# Main-Group Metalated Heterocycles through Lewis Acid Cyclization

Chao Gao, Suzanne A. Blum*

Department of Chemistry, University of California, Irvine, California 92697-2025, United States

ORCiD: orcid.org/0000-0003-3662-6518 (C. Gao); orcid.org/0000-0002-8055-1405 (S.A. Blum)

*Correspondence: blums@uci.edu (S.A. Blum)

**Abstract**

Main-group metalated heterocycles have broad applications in synthesis, drug development, and materials science. In this Review, we highlight recent progress in synthesizing isolable main-group heterocycles of boron, indium, silicon, tin, selenium, and tellurium via Lewis acid cyclization pathways, together with a discussion of mechanistic insights. Different from traditional two-step synthetic routes in which heterocycles are constructed first followed by metalation, the herein-described Lewis acid cyclization reactions construct the heterocyclic core and install the metal in one synthetic step. These cyclization reactions proceed with predictable regioselectivity and with high functional group tolerance. While all the described reactions are Lewis acid cyclization reactions onto carbon–carbon $\pi$ bonds, mechanistic studies show different metals/reagents can proceed through different intermediates.

**Keywords:** Heterocycles; Lewis acid; Cyclization; Metalation; Synthesis; Mechanistic studies

## Introduction to synthetic methods to generate metalated heterocycles: past and present

**Heterocyclic scaffolds** (see glossary) are present in greater than 85% of biologically active compounds [1]. Metalated heterocycles are of interest because they enable the synthesis of diversely functionalized heterocycles, through the cross-coupling [2–4], conjugate addition [5,6], and oxidation [7,8] reactivity of their metal–carbon bonds. Therefore, development of synthetic methods for the generation of metalated heterocycles has garnered significant attention. Traditionally, metalated heterocycles are constructed by synthesis of the heterocyclic core first, followed by metalation of this core second (Figure 1A). Such a two-step strategy results in elongated synthetic routes, and often poor regioselectivity and/or limited functional group compatibility due to heavy reliance on lithiation [9] or C–H activation [10,11] methods in the second step. Conversely, the development of the Lewis acid cyclization routes to metalated heterocycles, described herein, enables the construction of the heterocyclic core and installation of the metal in one synthetic step (Figure 1B). These cyclization reactions proceed with predictable **regioselectivity** and with high functional group tolerance. In light of the aforementioned merits, this synthetic strategy has evolved rapidly in the past few years and accompanying mechanistic studies have resulted in better understanding of their reaction mechanisms. This recent extensive development of Lewis acid cyclization reactions has a threefold impact: 1) it expands the synthetic tools available for natural product, drug development, and materials synthesis; 2) it provides access to new metalated heterocycles that could not be accessed through prior two-step synthetic pathways, and 3) the divergence of **mechanisms** of the different Lewis acid cyclization reactions opens additional research avenues and provides inspiration for forthcoming methods development.

In this Review, we highlight the recent progress in synthetic methods development for isolable main-group heterocycles via Lewis acid cyclization pathways and survey the mechanistic insights of each newly developed synthetic method. Furthermore, we highlight how the accompanying advance in mechanistic understanding inspired the design and development of newer synthetic strategies (Figure 1C). As part of the treatment of metalated heterocycles, this review includes heterocycles containing main group metalloids because they provide access to valuable organic

scaffolds via downstream functionalization reactions through mechanistically similar cyclization reactions as their neighboring metals.

## Main-group metals and their recent reactivity as Lewis acids for heterocyclization reactions

*Boron*

Organoboron reagents, especially heterocycle-derived ones, are commonly used in synthetic [12] and medicinal chemistry [13,14] as building blocks because of their low toxicity [15] and broad downstream reaction types [16]. Moreover, organoboron reagents are also used for making boron containing polymers, which have attracted significant attention in material science due to the special physical and chemical properties of boron [17]. Organoboron compounds also have direct usage as catalysts [18], delivery agents for neutron capture therapy of cancer [19], and molecular imaging probes [20,15].

One way to access borylated heterocycles through the Lewis acid cyclization approach is to synthetize B–X bond-containing substrate **1** first, followed by *in situ* cyclative addition of the B–X bond across alkynes to afford the desired borylated heterocyclic products **2** (Figure 2A). Since the B–X bond is added across the alkyne, we find it helpful to call this type of reaction *direct boron–element addition* [21]. Typically, direct addition requires Lewis acidic catalysis (e.g., Au, Cu, or $B(C_5F_6)_3$), and products **2** are air-unstable Bcat or 9-BBN derivatives. Therefore, *in situ* transformation to more stable boron compounds (i.e., Bpin, Bdan) is typically required.

In 2014, Blum developed this B–X direct addition concept via the first direct oxyboration reaction, generating isolable borylated benzofurans (**2a**) [22,23]; this reaction proceeds through gold Lewis acid activation of the alkyne and a subsequent nucleophilic cyclization by oxygen of the preformed B–O bond. Since then, this group has expanded the Au-catalyzed direct borylation methodology to access a variety of borylated heterocycles (**2a**–**2e**) [24–26]. In 2019, a conceptually similar Cu-catalyzed aminoboration for making borylated pyrazoles (**2f**) was reported [27]. Interestingly, cyclization for **2b** also proceed without a catalyst, albeit higher reaction temperature and elongated reaction times were required [24].

Along with method development, Blum conducted a series of mechanistic studies and the generic reaction mechanism of Au/Cu-catalyzed direct borylation as proposed is shown in Figure 2B. In the catalytic cycle, the alkyne is activated by the carbophilic Au/Cu catalyst first via coordination. Second, the nucleophilic heteroatom attacks the activated alkyne to afford **intermediates 4a** and **4b**. After gold-to-boron **transmetalation** [28], the desired borylated heterocyclic compound **2-Bcat** is formed and the catalyst is regenerated [21]. Early reports proposed that the Lewis basic **ligand** *Y* also coordinates to the boron in a "double activation" mode (**3b**). However, later mechanistic studies suggested that this double activation mode might not be necessary (**3a**) [29].

In 2017, Wang published a $B(C_5F_6)_3$ (BCF)-catalyzed direct aminoboration reaction (Figure 2A, compound **2g**) [30]. Substrates containing 9-BBN were reactive in this reaction, complimentary to previous reports with Bcat. There are two proposed plausible mechanisms, as summarized in Figure 2C. The first option is similar to the Au/Cu-catalyzed counterparts in which the alkyne of substrate **1g** is activated by BCF forming a possible **activation structure**, **5**, [31] followed by nucleophilic attack to the activated alkyne to form intermediate **6**. After a borenium exchange (analogous to transmelatation), the desired product **2g** is produced together with BCF regeneration. In option 2, the borenium containing intermediate **6** is used to activate the alkyne of another substrate **1g**, followed by cyclization to form **7a** and counter ion **7b**. The intermediate **7a** also contained a borenium ion that could activate the alkyne of the third substrate **1g** to both generate the desired product **2g** and "regenerate" **7a**; although **7a** is generated in each catalytic cycle, it is a new/different molecule of **7a** each time around the cycle. In option 2, BCF acts as an initiator and the compound **7a** is the active catalytic species.

We find it helpful to refer to another type of reaction as *formal boron/element addition*. In this type of reaction, the formation of a X–B bond is not a prerequisite, nor is such a bond along the productive reaction pathway. Instead, separate reagents are employed, resulting in a net formal addition of B/X equivalents [21]. The source of the element X for the addition is from the substrate and the source of boron is from an external reagent.

These types of reactions were initially developed by Melen and Stephen, wherein BCF was used to induce formal oxyborations [32,33]. A recent example by Melen with BCF is presented in Figure 3A. When substrate **8** is treated with BCF, nucleophilic attack to the BCF-activated alkyne **9** yields zwitterionic product **10** with up to 65% yield. An advantage of employing this reagent is that the high Lewis acidity of BCF leads to low temperature (−40–25 ˚C) reactions. [32] A drawback is that the BCF-**zwitterionic** products are generally inert to the well-known classes of further downstream functionalization reactions (e.g., conjugate addition and Suzuki cross-coupling reactions) [21,34].

Starting in 2016, Blum developed ClBcat induced formal borylation–dealkylation/deacylation reactions to synthesize borylated isocoumarins and thiophenes (**12a**–**12d**) [35–37]. These reactions require elevated temperatures but produce borylated heterocyclic building blocks primed for use in established boron downstream functionalization reactions through the known reactivity of Bcat, Bpin, BMIDA, and $B(OH)_2$ groups [38]. In some cases, the Bcat products from these reactions could be isolated directly without needing air-free techniques, and without boron group swaps to increase their stability [39].

In 2017, Fu expanded this methodology to make borylated indoles with up to 73% yield, in a case where DFT calculation inspired new methodology (Figure 3B) [40]. Similarly, Ingleson [34] and Shi [41] reported $BCl_3$-induced formal borylation reactions in 2016 and 2018, respectively (Figure 3C). Plausibly due to the stronger Lewis acidity of $BCl_3$ over ClBcat, ethers and amides could be dealkylated to synthesize benzofurans (**14a**, X = O) and benzolactams (**14c**), a process not previously reported with the ClBcat reagent. Multiple reports of formal $BCl_3$-induced borylative heterocyclizations have been reported by Li, C. Yang, and Z. Yang since 2015 with good yields; these reactions are notable because they result in cyclization onto alkenes and allenes instead of alkynes (Figure 3C) [42–44].

Based on experimental and theoretical studies, a general mechanism of cyclative formal boron/element addition is proposed (Figure 3D). Nucleophilic attack on the activated alkyne **15**

by the heteroatom generates zwitteronic intermediate **16**. Dealkylation, deacylation, or deprotonation by chloride generates the product [45]. Blum originally proposed that free chloride was the dealkylation agent [45], however, subsequent density functional theory (DFT) calculations by Fu [40] and Yasuda [46] suggested that $[Cl_2Bcat]^-$ is more likely. Regarding the mechanism of $BCl_3$-induced alkene formal borylation, the original report proposed the generation of X–$BCl_2$ as the first step instead of the alkene activation [42]; however, newer computational studies suggest that the alkene is directly activated by $BCl_3$ followed by cyclization (the same pathway as the alkyne counterparts shown in Figure 3D) [47].

*Criteria for choosing ClBcat-induced direct boron–element addition or formal boron/element addition as a synthetic strategy*: Based on experimental observations, Blum suggested a p$K_a$ approach: When p$K_a$ of the corresponding X–H is less than 10, ClBcat-induced formal boron/element addition is the better choice because the X will be both sufficiently nucleophilic for cyclization and a sufficiently good leaving group for dealkylation/deacylation [21]. Based on DFT calculations, Fu suggested a conceptually similar consideration that included balance of nucleophilicity and leaving group ability [40].

*Indium*

Organoindium compounds were not widely appreciated in organic synthesis until the 1980s [48]. In recent years, increasing attention has been paid to organoindium reagents due to their unique chemical properties and their relatively low toxicity. Advantages of organoindium reagents include: 1) low basicity and mild nucleophilicity, resulting in broad functional group tolerance in cross-coupling reactions (including for useful hydroxyl groups); 2) tolerance of protic solvents; 3) minimization of side reactions, such as β-hydride elimination and homocoupling; and, 4) improved or complementary regio- and stereoslectivity compared to other organometallics [48–50].

Harnessing the aforementioned complementary regioselectivity of indium, Yasuda developed a formal oxyindation reaction of alkynyl esters with high isolated yields in 2018 and 2019 (Figure

4A) [46,51]. In this reaction, $InI_2$-lactone derivatives could be synthesized by treating alkynyl esters **17** with $InI_3$. The resulting metalated heterocycles were either directly isolated as the organoindium compounds, or transformed *in situ* into the corresponding organoiodides. This reactivity is attractive because both the nucleophilic (organometallic) and electrophilic (alkenyliodide) cross-coupling partners could be synthesized using this method. Notably, this method provides complementary regioselectivity in that it accesses 6-membered ring products on terminal alkyne substrates: both ClBcat formal oxyboration [35] and Larock halocyclization direct-to-the-iodide [52] reactions are selective for the 5-membered ring products instead (e.g., **22** and **23** in Figure 4B).

The indium cyclization reaction mechanism is similar to that for formal boron/element cyclization. As shown in Figure 4A, nucleophilic cyclization onto the indium-activated alkyne and subsequent dealkylation yields the final product **19.** DFT calculations suggest that the regioselectivity difference between boron and indium arises from the large polarizability of indium and iodine, which makes the cyclization step of oxyindation reversible. The dealkylation step is thus the rate-determining, and the 6-membered ring products are formed. In contrast, for oxyboration, the low polarizability of boron and chlorine makes the initial cyclization step the rate-determining step, so the 5-membered product is favored [46].

*Silicon*

Organosilicon reagents feature prominently in synthetically useful reactions, such as the Hiyama coupling [53,54], Tamao oxidation [8], and Hosomi-Sakurai [55] reactions [56]. They possess the advantages of high stability, nontoxicity, and ease of handling [53,54]. These advantages particularly stand out in comparison to their organoboron alternatives, especially after toxicological issues regarding some organoboron reagents were suggested in 2011 [53]. Because sila-substitution of drug molecules can increase lipophilicity, improve potency, and alter metabolism rate, organosilicon compounds, especially ones derived from heterocycles, have also found direct applications in medicinal chemistry and drug development [57]. Furthermore,

organosilicon compounds are useful for biological imaging, drug release technology, and mapping inhibitor binding [58].

Although silanes are typically not π Lewis acidic enough to promote cyclization reactions, Yan recently develop a BCF-catalyzed formal silylative cyclization (Figure 5A) [59]. In this intriguing reaction, 3-silylated benzothiophenes (**24a**), benzofurans (**24b**), and indoles (**24c**) were successfully obtained in good yields. Yan proposed that the hydrosilane is activated by BCF via a B–H interaction (**25**). Generation of cationic silylium ion **26** and $[H–BCF]^-$ (**27**) follows. The silylium ion, **26**, activates the alkyne, and ring closure forms **29**. Finally, **29** undergoes demethylation by hydride donor **27** to generate the desired product and regenerate the BCF catalyst. We find this mechanism inspiring because it suggests that other metal or metalloid hydrides could also be potentially converted into sufficiently π Lewis acidic species with a secondary Lewis acid catalyst, enabling the synthesis of their corresponding metalated heterocycles that are otherwise hard to access.

*Tin*

Organotin (organostanne) reagents are particularly well known for their applications in C–C bond formation (i.e., Stille cross-coupling reactions) [60]. Due to their high toxicity, however, their popularity in medicinal chemistry has faded [61]. Yet, organostanne reagents still hold irreplaceable merits, such as their higher reliability in synthesis of complicated molecules and their tolerance of harsh reaction conditions [60]. These merits were highlighted by Pfizer in a comparative study on large-scale preparation of an imidazole-thienopyridine based VEGFR kinase inhibitor [62].

Probably due to this high toxicity, there are limited cyclizative stannaylation reactions reported in recent years. One notable example is of a Ag-catalyzed cascade formal aminostannylation reaction, reported by Liu in 2013 (Figure 6A) [63]. This reaction affords 3-stannylated indoles with good yields and good functional group tolerance, with relatively mild reaction conditions.

The plausible reaction mechanism is composed of two independent catalytic cycles: a heterocyclization cycle and a stannyl cation generation cycle (Figure 6B). The reaction is initiated by formation of **32** via Ag–alkyne coordination. Then, the subsequent attack of the activated alkyne by the nitrogen forms 3-silverindole intermediate **33**. Separately, another silver generates stannylium ion **36** and organosilver **35** by transmetalation with 2-stannylfuran **34**. Finally, transmetalation of **33** with **36** forms the desired product and regenerates one of the silver catalysts. The other silver catalyst is regenerated by **protodemetalation** of **35**.

*Selenium*

Organoselenium compounds often show different reactivity than other organometallic compounds: Once formed, the resulting Se and Se–C bonds in the metalated heterocycles display both electrophilc and nucleophilc behavior [64,65]. For example, in cross-coupling reactions, the typical organohalide electrophilic partner can be replaced by an organoselenium partner [66], whereas most other organometallic reagents serve exclusively as nucleophilic partners in cross-coupling reactions. Further, many heterocyclic orgnoselenium compounds show biological activity [67].

A canonical method to make organoselenium heterocycles is the classic "Larock-type" electrophilic selenocyclization reaction [68]. A recent example of this type of reaction was reported by Perin and Roehrs in 2017, whereby treatment of alkynyl selenoether **37** with electrophilic PhSeBr formed 3-selanylbenzoselenophenes **39** in high yields (Figure 7A) [69]. The proposed reaction mechanism involves formation of key seleniranium ion intermediate **38** and its subsequent dealkylation with bromide (Figures 7A,E). A general drawback of using phenylselenyl halide reagents for selenocyclization, however, is that the halide ions generated in the reaction may give undesirable incorporation of halide into other locations in the products. To avoid this, electrophilic selenium reagents with less nucleophilic counter ions may be used [68].

Recent approaches for making selanylheterocycles through Lewis acid cyclization have focused on diselenide reagents (Figures 7B–F). Because diselenides are not electrophilic enough on their

own to enable cyclization, additives are required for generation of a sufficiently electrophilic selenium species. We find it helpful to divide these additives into two conceptual classes on the basis of their reactivity (Figure 7E): The type 1 additive (i.e., NFSI or Oxone®) converts diselenides into the analogs of "classic" phenylselenyl halide reagents [67,70]. Other recent examples of type 1 additives include CuI and SelectFluor® (Figure 7F) [71,72]. The type 2 additive (i.e., $FeCl_3$) is a secondary Lewis acid that coordinates to the diselenide. Control mechanistic studies showed that $FeCl_3$ is not the Lewis acid responsible for the cyclization step directly [73], but rather that it activates the diselenide, plausibly by forming electrophilic iron–diselenide complex **48′**. Then, **48′** induces electrophilic cyclization (Figure 7E).

In 2020, Shao, Li and Chen reported the first formal aminoselenation using alk*enyl* anilines to generate selanylindoles (Figure 7B) [67]. By using NFSI as the activator under basic conditions, the indoline products could be oxidized in a basic oxidation/elimination sequence in situ to form indole products. This discovery was unique since indoles are typically generated from alk*ynyl* substrates. This reactivity suggests that when developing new Lewis acid cyclization reactions of other metal types, the potential may exist to employ readily available alkene substrates if *in situ* oxidation can be induced on demand.

Oxone® was another effective activation reagent, as demonstrated by Perin (Figure 7C). Various selenated heterocycles (**43a**–**43c**) were afforded with high yields [74–76]. Additionally, ultrasound afforded **43d**–**43g** with high yields [70], [77–79].

If *alkyl*diselenides are used in combination of diyne (or triyne) substrates, formal tandem heteroselenation reactions can be achieved, resulting in a sequence of two or more cyclization reactions within the same substrate (Figure 7D). In 2016, Zeni reported an Fe-induced formal heteroselenation for the synthesis of fused selenylheterocycles **46a** [80]. Later, Zeni expanded this reaction with a range of heteroatom nucleophile substrates (**46b**) [73]. Recently, Koketsu reported an Fe-mediated heteroselenation to make selenated heteroacenes (**46c**) [81]. Although the mechanism "on paper" suggested that $FeCl_3$ could be used as a catalyst to activate selenium,

excess $FeCl_3$ was required in practice. Since 2019, Perin has been expanding Oxone®-promoted methods for tandem reactions, for example to generate **46d** [82]. In some cases, identical substrates have been reported by Zeni for $FeCl_3$-promoted and by Perin for Oxone®-promoted reactions, enabling a "head-to-head" comparison of activating agents; both result in high yields e.g., of **46a** [80,83]. The key idea that enabled these tandem reactions was the use of *alkyl*diselenide reagents. Because the intermediate **45** contained an $S_N2$-reactive *alkyl* group on the nucleophilic selenium, the second and third formal selenoselenation reactions were possible.

*Tellurium*

Similar to organoselenium reagents, organotellurium reagents also possess "two faces" in their amphiphilic chemical properties. The nucleophilic character is accessed upon transmetalation or formation of "ate" complexes with other metals, including lithium and copper [84,85]. For example, organotellurium-derived cuprates are suitable nucleophiles to open epoxides [86] or to cross couple with alkynyl halides [87,88]. Conversely, organotellurium reagents used directly serve in the electrophile role in place of organohalides in cross-coupling reactions [84,65].

In a series of publications from 2016 to 2018, Onysko reported formal thiotelluration reactions of both cyclic and acyclic thiourea derivatives with aryltellurium trichloride as the Lewis acidic telluration reagent (Figure 8A) [89–91]. Being a co-member of chalcogen elements, the proposed mechanism of thiotelluration shares similar features to that of the previously discussed formal heteroselenation reaction (Figure 7E) (e.g., three-membered ring telluronium cation intermediate **54**; Figure 8A). However, different from the heteroselenation mechanism, the telluronium ion is proposed to be opened by a dissociated chloride ion, forming **55**. Subsequent nucleophilic attack of the sulfur on the alkylchloride yields isolable tellurium(IV) HCl salt **56** in up to 75% yield. The HCl salt **56** could be reduced to tellurium(II) product **57** upon treatment with $Na_2SO_3$. Evidence for the generation of an apparent chlorotelluration intermediate was obtained by studies on acyclic thiourea substrates, through which isolable chlorotelluration products **59** were obtained (Figure 8B) [91].

Recently, Zeni, Perin, Schumacher and Silva demonstrated iron-, Oxone®-, or SelectFluor®-promoted formal (tandem)heterotelluration reactions using ditelluride reagents to generate **62a**–**62e** [70,72,73,76]. Although detailed mechanistic studies of these reactions have not been reported, the mechanisms plausibly share features with the corresponding formal heteroselenation reactions using diselenides (*vide supra*).

## Concluding remarks

In this Review, we highlighted recent developments of synthetic methods for the generation of isolable main-group metalated heterocycles via Lewis acid heterocyclization reactions. Mechanistic features of different cyclization reactions were also summarized. Despite tremendous progress made in this field, there are still many unanswered questions (See Outstanding Questions). For example, studies showed that the stability of boron groups is highly heterocycle dependent [39], and the trends are not fully understood. If fully understood, a general isolation guide for borolative heterocyclization reactions could be established. Furthermore, only Bcat and 9-BBN groups have shown reactivity in direct borylative heterocyclizaiton reactions, but what strategies there are for expanding the toolkit (e.g., to Bpin) remain undefined.

Unexplored areas also remain in broadening heteroindation reactions. To date, only cyclative oxyindation of alkynes has been reported. Can other nucleophiles, such as amines, and other electrophiles, such as alkenes and allenes, be developed for cyclative heteroindation? Furthermore, if heteroindation of alkenes is possible, will it exhibit the unique regioselectivity of its alkyne counterparts? Regarding group 4 elements, can the seminal BCF-catalyzed formal heterosilylation reaction [59] been expanded to other group 4 metals, e.g., to develop a BCF-catalyzed formal heterostannelation reaction? Or is it possible to even expand the BCF-catalyzed reaction to metal hydrides in different groups?

As for the pairs of electrophiles and cyclization substrates, alkene (and allene) cyclizations are underdeveloped compared to alkynes. Currently, there are only a few examples of alkene and

allene cyclizations, focusing on $BCl_3$ [42–44]. For these limited reports on alkenes, only *exo* cyclization has been observed. On the contrary, most of the reported cyclization reactions on alkynes, with various metals, are *endo* cyclizations. Therefore, it is natural to ask if it might be possible to design reactions to control the selectivity.

One can also wonder if some of the reaction intermediates can be intercepted without isolation for relay or dual-catalytic transformations. For example, because it has been demonstrated that the indium-containing products of oxyindation are reactive towards in situ cross-coupling reactions [46,51], can systems catalytic in indium or other main group metals be developed as part of dual-catalytic cross-coupling reactions? With such intriguing questions yet unanswered, the next coming years may hold as many developments as the recent past.

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**Declaration of interests**

The authors declare the following competing interest(s): U.S. patent 9,238,661.

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**Glossary**

**Activation structure:** an intermediate or transition state along the reaction pathway that shows the Lewis acid activation of the $\pi$ system.

**Heterocyclic scaffolds:** cyclic compounds having at least one ring-member atom of an element other than carbon. Also known as heterocyclic compounds and heterocycles.

**Intermediate:** a species that exists between reactants and products in a stage corresponding to local energy minimum on the reaction's potential energy surface. Some reaction intermediates are isolable, but most are not; others can be detected spectroscopically.

**Ligand:** a group that binds to a metal center in a complex.

**Mechanism:** the processes over time in which the chemical steps necessary for one molecule to be transformed into another occur through intermediates and transition states. Also known as a reaction mechanism.

**Protodemetalation:** a reaction in which the metal of a metal–carbon bond in an organometallic compound is replaced with a proton, yielding a hydrogen–carbon bond.

**Regioselectivity:** the preference of formation (or breaking) of chemical bonds at one site in a molecule over others. Regioselective reactions yield only one (or predominately one) constitutional isomer when multiple constitutional isomers are possible products.

**Transmetalation (alt spelling: transmetallation):** a type of organometallic reaction in which two (typically different) metals swap their X type ligands.

**Zwitterion:** a molecule that contains an equal number of positively and negatively charged functional groups. Also known as inner salt.

**Figure Captions.**

**Figure 1.** Introduction to this manuscript. (A) Traditionally, metalated heterocycles are synthesized by constructing the heterocycle first, followed by metalation. (B) This review describes Lewis acid induced main-group metalative heterocyclization, which can access metalated heterocycles in one step. (C) Schematic of interplay of progress in methods development and its relationship to mechanistic studies and applications in synthesis.

**Figure 2.** Borylative heterocyclizations by direct addition. (A) Generic reaction scheme of direct cyclative boron–element addition reactions and classes of accessible borylated heterocycles. (B) Proposed mechanism of Au/Cu-catalyzed direct cyclative boron–element addition. (C) Proposed mechanisms of BCF-catalyzed direct aminoboration.

**Figure 3.** Borylative heterocyclizations by formal addition. (A) BCF-induced oxyboration showing possible activation structure. (B) Generic reaction scheme of ClBcat induced formal borylation–dealkylation/deacylation and classes of accessible borylated heterocycles. (C) Generic reaction scheme of $BCl_3$ induced formal borylation–dealkylation/deprotonation and classes of accessible borylated heterocycles. (D) Proposed reaction mechanism of ClBcat and $BCl_3$ induced formal cyclative boron/element addition.

**Figure 4.** Indium heterocyclizations. (A) Reaction scheme of 6-membered ring selective oxyindation with key proposed activation structure and isolation methods. (B) Contrasting regioselectivity of other methods, showing complementary regioselectivity of indium in part A.

**Figure 5.** Silylative heterocyclizations. (A) Generic reaction scheme of BCF-catalyzed formal silylative cyclization and classes of accessible silylated heterocycles. (B) Proposed mechanism of BCF-catalyzed cyclative formal silicon/element addition.

**Figure 6.** Stannylative heterocyclizations. (A) Reaction scheme of Ag-catalyzed cascade formal aminostannylation. (B). Proposed reaction mechanism of Ag-double-catalytic cascade formal aminostannylation.

**Figure 7.** Selenium heterocyclizations. (A) Example of "classic Larock-type" PhSeBr-induced selenocyclization with key activation intermediate. (B) NFSI-induced formal aminoselenation using alkene as substrates. The benzoindoline products could be autoxided into benzoindole products. (C) Oxone®-induced formal heteroselenation and classes of accessible selenated heterocycles. Products could not be autoxided in this type of reactions when alkene substrates used. (D) Formal tandem heteroselenation and classes of accessible selenated fused heterocycles. The $S_N2$-reactive alkyl selenium reagent enables the second and third cyclizations. (E) Plausible key mechanistic steps of formal cyclizative heteroselenation and generation of sufficiently Lewis acidic selenium species from inert diselenide reagents. (F) Generation of activated selenium reagents from other activation agents for diselenides.

**Figure 8.** Tellurium heterocyclizations. (A) Generic reaction scheme of formal thiotelluration of cyclic thiourea substrates with proposed key intermediates. (B) Mechanistic insight through isolable related compounds. (C) Fe(III)- and Oxone®-induced formal heterotelluration and classes of accessible tellurated heterocycles.

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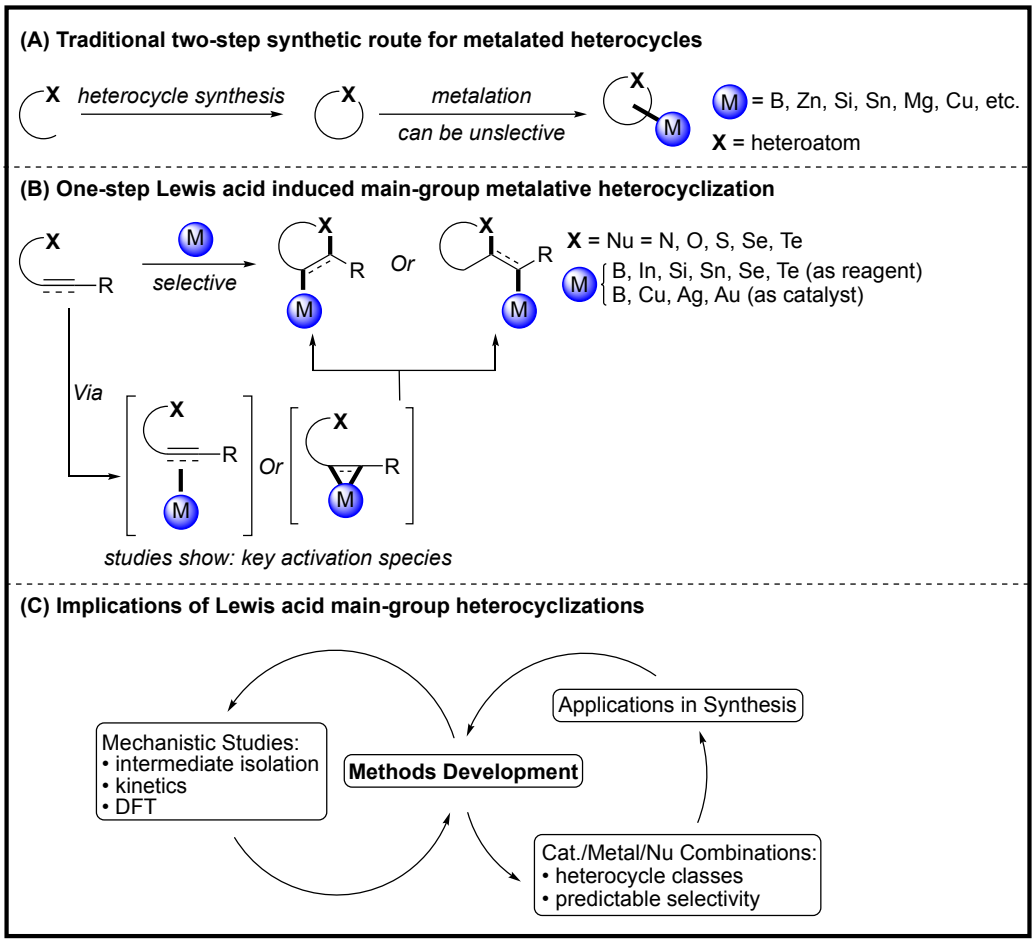
672 **Figures.**




673

674 **Figure 1.**

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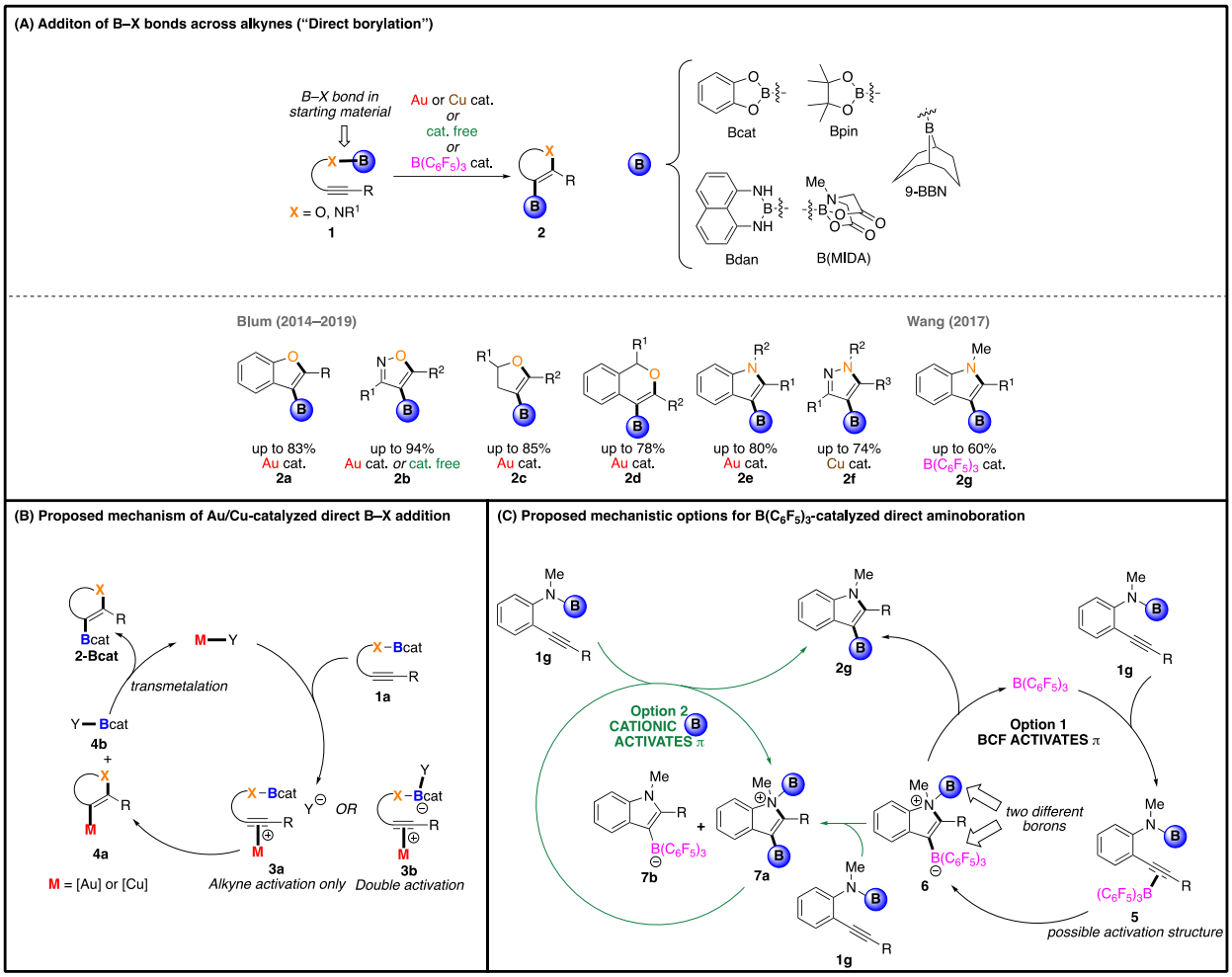
(A) Additon of B–X bonds across alkynes ("Direct borylation")
B–X bond in starting material
Au or Cu cat.
or
cat. free
or
B(C6F5)3 cat.
X = O, NR1
1
2
Bcat
Bpin
9-BBN
Bdan
B(MIDA)
Blum (2014–2019)
Wang (2017)
up to 83%
Au cat.
2a
up to 94%
Au cat. or cat. free
2b
up to 85%
Au cat.
2c
up to 78%
Au cat.
2d
up to 80%
Au cat.
2e
up to 74%
Cu cat.
2f
up to 60%
B(C6F5)3 cat.
2g
(B) Proposed mechanism of Au/Cu-catalyzed direct B–X addition
2-Bcat
transmetalation
4b
1a
4a
3a
Alkyne activation only
3b
Double activation
OR
M = [Au] or [Cu]
(C) Proposed mechanistic options for B(C6F5)3-catalyzed direct aminoboration
1g
2g
Option 2
CATIONIC
ACTIVATES π
Option 1
BCF ACTIVATES π
7b
7a
6
two different borons
5
possible activation structure

**Figure 2.**

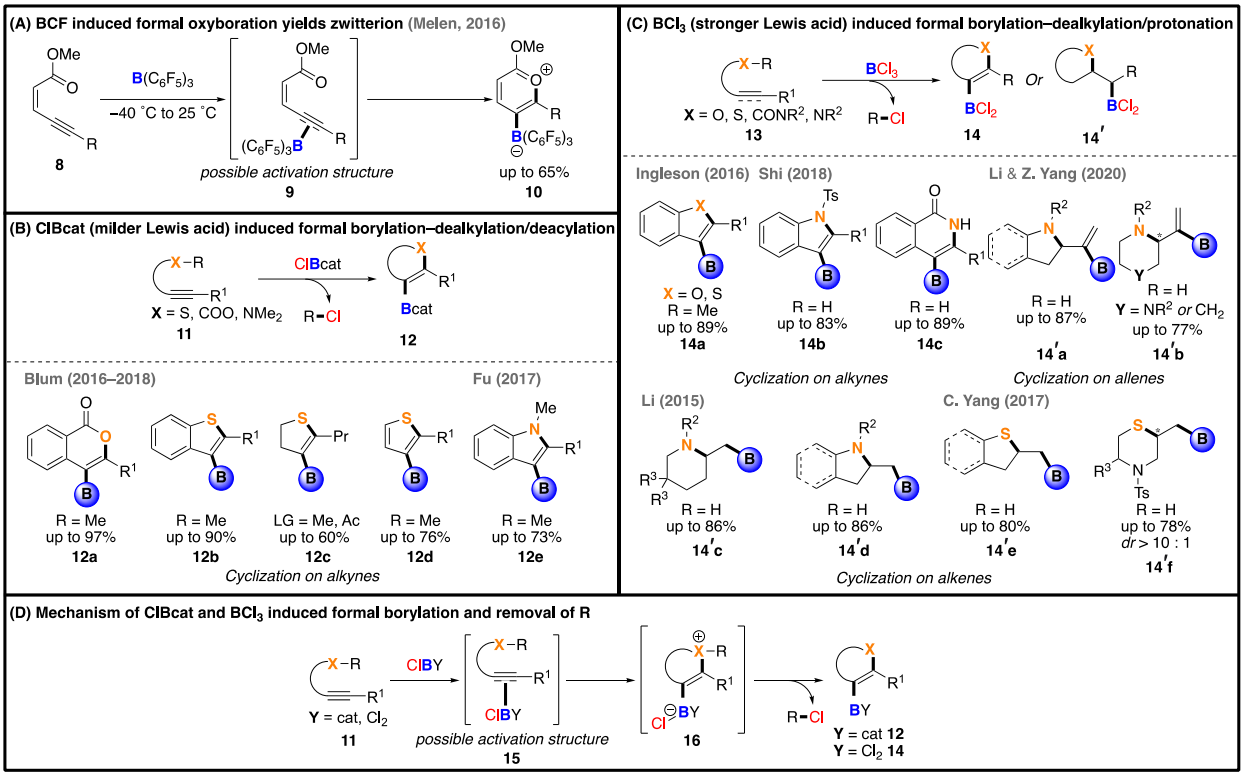
(A) BCF induced formal oxyboration yields zwitterion (Melen, 2016)
B(C6F5)3
−40 °C to 25 °C
possible activation structure
9
up to 65%
10
8
(B) ClBcat (milder Lewis acid) induced formal borylation–dealkylation/deacylation
X = S, COO, NMe2
11
ClBcat
R–Cl
Bcat
12
Blum (2016–2018)
Fu (2017)
R = Me
up to 97%
12a
R = Me
up to 90%
12b
LG = Me, Ac
up to 60%
12c
R = Me
up to 76%
12d
R = Me
up to 73%
12e
Cyclization on alkynes
(C) BCl3 (stronger Lewis acid) induced formal borylation–dealkylation/protonation
X = O, S, CONR2, NR2
13
BCl3
R–Cl
14
Or
14′
Ingleson (2016) Shi (2018)
Li & Z. Yang (2020)
X = O, S
R = Me
up to 89%
14a
R = H
up to 83%
14b
R = H
up to 89%
14c
R = H
up to 87%
14′a
R = H
Y = NR2 or CH2
up to 77%
14′b
Cyclization on alkynes
Cyclization on allenes
Li (2015)
C. Yang (2017)
R = H
up to 86%
14′c
R = H
up to 86%
14′d
R = H
up to 80%
14′e
R = H
up to 78%
dr > 10 : 1
14′f
Cyclization on alkenes
(D) Mechanism of ClBcat and BCl3 induced formal borylation and removal of R
Y = cat, Cl2
11
ClBY
possible activation structure
15
16
R–Cl
Y = cat 12
Y = Cl2 14

**Figure 3.**

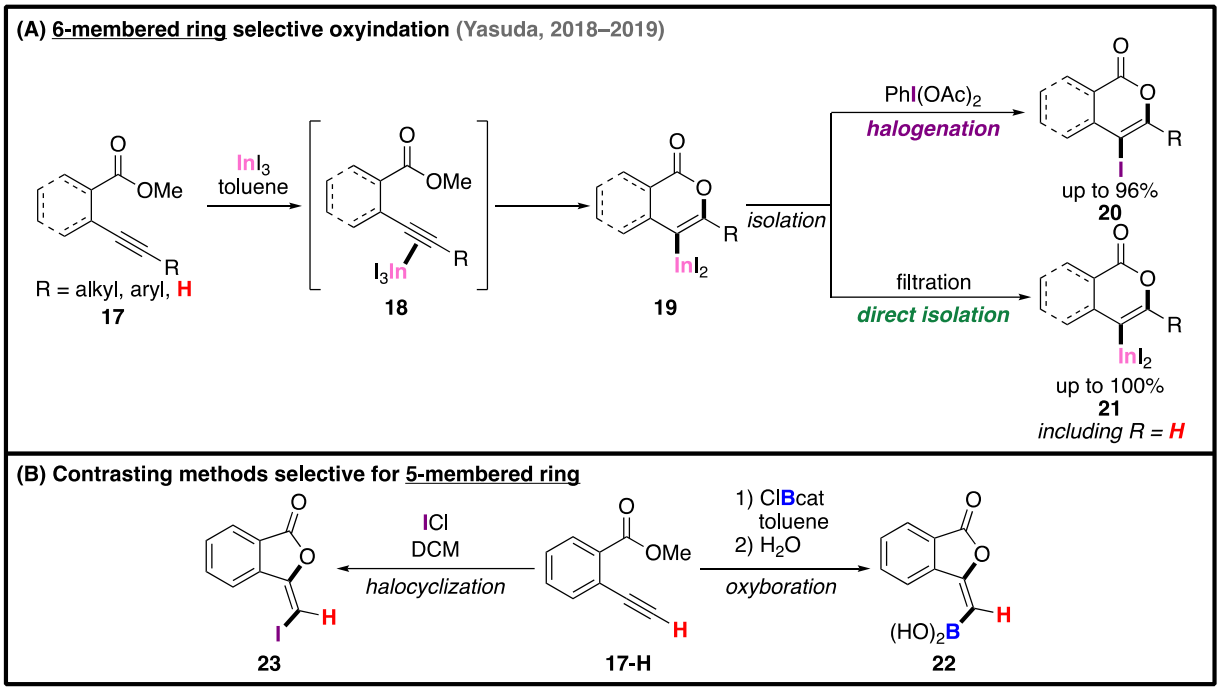
(A) 6-membered ring selective oxyindation (Yasuda, 2018–2019)
OMe
R
R = alkyl, aryl, H
17
InI3
toluene
OMe
I3In
R
18
19
isolation
PhI(OAc)2
halogenation
up to 96%
20
filtration
direct isolation
up to 100%
21
including R = H
(B) Contrasting methods selective for 5-membered ring
ICl
DCM
halocyclization
23
17-H
1) ClBcat
toluene
2) H2O
oxyboration
(HO)2B
22

**Figure 4.**

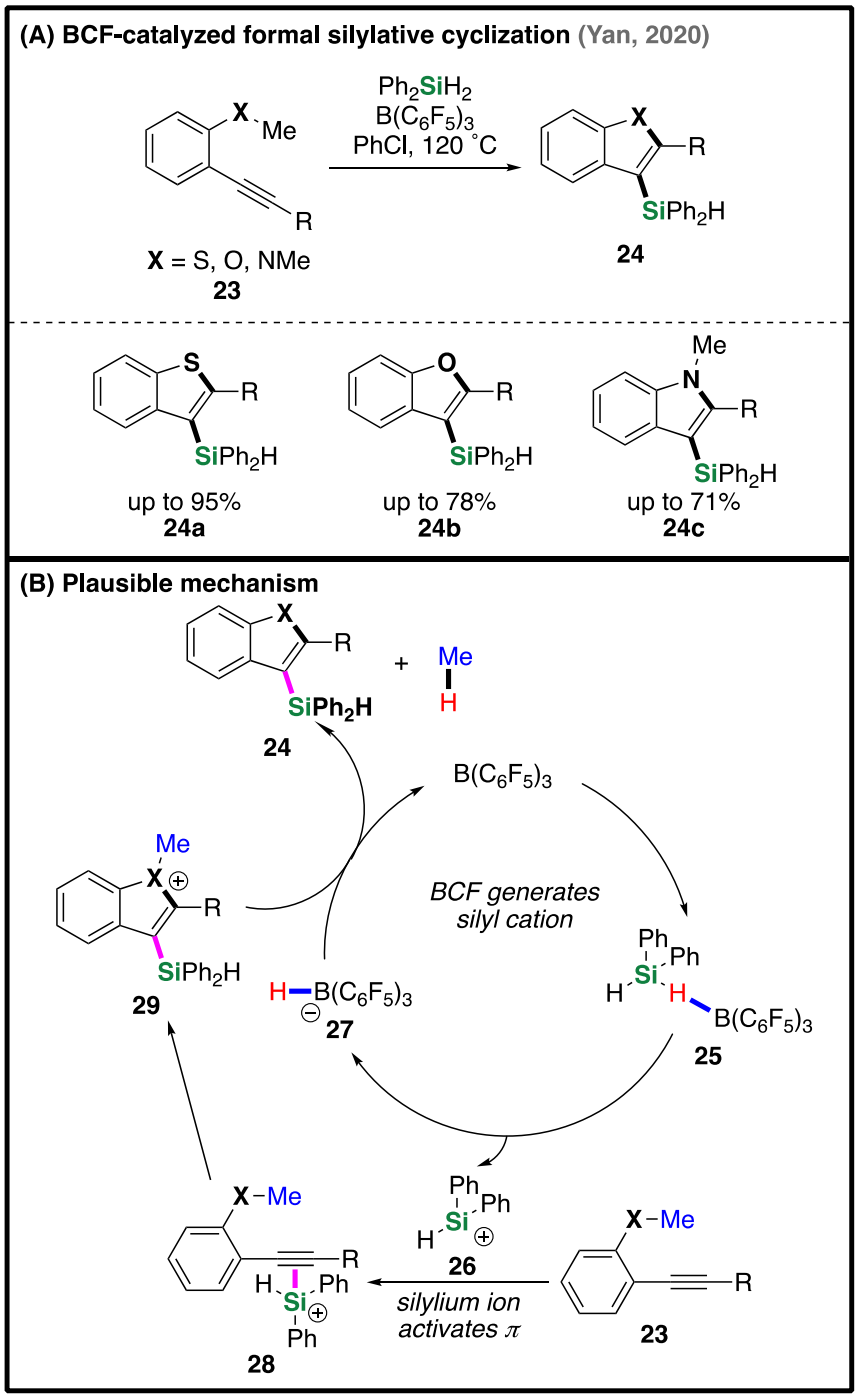
(A) BCF-catalyzed formal silylative cyclization (Yan, 2020)
Ph2SiH2
B(C6F5)3
PhCl, 120 °C
X = S, O, NMe
23
24
up to 95%
24a
up to 78%
24b
up to 71%
24c
(B) Plausible mechanism
24
29
27
25
26
23
28
BCF generates
silyl cation
silylium ion
activates π

**Figure 5.**

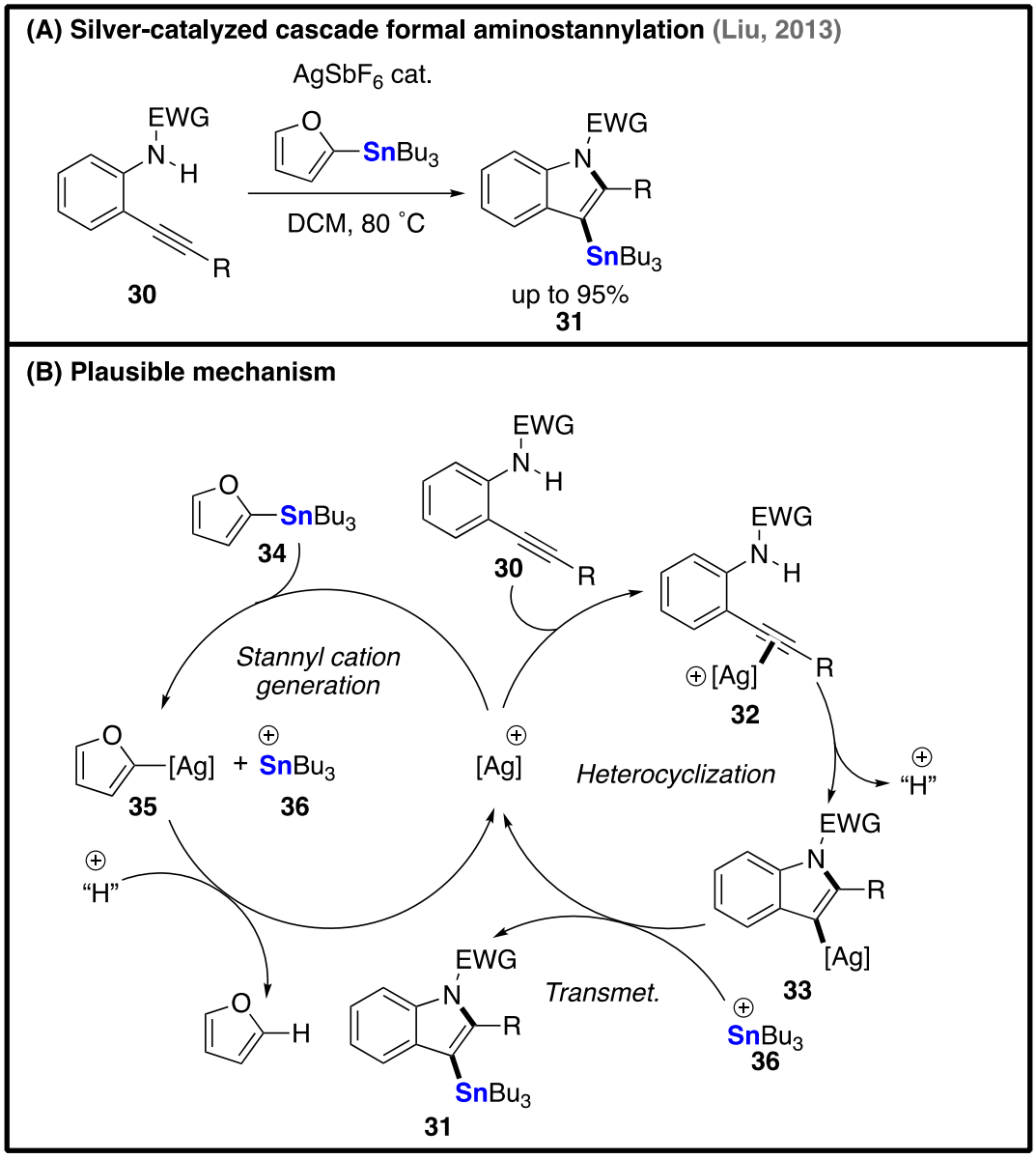
(A) Silver-catalyzed cascade formal aminostannylation (Liu, 2013)
AgSbF6 cat.
EWG
N
H
R
30
SnBu3
DCM, 80 ˚C
EWG
N
R
SnBu3
up to 95%
31
(B) Plausible mechanism
SnBu3
34
EWG
N
H
30
R
Stannyl cation
generation
EWG
N
H
[Ag]
R
32
[Ag]
35
+
SnBu3
36
[Ag]
Heterocyclization
"H"
EWG
N
R
[Ag]
33
"H"
EWG
N
R
SnBu3
31
Transmet.
SnBu3
36
H

**Figure 6.**

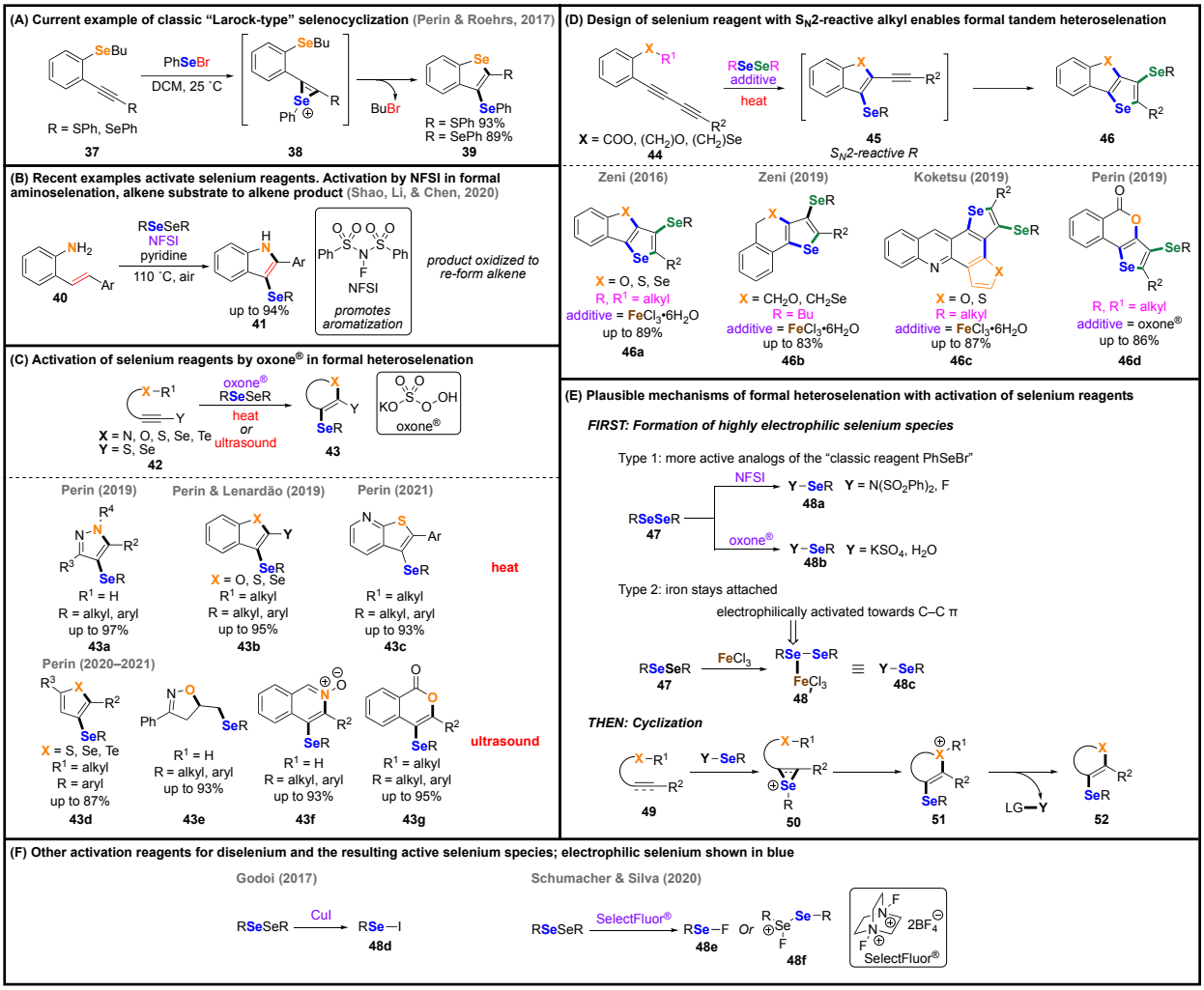
(A) Current example of classic "Larock-type" selenocyclization (Perin & Roehrs, 2017)
PhSeBr
DCM, 25 °C
BuBr
R = SPh, SePh
37
38
R = SPh 93%
R = SePh 89%
39
(B) Recent examples activate selenium reagents. Activation by NFSI in formal aminoselenation, alkene substrate to alkene product (Shao, Li, & Chen, 2020)
RSeSeR
NFSI
pyridine
110 °C, air
40
up to 94%
41
NFSI
promotes aromatization
product oxidized to re-form alkene
(C) Activation of selenium reagents by oxone® in formal heteroselenation
X = N, O, S, Se, Te
Y = S, Se
42
oxone®
RSeSeR
heat
or
ultrasound
43
oxone®
Perin (2019)
Perin & Lenardão (2019)
Perin (2021)
heat
R1 = H
R = alkyl, aryl
up to 97%
43a
X = O, S, Se
R1 = alkyl
R = alkyl, aryl
up to 95%
43b
R1 = alkyl
R = alkyl, aryl
up to 93%
43c
Perin (2020–2021)
X = S, Se, Te
R1 = alkyl
R = aryl
up to 87%
43d
R1 = H
R = alkyl, aryl
up to 93%
43e
R1 = H
R = alkyl, aryl
up to 93%
43f
R1 = alkyl
R = alkyl, aryl
up to 95%
43g
ultrasound
(D) Design of selenium reagent with SN2-reactive alkyl enables formal tandem heteroselenation
X = COO, (CH2)O, (CH2)Se
44
RSeSeR
additive
heat
45
SN2-reactive R
46
Zeni (2016)
Zeni (2019)
Koketsu (2019)
Perin (2019)
X = O, S, Se
R, R1 = alkyl
additive = FeCl3•6H2O
up to 89%
46a
X = CH2O, CH2Se
R = Bu
additive = FeCl3•6H2O
up to 83%
46b
X = O, S
R = alkyl
additive = FeCl3•6H2O
up to 87%
46c
R, R1 = alkyl
additive = oxone®
up to 86%
46d
(E) Plausible mechanisms of formal heteroselenation with activation of selenium reagents
FIRST: Formation of highly electrophilic selenium species
Type 1: more active analogs of the "classic reagent PhSeBr"
RSeSeR
47
NFSI
Y = N(SO2Ph)2, F
48a
oxone®
Y = KSO4, H2O
48b
Type 2: iron stays attached
electrophilically activated towards C–C π
FeCl3
48
≡ Y–SeR
48c
THEN: Cyclization
49
50
51
LG–Y
52
(F) Other activation reagents for diselenium and the resulting active selenium species; electrophilic selenium shown in blue
Godoi (2017)
CuI
48d
Schumacher & Silva (2020)
SelectFluor®
48e
Or
48f
2BF4
SelectFluor®

**Figure 7.**

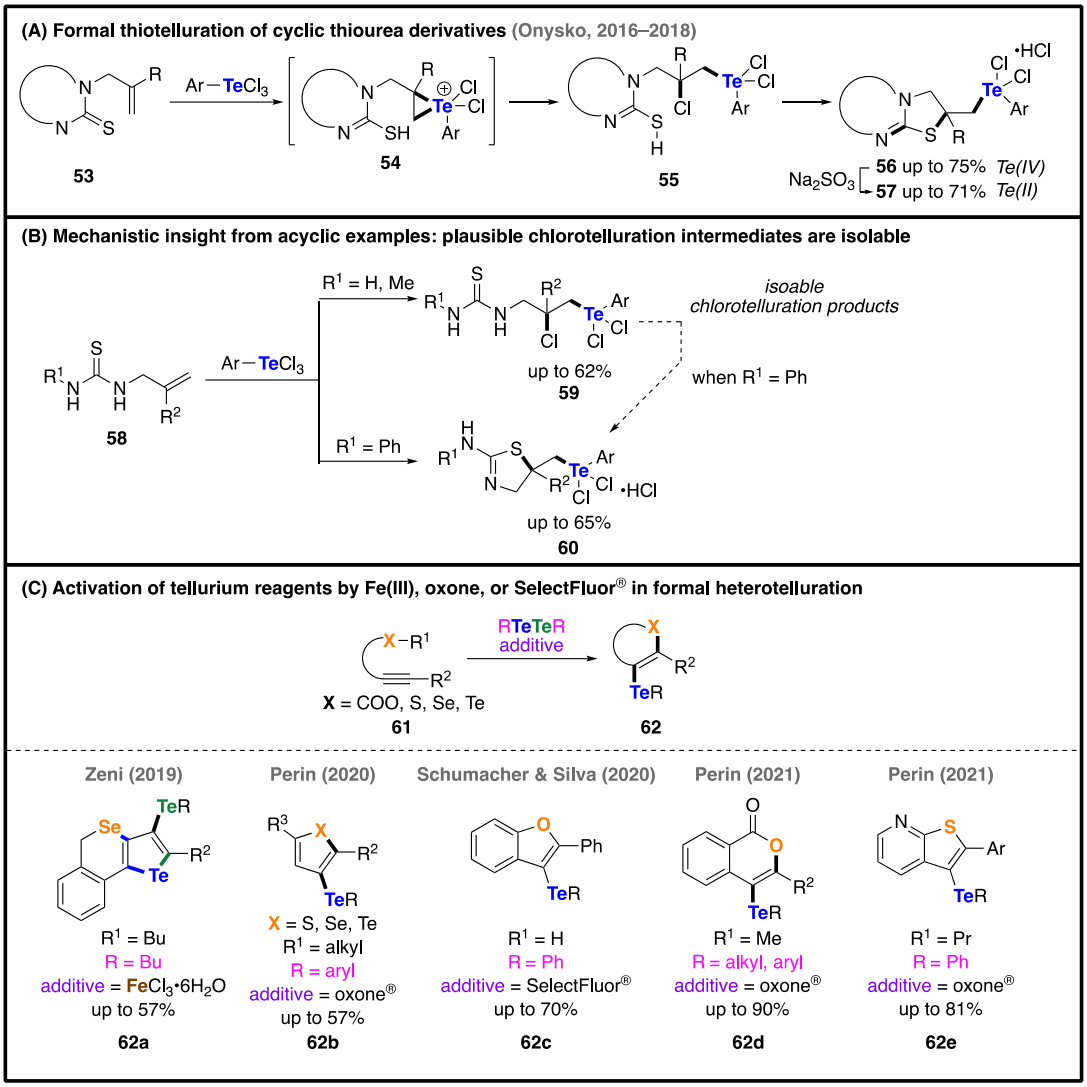
(A) Formal thiotelluration of cyclic thiourea derivatives (Onysko, 2016–2018)
Ar—TeCl3
53
54
55
Na2SO3
56 up to 75% Te(IV)
57 up to 71% Te(II)
(B) Mechanistic insight from acyclic examples: plausible chlorotelluration intermediates are isolable
R1 = H, Me
R1 = Ph
58
up to 62%
59
isoable chlorotelluration products
when R1 = Ph
up to 65%
60
(C) Activation of tellurium reagents by Fe(III), oxone, or SelectFluor® in formal heterotelluration
RTeTeR
additive
X = COO, S, Se, Te
61
62
Zeni (2019)
R1 = Bu
R = Bu
additive = FeCl3•6H2O
up to 57%
62a
Perin (2020)
X = S, Se, Te
R1 = alkyl
R = aryl
additive = oxone®
up to 57%
62b
Schumacher & Silva (2020)
R1 = H
R = Ph
additive = SelectFluor®
up to 70%
62c
Perin (2021)
R1 = Me
R = alkyl, aryl
additive = oxone®
up to 90%
62d
Perin (2021)
R1 = Pr
R = Ph
additive = oxone®
up to 81%
62e

**Figure 8.**