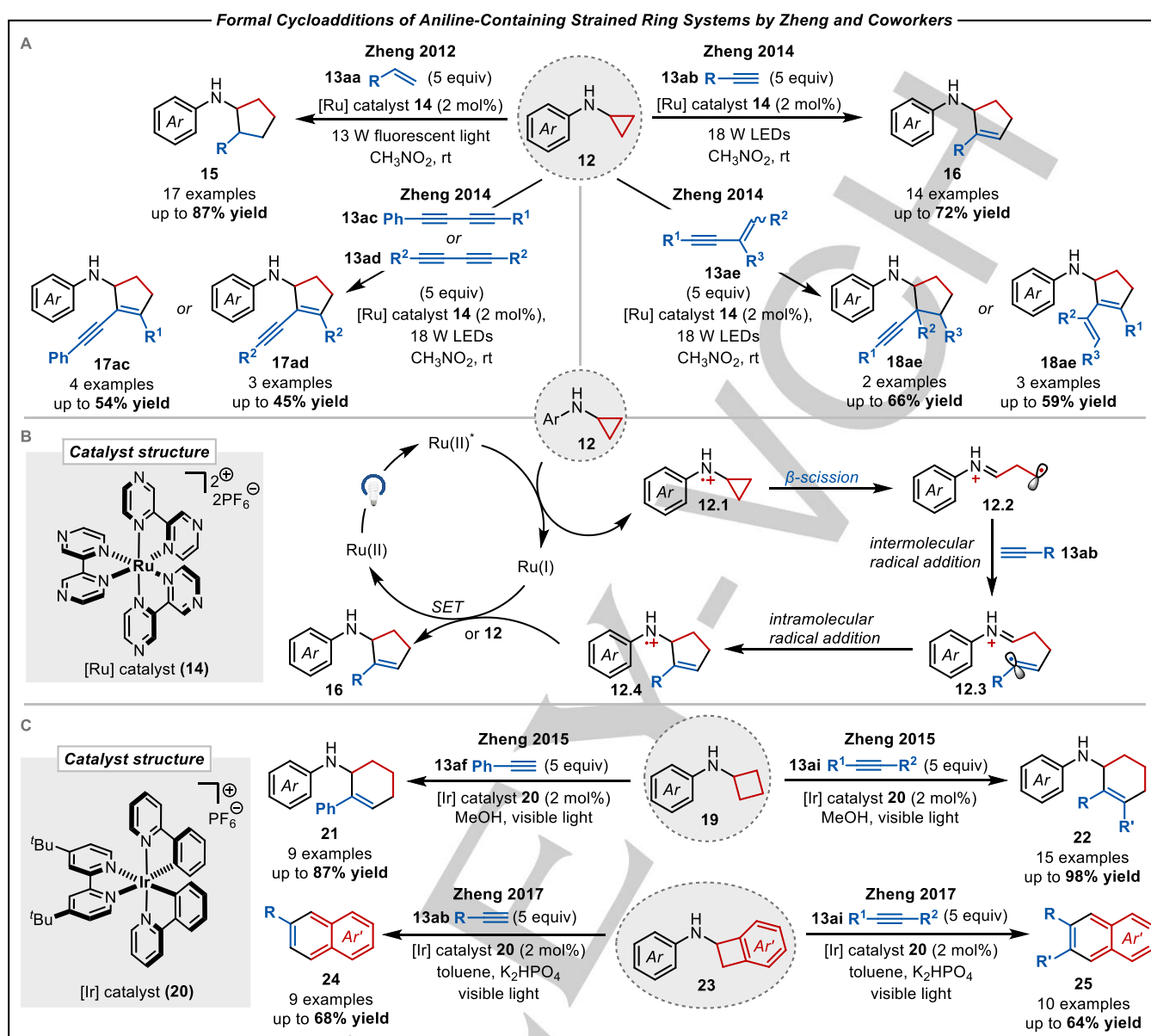


Figure 3. Oxidatively-driven synthesis of sulfur-containing 3.3.0 systems



**Figure 4.** Oxidatively-driven FCA of strained-ring aniline systems

In a deviation from the photoredox approach, Zheng, Zare, Chen, and coworkers reported that FCA of cyclopropylanilines and alkynes can be triggered by electrochemical oxidation.<sup>[17]</sup>

In 2022, Barriault described the *direct* photochemical FCA of cyclopropyl- and cyclobutylanilines with alkenes (Figure 5). While  $\alpha$ - $\beta$  unsaturated carbonyls were mainly used, styrene was also effective, reacting with cyclopropylaniline in 84% yield. Such uncatalyzed reactivity with styrene had been observed by Zheng and coworkers, albeit in modest yields.<sup>[23]</sup> The mechanism of N-centered radical generation remains ambiguous.

Catalytic, asymmetric approaches have also been disclosed. Huang, Jiang, and coworkers, for example, employed a chiral Brønsted acid catalyst **30** in the oxidatively-driven reaction of cyclopropylanilines with vinyl heteroarenes (Figure 5).<sup>[20]</sup> The observed asymmetric induction does not involve the photocatalytic cycle, but instead requires the catalyst protonate a vinyl heteroarene molecule, activating it for radical addition relative to the unprotonated bulk. Ideally, only this catalyst-bound material undergoes the downstream enantiodetermining cyclization step, the facial selectivity of which is controlled by H-bonds with the catalyst. Zhao, Cao, Jiang, and coworkers have

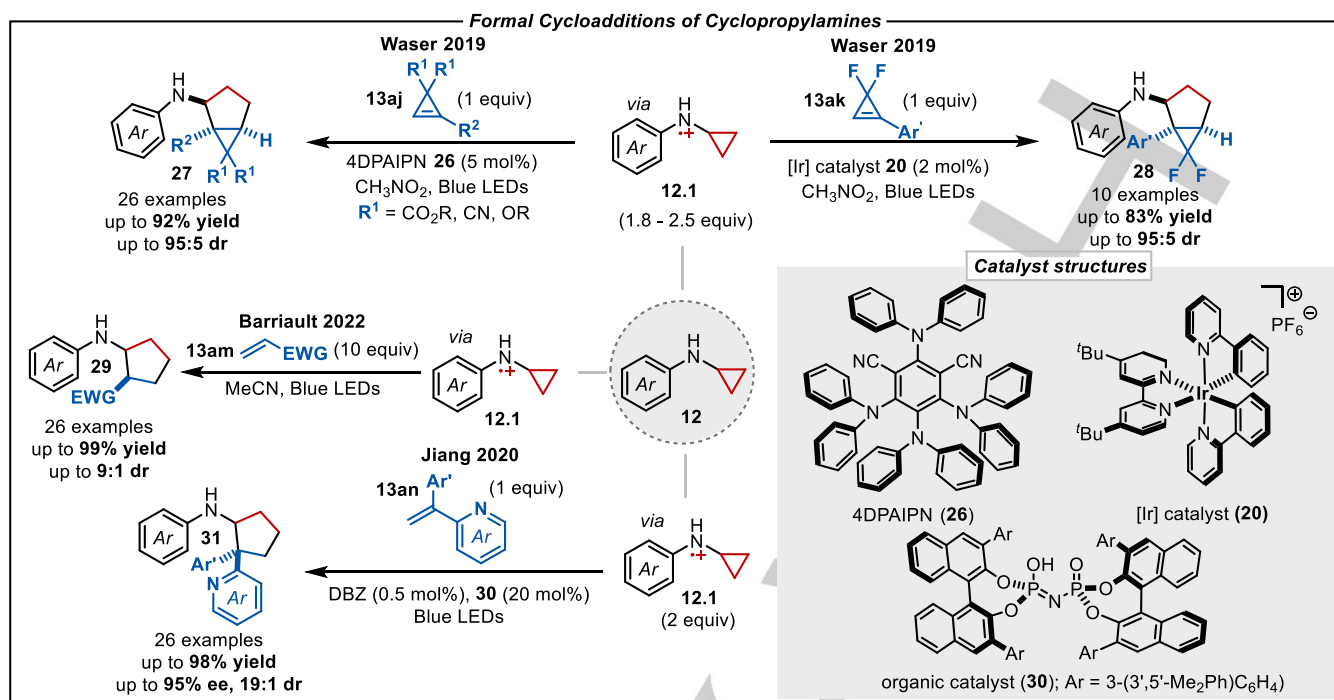


Figure 5. Oxidatively-driven FCA of strained-ring aniline systems

since reported an analogous approach using a chiral phosphoric acid catalyst.<sup>[21]</sup>

Frailé and Aleman showed that chirality at a Rh photocatalyst's metal center can also lead to asymmetric (3+2)-CA of cyclopropylanilines with bidentate, imidazole-containing enones, though the alkene scope is limited by the transient chelation

requirement (Figure 6).<sup>[22]</sup> Though electron transfer occurs in the outer sphere, the enantiodetermining radical addition occurs near the metal. In the subsequent cyclization, the established C3 stereocenter dictates the stereochemistry at C2, but not at C1.

Wang and coworkers have shown that cyclopropylanilines undergo FCA with activated alkenes, alkynes, enynes, and diynes in the presence of dinuclear Rh complexes (Figure 6). The authors propose coordination to rhodium facilitates N-H homolysis, and that the reaction proceeds through a chain hydrogen atom transfer (HAT) mechanism.<sup>[18]</sup> Despite employing chiral ligands, only racemic products were observed.

Cyclopropylaniline F-(3+2)-CAs based on chiral auxiliaries are also known. For example, alkenes with a chiral diazaborolidine substituent give excellent *d.r.* under Zheng's conditions and can be oxidized to give enantioenriched alcohols.<sup>[19]</sup>

### 2.3. Nitrogen: miscellaneous

The amine oxidation approach to FCA is not limited to anilines. Indeed, the earliest work in the area was focused on

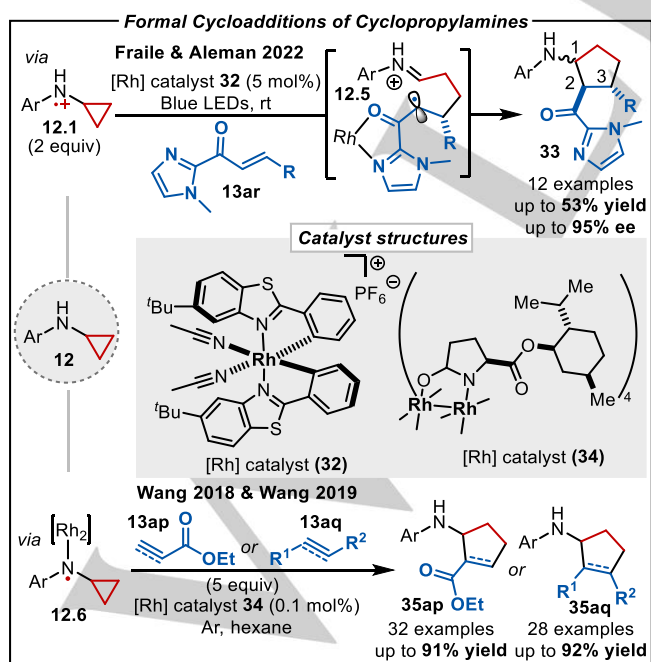


Figure 6. Rh-promoted FCAs of cyclopropylanilines

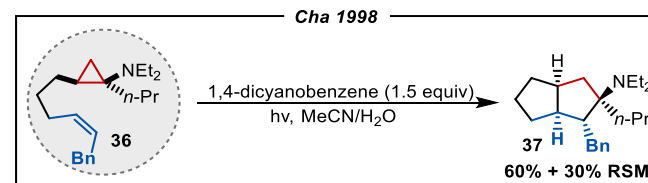
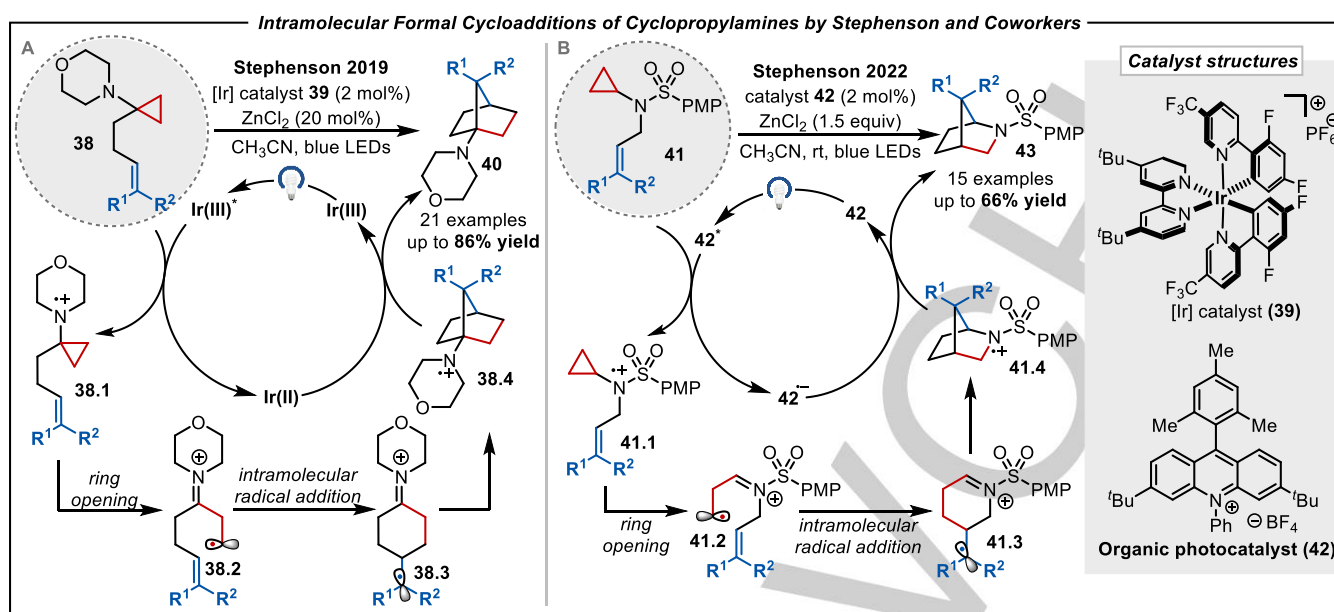


Figure 7. Early trialkylamine FCA



**Figure 8.** Photoredox FCA approaches to bicyclic amines

with Cha in 1998 (Figure 7) reporting intramolecular F-(3+2)-CAs of cyclopropylamines with “ $\beta$ ”-tethered alkenes/alkynes to generate [3.3.0] fused systems, in analogy to Iwata’s earlier cyclopropyl sulfide work (*vide supra*, Figure 3).<sup>[24]</sup>

In 2019, our lab reported a photoredox approach to intramolecular FCA of trialkyl cyclopropylamines with “ $\alpha$ ”-tethered alkenes **38** (Figure 8A).<sup>[25]</sup> Lewis acid additives, which lower the oxidation potential of the starting material, led to improved yields. In the same vein, our group has disclosed a FCA route to 2-azanorbornanes **43** using a strongly oxidizing organic photocatalyst **42** (Figure 8B).<sup>[26]</sup> Sulfonamides of cyclobutylamine also undergo the latter transformation, albeit in lower yield.

While tertiary sulfonamides are challenging to oxidize, sulfonamide anions are readily oxidized to neutral, N-centered radicals. Booker-Milburn and Aggarwal took this approach to the F-(3+2)-CA of secondary sulfonamides with electron-deficient alkenes (Figure 9A).<sup>[27]</sup> The *trans* selectivity observed is attributed to repulsions in an *anionic* 5-*exo*-*trig* cyclization following radical/polar crossover. Analogous (3+2)-CA reactivity has since been achieved by Banerjee and coworkers through the electrochemical oxidation of sulfonamide anions, via the same proposed mechanism (Figure 9A).<sup>[28]</sup> A single example involving an alkyne, ethyl propiolate, was included.

Secondary sulfonamides were also employed as activating groups for FCA by Verma and Reiser under Cu<sup>I</sup>-catalysis. (Figure 9A).<sup>[29]</sup> The authors propose that an in-situ generated Cu<sup>I</sup> sulfonamide undergoes photo-assisted dissociative ligand to metal charge transfer (LMCT), generating the requisite N-centered radical.  $\beta$ -scission and addition to Cu<sup>I</sup> gives a Cu<sup>I</sup> alkyl, which can undergo migratory insertion into an alkene. Subsequent migratory insertion into the N-sulfonyl imine occurs with exquisite *trans* selectivity.

Ooi and coworkers have exploited the anion-binding ability of cyclopropylureas **49** to encourage pre-organization with a racemic photoactive cation and its single-enantiomer counterion (Figure 9B).<sup>[30]</sup> Excitation of the cation leads to oxidation of the anion-bound urea, forming a radical ion pair that undergoes rapid ring opening and FCA. Urea hydrolysis reveals a primary amine group without e.e. erosion, albeit under harsh conditions.

Reductively-driven FCA of nitrogen-substituted strained rings is also possible. Lu reported the F-(3+2)-CA of nitro cyclopropanes **52** with activated styrenes and dienes via photoredox catalysis (Figure 9C). Triethylamine serves as the reductive quencher, and the resulting Ru<sup>I</sup> reduces the nitro group to a radical anion (proposed to be stabilized by Li<sup>+</sup>), triggering the FCA cascade.<sup>[23, 31]</sup>

#### 2.4. Nitrogen: imines

All approaches described above involve the formation of a species with discrete radical character through electron-transfer events. However, FCA processes are redox-neutral, and electron transfer is not a prerequisite for such reactivity.

Sampedro and coworkers have shown that upon irradiation with ultraviolet light, cyclopropylamine-derived imines **55** can open to give biradicals that close to give 1-pyrrolines (Figure 10A).<sup>[32]</sup> Our group has demonstrated the capture of such biradicals with alkenes to achieve F-(3+2)-CA, both intra- and intermolecularly. Intramolecular reaction with “ $\alpha$ ”-tethered alkenes followed by mild imine hydrolysis provided benzo-fused 1-aminorbornanes **59** (Figure 10B).<sup>[33]</sup> This behavior contrasts with that observed by Yasui and Yamamoto, who report that analogous cyclopropanol substrates **61**, when subjected to an HAT catalyst, undergo only 1 cyclization.<sup>[34]</sup> On the other hand, we showed that 1-aminorbornanes can be converted to 1-hydroxynorbornanes **60**, which to date have not been directly accessed by FCA. This

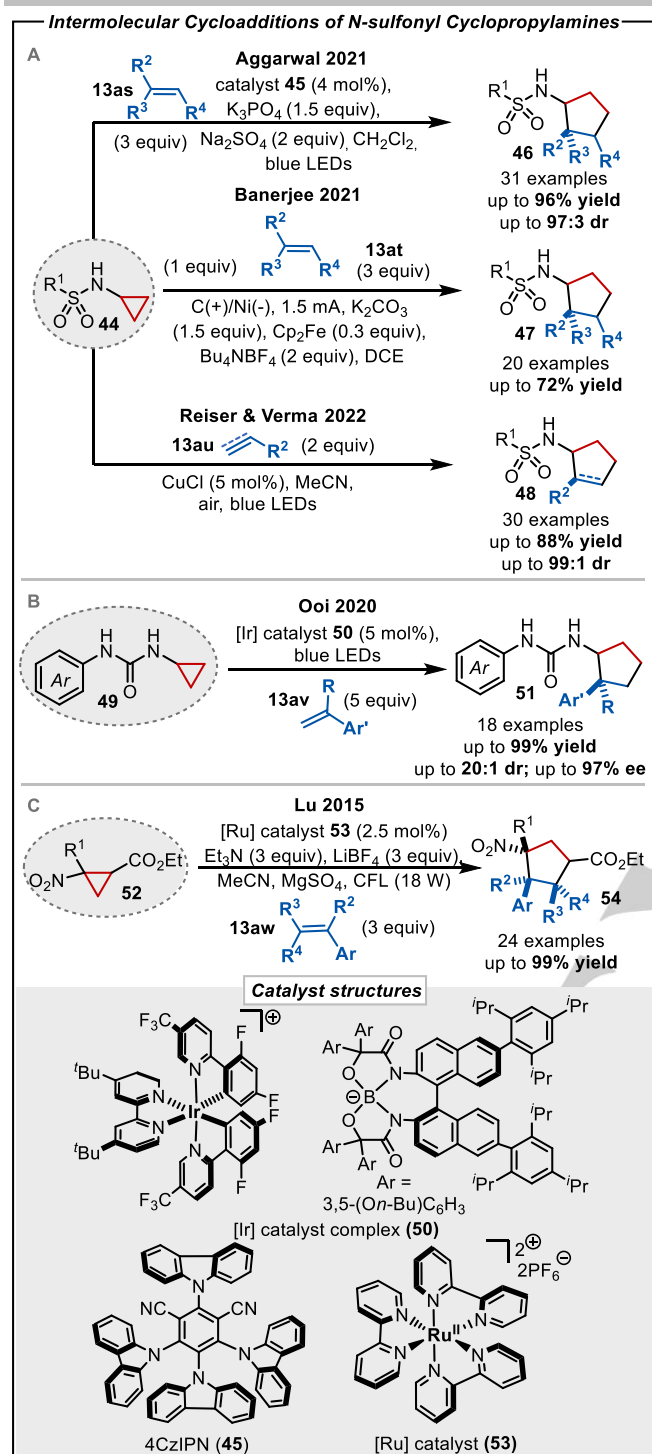


Figure 9. FCAs of sulfonamides and ureas

is a testament to the importance of open-shelled atom identity and radical generation strategy to route design involving FCA.

In the intermolecular variant of the reaction, activated alkenes such as styrenes and acrylonitriles were required to compete with background 1-pyrroline formation (Figure 10C).<sup>[35]</sup> While FCA gave good yields, particularly when followed by a one-pot solvolysis and acylation sequence, low *d.r.* was observed in all cases. Though initial efforts to expand the scope to

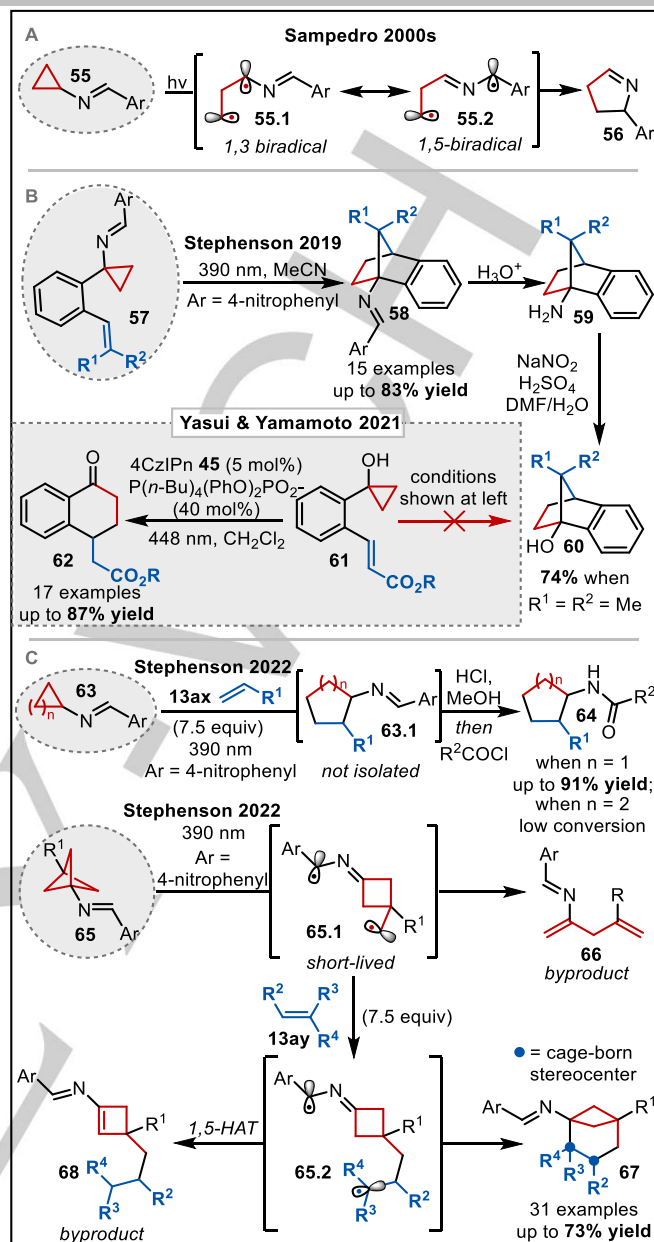


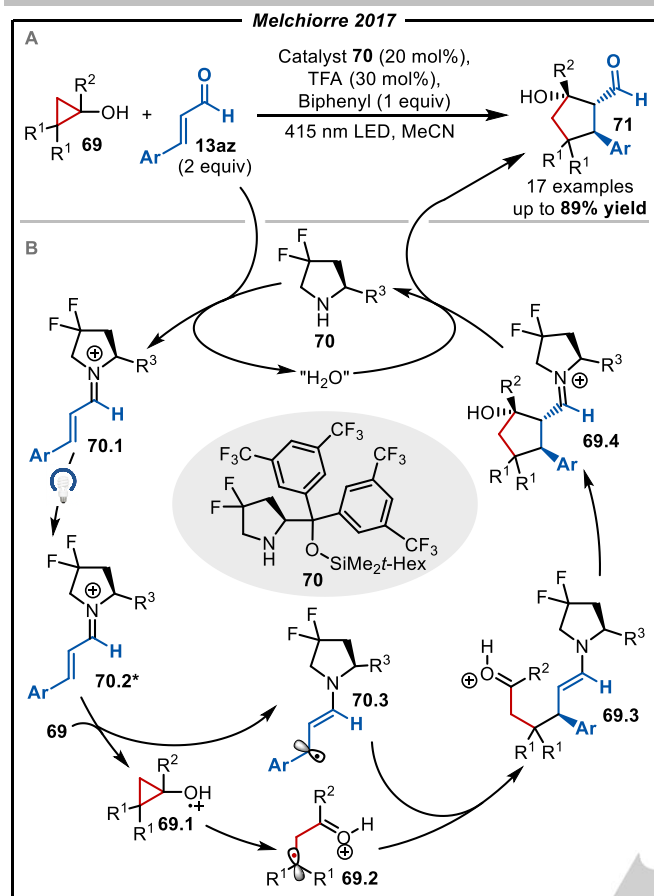
Figure 10. FCAs of imines

cyclobutylimines were unfruitful due to slow conversion, the approach is not limited to cyclopropanes. We have shown that imines derived from bicyclo[1.1.1]pentan-1-amines **65** undergo analogous intermolecular reactivity with alkenes to yield bicyclo[3.1.1]heptan-1-amine derivatives **67**, though the short lifetime of **65.1** further limits the alkene scope (Figure 10C).<sup>[36]</sup> **65.2** can also divert from the productive pathway via competitive 1,5-HAT.

## 2.5. Oxygen: O-H

The FCA chemistry of strained alcohols is limited by the extreme propensity of alkoxy radicals on medium-sized rings to undergo  $\beta$ -scission. This strongly disfavors the cyclization step of FCA. However, several methods have been reported that exploit or bypass this phenomenon. In neither case is the reversible



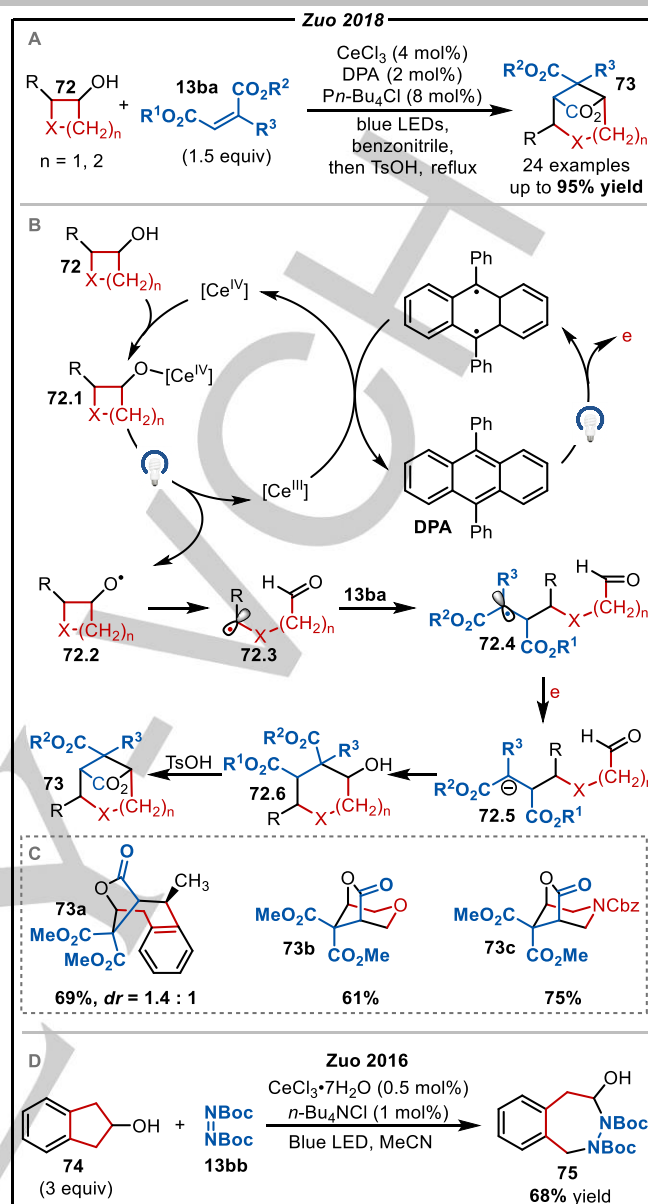


**Figure 11.** Asymmetric organocatalytic FCA

cyclization of a radical onto a carbonyl invoked in the proposed mechanism.

For instance, Melchiorre reported a F-(3+2)-CA of cyclopropanols catalyzed by a secondary amine, which is proposed to condense with a colorless aldehyde to form colored iminium ion **70.1** (Figure 11B).<sup>[37]</sup> The iminium ion is excited to a strongly oxidizing excited state, which is reduced by the cyclopropanol starting material.  $\beta$ -scission of **69.1** ablates the cyclopropanol's stereocenter and produces **69.2**. Combination of the **70.3** and **69.2** sets the first stereocenter, then intramolecular aldol reaction sets the rest. Hydrolysis of the resulting iminium ion turns over the catalyst.

Zuo and coworkers have reported FCA of 4- and 5-membered cyclic alcohols, including heterocycles, with alkenes (Figure 12).<sup>[38]</sup> The reported alkene scope is, however, limited to maleates. The authors propose the cerium alkoxide **72.1** generated *in situ* can be homolyzed on exposure to visible light, generating **72.2** via LMCT.  $\beta$ -scission produces **72.3**, which can add to the maleate. Reduction of **72.4** produces **72.5**, which can undergo intramolecular aldol reaction. Substituted anthracene serves as a photoinduced electron transfer catalyst. In cases where several diastereomers were possible, low selectivity was observed (Figure 12C). Zuo has shown that cycloalkanols react with di-*tert*-butyl azodicarboxylate by an analogous, anthracene-free mechanism (Figure 12D).<sup>[39]</sup>



**Figure 12.** LMCT-based FCA strategies

## 2.6. Carbon: C-X

C-X bond reduction via photoredox catalysis has been widely employed for C-centered radical generation in redox-neutral atom transfer radical addition (ATRA) reactions. Li and Yao drew analogy to such ATRA reactions in the development of an FCA method using **76** (Figure 13). Though polarity-matched electron-rich alkenes were top performers, the addition of Zn(OAc)<sub>2</sub> enhanced the electrophilicity of dicarbonyl radical intermediate, allowing variety of unactivated alkenes and alkynes to also be tolerated.<sup>[40]</sup>

## 2.7. Carbon: C=C/alkyne

In the 1990s, Singleton published a series of papers describing the FCA of alkenes/alkynes with methylenecyclopropanes **79** catalyzed by thiyl or stannyl radicals via a "radical covalent

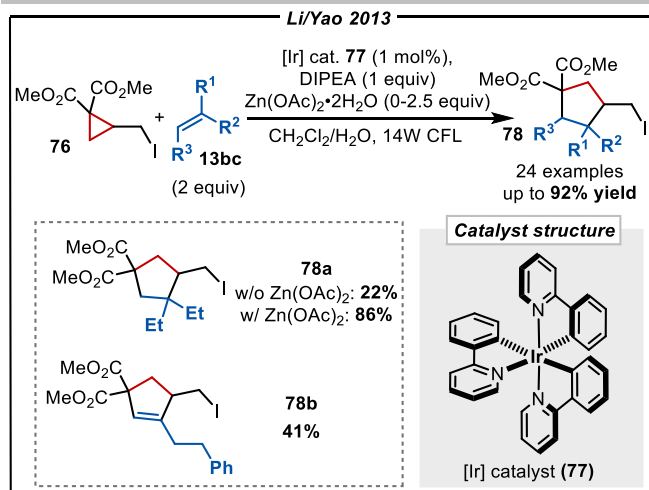


Figure 13. ATRA-type FCA

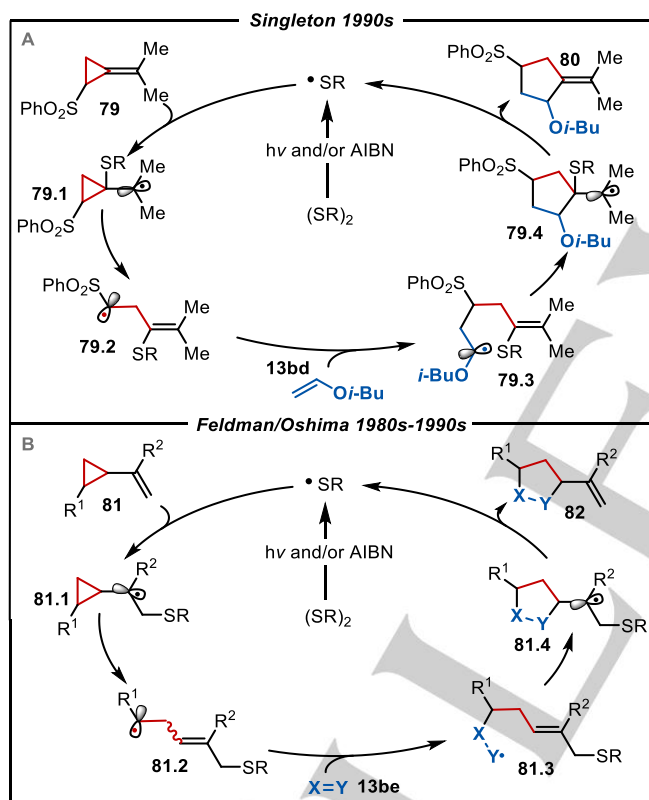


Figure 14. Early FCAs via radical covalent catalysis

catalysis" (Figure 14A).<sup>[41]</sup> Around the same time, Feldman and Oshima independently reported the thiol radical-catalyzed FCA of alkenes/alkynes/O<sub>2</sub> with vinylcyclopropanes (Figure 14B).<sup>[42]</sup>

The last decade has seen a resurgence in the publication of FCAs involving radical covalent catalysis. Vinylcyclopropanes with geminal dicarbonyl substitution have been preferred in recent years. Upon addition of the catalyst, these substrates reliably open to give electron-deficient radicals, allowing for a

polarity match with electron-rich (and sometimes with unactivated) alkenes for the radical addition step.

Maruoka and coworkers took this approach in designing chiral thiol catalyst **84** that leads to vinylcyclopentanes **85** in good *d.r.* and *e.e.* (Figure 15A).<sup>[43]</sup> Cyclization, the enantio-determining event, occurs at a great distance from the sulfur atom, so the catalyst was made to extend far towards the reactive alkene center. Maruoka has reported analogous racemic reactivity with 2-vinyl-N-tosylaziridines (**94**), which open to give electron-deficient N-centered radical intermediates that "match" with electron-rich alkenes (Figure 15B).<sup>[44]</sup> Miller has likewise achieved enantioselective vinylcyclopropane FCA with thiol catalyst **86** generated from small, disulfide-bridged peptides (Figure 15A).<sup>[45]</sup>

Miyake and coworkers have shown that Br·, generated from cinnamyl bromide via energy transfer (EnT) catalysis, also catalyzes the FCA of vinylcyclopropanes and alkenes (Figure 15A).<sup>[46]</sup> However, the Br atom exerts little stereochemical influence, and the process is thus poorly diastereoselective.

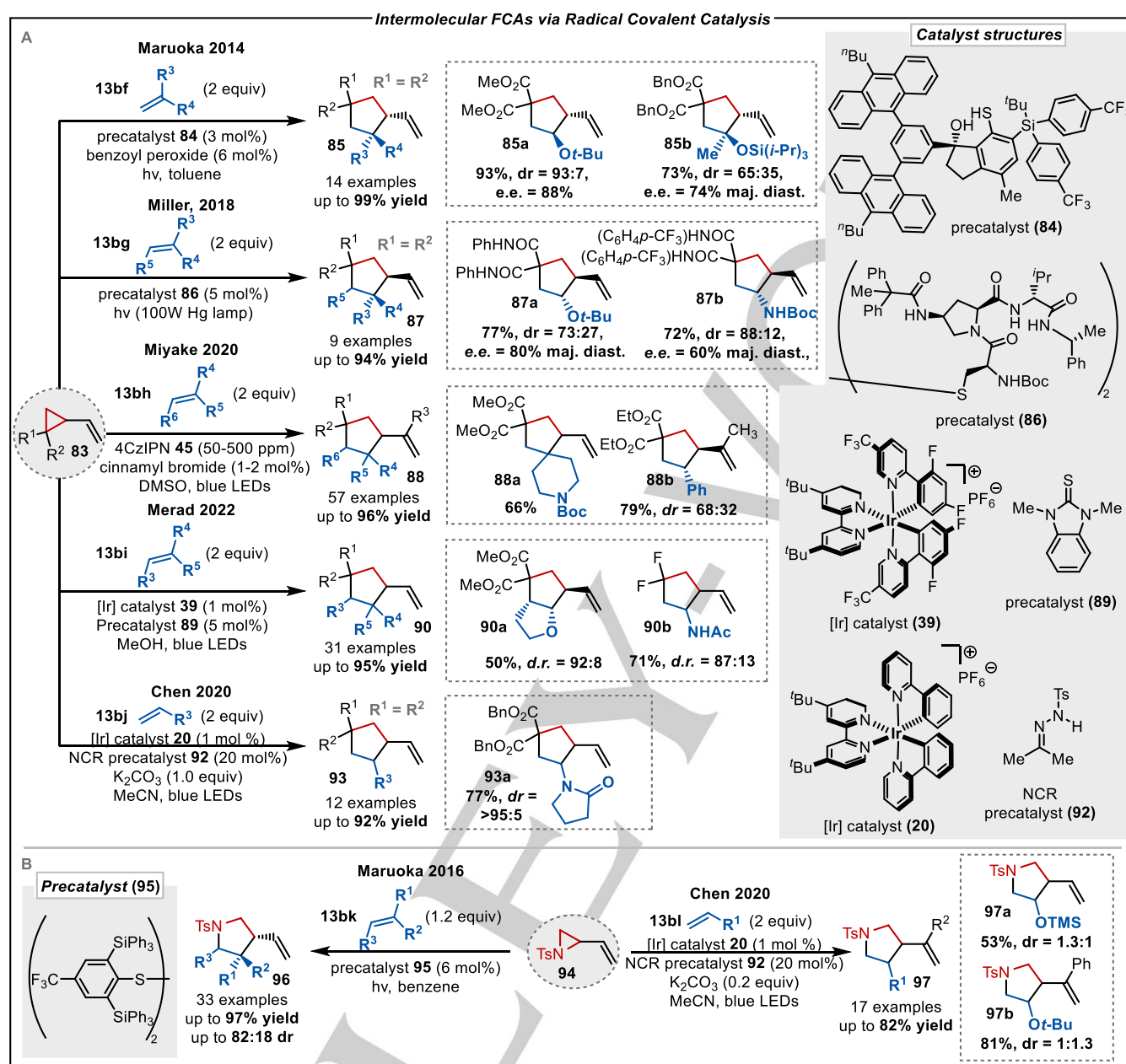
Isothiouroyl radical cations are also effective catalysts for vinylcyclopropane/alkene FCA.<sup>[47]</sup> While most cyclopropanes substrates studied bore the privileged dicarbonyl motif, several more medchem-relevant examples were reported. For example, reaction of 1-vinyl-2,2-difluorocyclopropane with N-vinylacetamide gave **90b** in 71% yield. The work is further distinguished by the ease of library generation for potential thiourea precatalysts, and Merad and coworkers allude to the study of chiral variants. Chen has reported that N-centered radical catalyst **92**, generated using a visible-light absorbing photosensitizer, can similarly catalyze the FCA of vinylcyclopropanes (**83**) and 2-vinylaziridines (**94**) with alkenes (Figure 15A-B).<sup>[48]</sup>

Triplet sensitization of vinylcyclopropanes can also be exploited for intermolecular FCA. Opatz recently reported such an FCA with arylacetylenic sulfones, proposed to operate via EnT catalysis (Figure 16).<sup>[49]</sup> The process is promoted by photocatalysts with a wide range of triplet energies, including some with significantly lower triplet energies than the substrate. To reconcile the apparent endergonicity of EnT (up to ~10 kcal/mol), the authors proposed a "concerted" EnT/ring-opening process, which is net exergonic and produces an intermediate unlikely to undergo back-EnT. This counterintuitive result highlights the power of strain-driven homolysis in reaction design.

FCA has also been achieved using aryl-substituted cyclopropanes, though this area is less developed. For instance, Yoon and coworkers showed the oxidation of electron-rich cyclopropyl arenes (**100**) leads to distonic radical cations (**100.1**) capable of engaging in F-(3+2)-CA with O<sub>2</sub> (Figure 17).<sup>[50]</sup>

## 2.8. Carbon: C=O

In 2011, Yoon and coworkers reported an intramolecular FCA of cyclopropyl phenyl ketones with olefins operating via photoredox catalysis (Figure 18A).<sup>[51]</sup> Intermolecular racemic and asymmetric variants of the reaction were limited in alkene scope to activated alkenes such as styrenes, dienes, and enamines (Figure 18C).<sup>[52]</sup> The proposed mechanism mimics Yoon's seminal photoredox-mediated F-(2+2)-CA and is shared by Lu's



**Figure 15.** Modern approaches to FCA via radical covalent catalysis

nitrocyclopropane FCA (*vide supra*, Figure 9C).<sup>[31, 53]</sup>

When attempting to replace the olefin reactant with an N=N species, Yoon found deleterious side-reactivity associated with the tertiary amine reductive quencher.<sup>[54]</sup> An N-methylimidazole redox auxiliary (**13bp**) was introduced to circumvent the need for an amine additive, a strategy that had previously been demonstrated in the F-(2+2)-CA context (Figure 18C).<sup>[55]</sup>

While Yoon's methods involve outer sphere electron transfer, Meggers and coworkers developed a diastereo- and enantioselective FCA featuring direct photo-induced metal to ligand charge transfer from a stereogenic rhodium center to a reversibly ligated cyclopropyl ketone (Figure 19A).<sup>[56]</sup> Following

$\beta$ -scission, radical addition to alkenes or alkynes, and cyclization, turnover is achieved by LMCT and dissociation of the product.

The reversible reduction of carbonyls can also be achieved thermally via metal-based "radical relay" strategies. Lin and coworkers have shown that a Ti<sup>III</sup> species can coordinate with strained-ring carbonyl compounds and engage in charge transfer to induce  $\beta$ -scission (Figure 19). The process was first accomplished with acyl aziridines (**123**) to generate Ti<sup>IV</sup> distonic radical anions (**123.2**), which react with activated alkenes, such as styrenes, acrylates, and acrylamides (Figure 19C).<sup>[57]</sup> Following cyclization, Ti<sup>III</sup> dissociates to close the catalytic cycle. Lin translated the same reactivity mode to ketones and rendered the reaction enantioselective using chiral

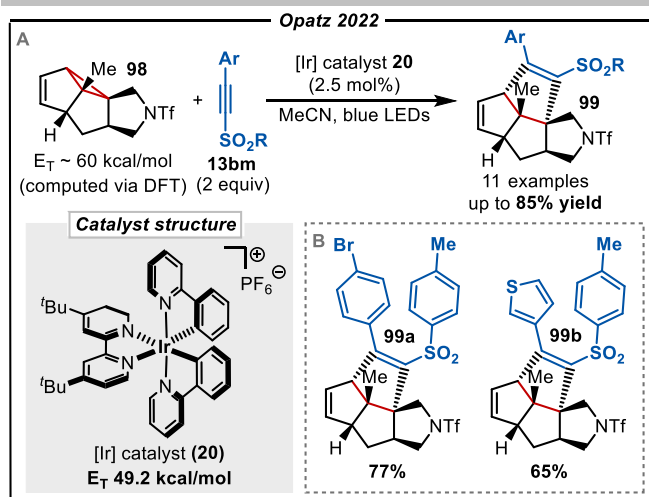


Figure 16. FCA via triplet alkene

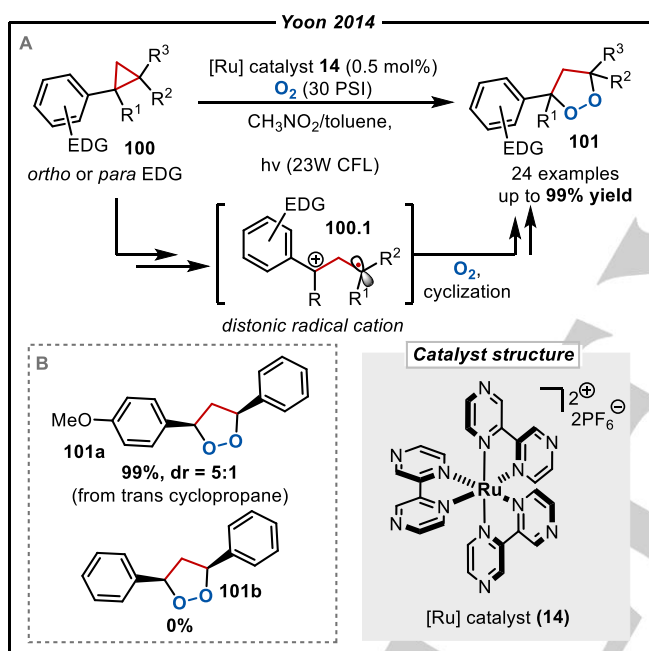


Figure 17. FCA via arene oxidation.

Ti complex **119** (Figure 19B).<sup>[58]</sup> To address the low enantioselectivity observed for certain substrates, Lin and Sigman used computational transition state modeling and multivariate linear regression statistical modeling to achieve substantial enantioselectivity improvements via minor ligand modifications (**120**, Figure 19B).<sup>[59]</sup>

Procter has reported similar reactivity of cyclopropylketones inter- and intramolecularly using  $Sm^{II}$ , typically with activated alkenes and alkynes (Figure 19B).<sup>[5, 60]</sup> Diastereoselectivity was poor with the few alkenes tested in the intermolecular case, but the alkyne-derived products can be hydrogenated in good *cis* diastereoselectivity. The authors found that cyclopropyl aryl ketones with *ortho* substituents were especially reactive (**116a-c**), a trend attributed to the enhanced C-centered radical

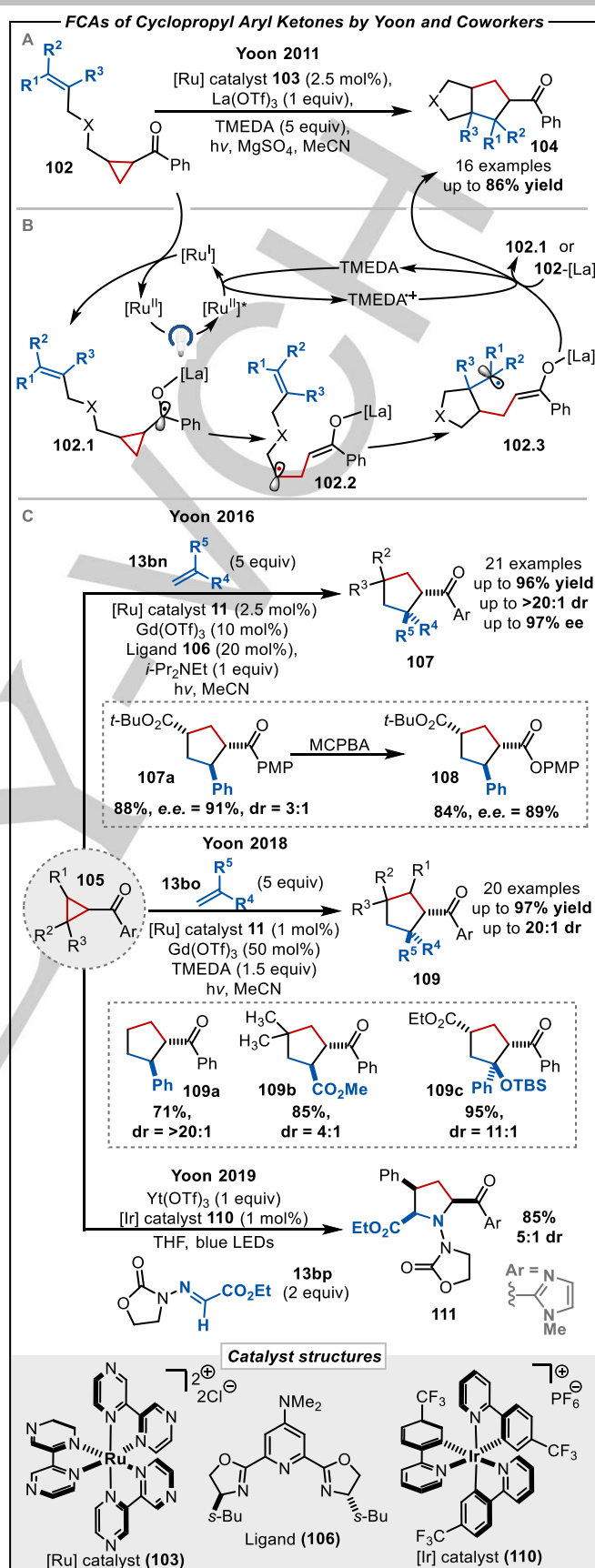
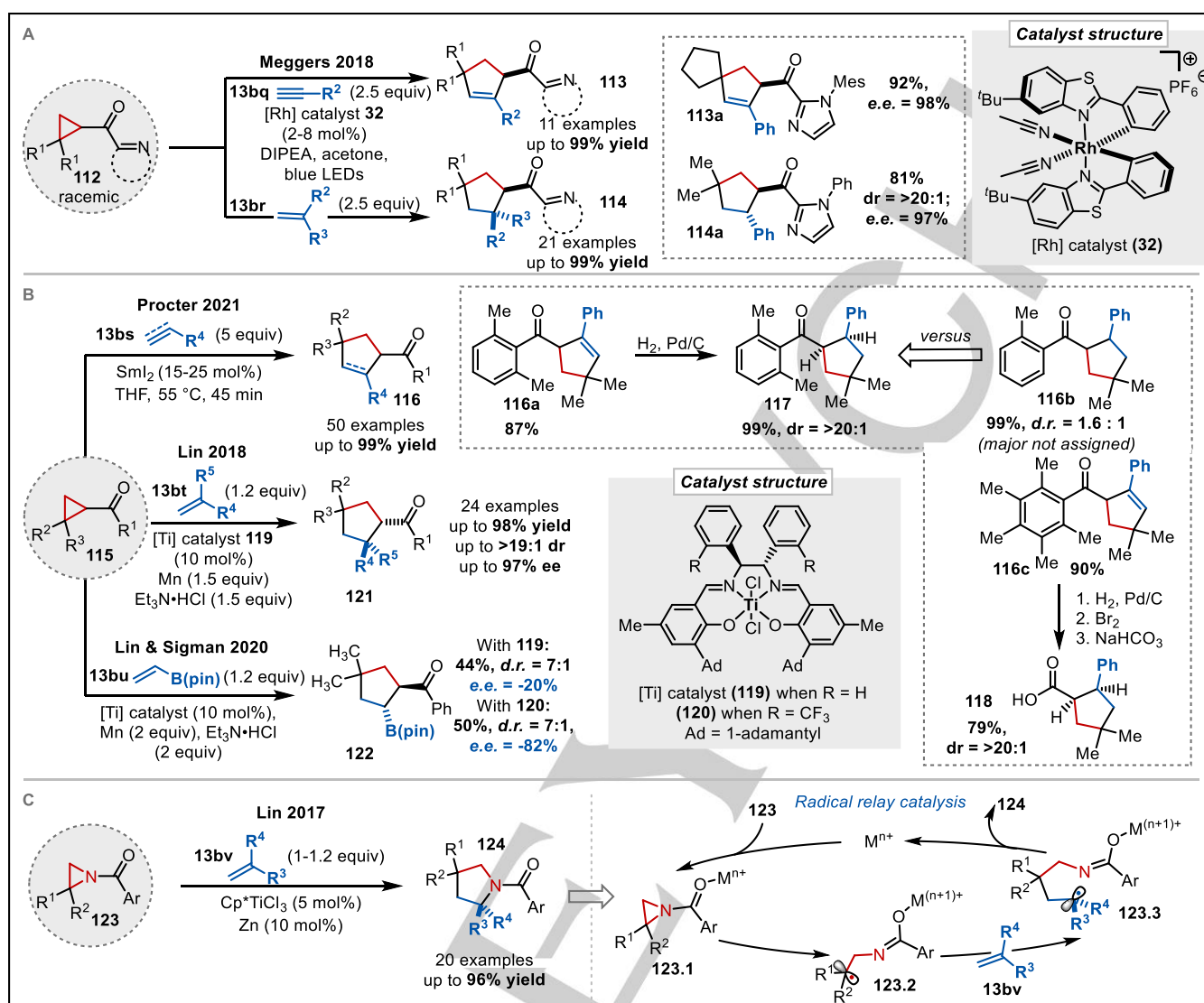


Figure 18. FCA via photoredox catalysis



**Figure 19.** FCA of carbonyl containing strained ring systems

character of the resulting ketyls. Some cyclopropyl alkyl ketones were also effective, but trends in their highly variable performance were not rationalized. Importantly, with appropriate choice of aryl group, the ketone functionality can be transformed in several steps to more synthetically useful moieties such as a carboxylic acid (118).

Procter and coworkers have subsequently shown the same reactivity can be achieved with bicyclo[1.1.0]butyl ketones (125, Figure 20).<sup>[61]</sup> Activated alkenes including acrylonitriles, acrylates, and vinyl sulfones were tolerated, giving bicyclo[2.1.1]hexane products (126a-b). Due to the symmetry of most bicyclobutane (BCB) substrates employed by the authors, the corresponding formal cycloadducts from achiral alkenes contain only one stereocenter. While this stereochemical simplicity is convenient, it should be noted that bicyclo[2.1.1]hexanes derived from chiral BCBs, or chiral alkenes, were produced with no diastereoselectivity.

Brown and coworkers have achieved an analogous bicyclo[2.1.1]hexane synthesis using the innate photochemistry of bicyclo[1.1.0]butyl naphthyl ketones (Figure 20).<sup>[62]</sup> The reactive triplet state 125.1 can be accessed either through direct excitation with UV-A light or via EnT catalysis. Naphthyl substitution of the ketone was key to tuning the triplet energy, allowing selective excitation of the ketone in the presence of styrenes when employing the appropriate xanthone-based photosensitizer.

### 3. Initial reactive intermediate NOT derived from strained-ring species

The  $\pi$ -like nature of some saturated, strained ring systems has allowed for the development of FCAs in which the ground state strained system engages with a different reactive intermediate in the initial bond-forming event. For instance, this has been explored at great length for the reaction of 1,3-dipoles with

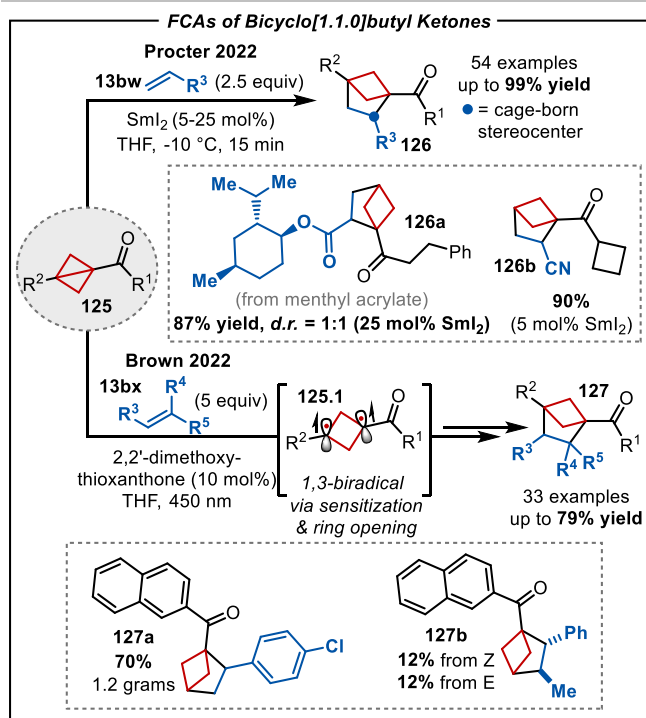


Figure 20. FCA of BCP ketones

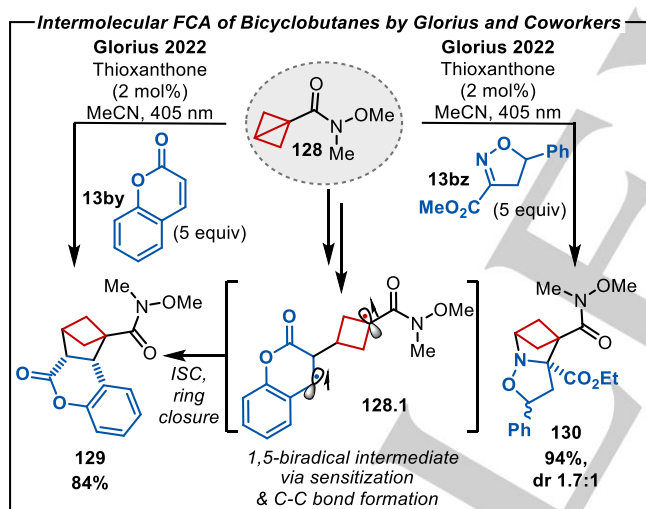


Figure 21. Intermolecular radical FCA of BCBs

strained carbocycles, stepwise reactions that have been designated “homo-dipolar CAs.”<sup>[63]</sup>

Remarkably few analogous strain-driven radical FCAs proceeding through addition of a discrete (bi)radical species to a strained  $\sigma$ -bond had been described until this year, when Glorius and coworkers took this approach to prepare bicyclo[2.1.1]hexanes from BCBs, despite a 50+ year history of radical polymerization of BCBs.<sup>[64]</sup> Glorius proposes capture of triplet alkenes or isoxazolines by BCBs generates 1,5-biradical intermediates (**128.1**), which cyclize to give the observed products (Figure 21).<sup>[65]</sup> We anticipate future reports of FCAs featuring addition of a 1,n-biradical equivalent to a strained ring

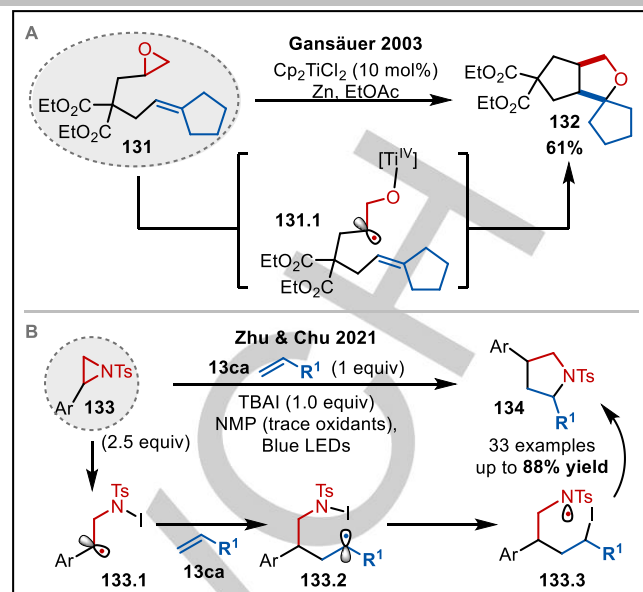


Figure 22. FCA via activation of strained-ring atom

system, though the number of conveniently synthesized ring systems containing sufficiently reactive  $\sigma$  bonds will likely pose a reaction design constraint.

#### 4. Initial reactive intermediate via activation of strained-ring atom

Strained rings can also be activated for FCA by interaction of a ring atom with an exogenous species besides the cycloaddition partner. An early example is the intramolecular Ti<sup>III</sup>-mediated FCA of epoxides and alkenes, published by Gansäuer in 2003 (Figure 22A).<sup>[66]</sup> Reductive epoxide opening gives C-centered radical **131.1** that is primed for the FCA cascade.

More recently, Zhu and Chu reported that the combination of tetrabutylammonium iodide, reagent grade N-methyl pyrrolidine, and light leads to the oxidative opening of N-tosylaziridines to give **133.1** (Figure 22).<sup>[67]</sup> Subsequent halogen atom transfer, radical polar crossover, and cyclization gives pyrrolidines (**134**). The apparent regiochemical outcome of alkene addition is opposite that observed in the radical covalent catalyzed FCAs of 2-vinyl-N-tosylaziridines (*vide supra*, Figure 15B).<sup>[44]</sup>

#### 5. Summary and outlook

Strain-driven FCAs operating via single-electron mechanisms have entered the mainstream consciousness of the synthetic chemistry community, paralleling the rise of photocatalysis and renaissance of radical chemistry at large. Photoredox catalysis, in particular, has lowered the barriers to entry for the area of synthetic photochemistry, bringing many new researchers into the radical FCA space.

The radical, strain-driven FCA strategy has achieved practicality across a variety of metrics. Modern methods frequently involve activation of the strained component using free or simply protected “native functionality,” allowing for convenient synthesis

of ring systems decorated with amine, carboxylic acid, or alcohol groups, all ubiquitous in medicinal chemistry. Bridged bicyclic reactants produce systems of potential value as phenyl bioisosteres and, more generally, as rigid scaffolds for drug design. Several reported methods generate single products as racemates or are highly diastereoselective. All these factors bode well for the adoption of many radical FCAs methods by end users.

However, the preparative value of currently published asymmetric, catalytic FCAs is limited by reliance on directing groups, lengthy catalyst syntheses, and/or modest enantioselectivity. Encouragingly, the field is trending towards practicality along all these dimensions, and we anticipate the imminent publication of enantioselective methods amenable to large-scale production.

A remaining gap in the radical FCA literature is a lack of data on ring systems besides cyclopropanes. Attempts at cyclobutane FCA are rarely described, despite several successful reports (vide supra). FCAs of strained heterocycles are also uncommon, despite the attractiveness of the resulting ring-expanded heterocycles as building blocks. The FCA of bicyclic ring systems, too, remain underexplored.

Lastly, the scope of  $\pi$  reactant (or " $\pi$ -like"  $\sigma$ -reactant) amenable to the various strain-driven FCAs described herein is frequently limited by radicals' short lifetimes and the diversity of their electronic preferences. We anticipate that catalytic cycles involving radical capture by 1<sup>st</sup>-row transition metals will increase the scope of FCAs and provide a practical, ligand-controlled platform for the development of asymmetric variants of these reactions.

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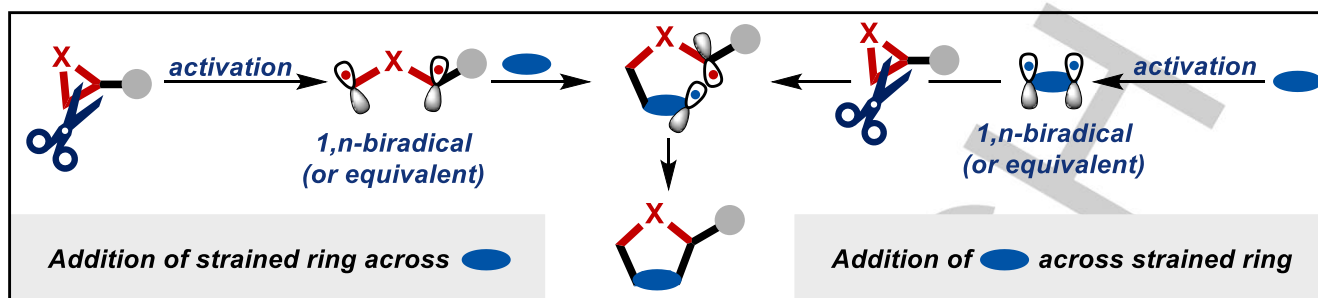
**Keywords:** strain-driven • cycloaddition • strained rings • radicals

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## Entry for the Table of Contents



Ring strain provides a driving force for the formation of reactive intermediates. Bonds of strained rings may undergo homolysis upon thermolysis, photolysis, radical addition, or following single electron transfer events. Regardless of homolytic method, intermediates competent in formal cycloaddition can be formed. Herein, we describe formal cycloadditions of strained systems operating via radical pathways.