

Perspective

Merging metals and strained intermediates

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SUMMARY

Strained intermediates such as cyclic alkynes and allenes are most commonly utilized in nucleophilic additions and cycloadditions but have seen increased use in a third area of reactivity: metal-mediated transformations. The merger of strained intermediates and metal catalysis has enabled rapid access to complex, polycyclic systems. Following a discussion of relevant landmark studies involving metals and strained intermediates, this perspective highlights recent advances in transition-metal-mediated transformations from our laboratory. Specifically, this includes the use of arynes in the synthesis of decorated organometallic complexes and the utilization of cyclic allenes to access enantioenriched heterocycles. Moreover, the broad applicability of such transformations and exciting future areas of research are discussed.

INTRODUCTION

Can alkynes exist within small rings? This intriguing question, first asked in 1902,¹ was initially met with skepticism. Now, 120 years later, the existence of cyclic alkynes and related species is widely accepted.^{2–17} The strain associated with these species can be leveraged strategically to access a number of important compounds, including ligands,¹⁸ fungicides,¹⁹ medicinal agents,²⁰ and natural products.^{4,5,17,21,22}

To pay tribute to key historical advances and highlight two major modes of strained intermediate reactivity, we feature pioneering studies from the 1950s and 1960s. In a seminal study by Roberts and co-workers, ¹⁴C-labelled chlorobenzene **1** was treated with potassium amide in liquid ammonia (Figure 1A).²³ The formation of aniline products **3** and **4** in equal amounts provided strong evidence for the *in situ* formation of benzyne (**2**). Two years later, Wittig and co-workers reported the first generation and trapping of an aryne in a cycloaddition.²⁴ 1-Bromo-2-fluorobenzene (**5**) underwent lithium halogen exchange followed by 1,2-elimination to afford benzyne (**7**) *in situ*, which was subsequently trapped with furan (**6**) to access cycloaddition product **8** in an 88% yield (Figure 1B). Soon thereafter, it was demonstrated that 1,2-cyclohexadiene (**11**) could be generated and intercepted in cycloaddition processes with styrene (**10**) and diphenylisobenzofuran (**14**) to access cyclobutane **12** and fused tetracycle **15**, respectively (Figure 1C).^{25,26}

The examples shown in Figure 1 highlight two major modes of reactivity of strained intermediates: nucleophilic additions and cycloadditions. Indeed, the majority of synthetically useful transformations of arynes and related strained intermediates involve these types of reactions. Related modes of aryne reactivity, such as nucleophilic annulation reactions, insertion reactions, and multicomponent reactions, have subsequently arisen and have been reviewed.^{3,5,7} However, following the development of mild conditions for generating strained intermediates, such as Kobayashi's 1,2 elimination of silyl triflates,^{3,27,28} a third major mode of strained intermediate

THE BIGGER PICTURE

Challenges and opportunities:

- Strained intermediates such as cyclic alkynes and allenes have been leveraged to access a wide variety of complex scaffolds. Although most are commonly utilized in nucleophilic additions or cycloadditions, strained intermediates can also be used in metal-mediated transformations.
- The merger of strained intermediates and metal catalysis allows for the rapid generation of molecular complexity to access a diverse set of heterocyclic scaffolds. An inherent challenge of such methodologies, however, is their reliance on the generation and coupling of two *in situ*-generated intermediates.
- Further evolution of this transformation class should facilitate access to increasingly complex molecular frameworks.

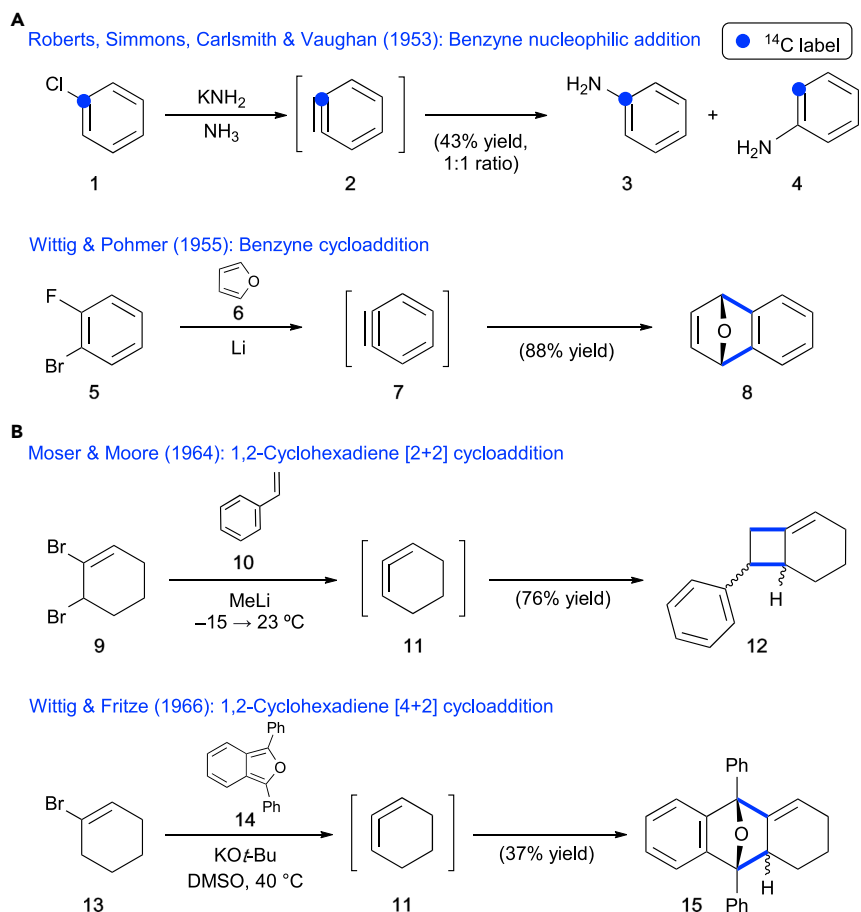


Figure 1. Seminal studies of strained, cyclic intermediates

(A) Validation of the intermediacy of benzyne through nucleophilic addition and cycloaddition experiments.

(B) First reported cycloadditions of 1,2-cyclohexadiene.

reactivity involving metal-catalyzed processes came to light. This perspective will highlight recent advances in metal-catalyzed transformations of arynes and strained, cyclic allenes to generate complexity in molecular scaffolds.

A number of landmark reports regarding the merger of arynes and metals were published in the late 20th century. It was reported by Dvorak and co-workers that subjection of titanium complex **16** to alkyne **17** at 80°C led to the formation of metallocycle **18** (Figure 2A).²⁹ A subsequent study by Erker and co-workers provided strong evidence for the intermediacy of titanium-stabilized benzyne complex **19** in this process.³⁰ The existence of metal-stabilized arynes was further validated by Schrock and co-workers in 1979, following the isolation and characterization of metal-stabilized benzyne **20** via X-ray crystallography (Figure 2B).³¹ Additional metal-stabilized arynes have since been reported,³² including Buchwald's zirconium complex **21**, which was characterized via X-ray crystallography and leveraged in a number of synthetic transformations.^{33–35} Moreover, in 1993, the first X-ray crystal structure of a metal-stabilized cyclic allene was reported (i.e., **22**).³⁶

Since the aforementioned studies, the field has evolved to focus on synthetically useful transformations of arynes and cyclic allenes that use transition metals as

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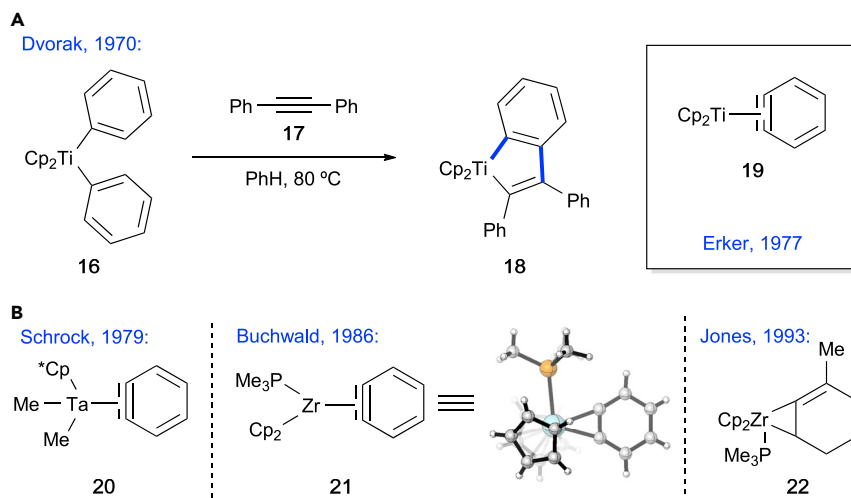


Figure 2. Transition-metal-stabilized strained intermediates

(A) Early studies support the existence of transition-metal-stabilized arynes.

(B) Examples of isolated transition-metal-stabilized arynes and a transition-metal-stabilized cyclic allene.

catalysts. Leveraging strained intermediates in transition-metal catalysis is powerful in complex molecule synthesis because it can allow for rapid access to a diverse set of scaffolds. However, numerous challenges can arise in developing such reactions, as they require merging of two reactive intermediates generated *in situ*. The first example of a metal-catalyzed reaction of arynes was not reported until 1998, roughly 50 years after the validation of benzyne. Guitián and co-workers reported a palladium-catalyzed cyclotrimerization reaction of *in-situ*-generated benzyne (7) using catalytic palladium (0) tetrakis(triphenylphosphine) (Figure 3A).³⁷ Using this method, cyclotrimerization product 24 was obtained in 83% yield.

Since Guitián and co-workers' seminal report, reactions that merge strained intermediates and metal catalysis have provided access to many unique scaffolds. For example, the naphthalene core of the natural product taiwanin C (25) was accessed via a late-stage palladium-catalyzed [2+2+2] cyclization involving an aryne.³⁸ In another example, the natural product flemichapparin C (26) was accessed via a palladium-catalyzed C–H activation of a 4-hydroxycoumarin, followed by C–C and C–O bond formation involving an aryne intermediate (Figure 3B).³⁹ Finally, the indoloquinoline core of isocryptolepine (27) was constructed via a copper-catalyzed cascade C–H/N–H annulation with benzyne.⁴⁰

Recent advances in the merger of strained intermediates and transition-metal catalysis have continued to allow access to increasingly complex scaffolds. This perspective highlights two recent advances from our laboratory. The first is the use of arynes to prepare complex organometallic compounds. The second is the use of strained, cyclic allenes to prepare polycyclic heterocycles bearing one or more stereocenters.

USE OF ARYNES TO ACCESS ORGANOMETALLIC COMPLEXES

While arynes have been utilized to access a wide array of organic compounds, an area where arynes have seen limited use is in the synthesis and derivatization

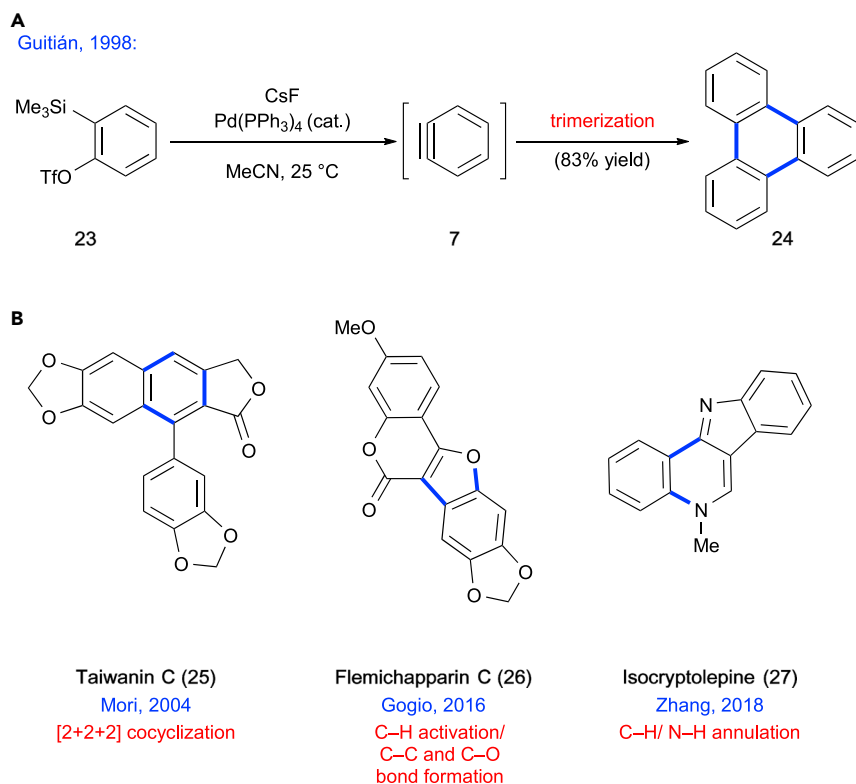


Figure 3. Transition-metal-catalyzed reactions of arynes

(A) First transition-metal-catalyzed reaction of an aryne.
(B) Representative compounds accessed through transition-metal-catalyzed reactions with strained intermediates.

of organometallic compounds. Few examples exist of arynes being utilized in so-called “chemistry-on-the-complex” reactions,⁴¹ where ligands are modified while bound to a metal center. The two earliest examples demonstrate that arynes can be utilized in Diels-Alder reactions on the complex when the organometallic complex bears a reactive diene ligand.^{42,43} For example, Wang and co-workers reported a Diels-Alder reaction between benzyne (via silyl triflate **23**) and iron complex **28** to afford cycloadduct **29** in 23% yield (Figure 4A).

Our laboratory became interested in utilizing metal-catalyzed transformations of arynes for the direct π extension of organometallic complexes.⁴⁴ Extended conjugation can impart important properties on metal complexes.⁴⁵ Metal complexes **30** (R = Ir or Ru) were found to undergo a palladium-catalyzed annulation with *in-situ*-generated arynes **31** to access metal complexes **32** (Figure 4B). Iridium complex **33** and ruthenium complex **34** are depicted as examples of adducts that could both be accessed in good to excellent yields. Additionally, ruthenium complex **35** participated in a triple annulation process with benzyne to extend all three ligands concurrently (Figure 4C). This reaction provided **36** in 57% yield through the formation of six C–C bonds in a single transformation. Of note, this product displays a significantly higher luminescence quantum yield and molar extinction coefficient compared with Ru(bpy)₃. Overall, this study demonstrates the ability of metal-catalyzed reactions of arynes to provide rapid access to organometallic complexes with extended conjugation. The scope

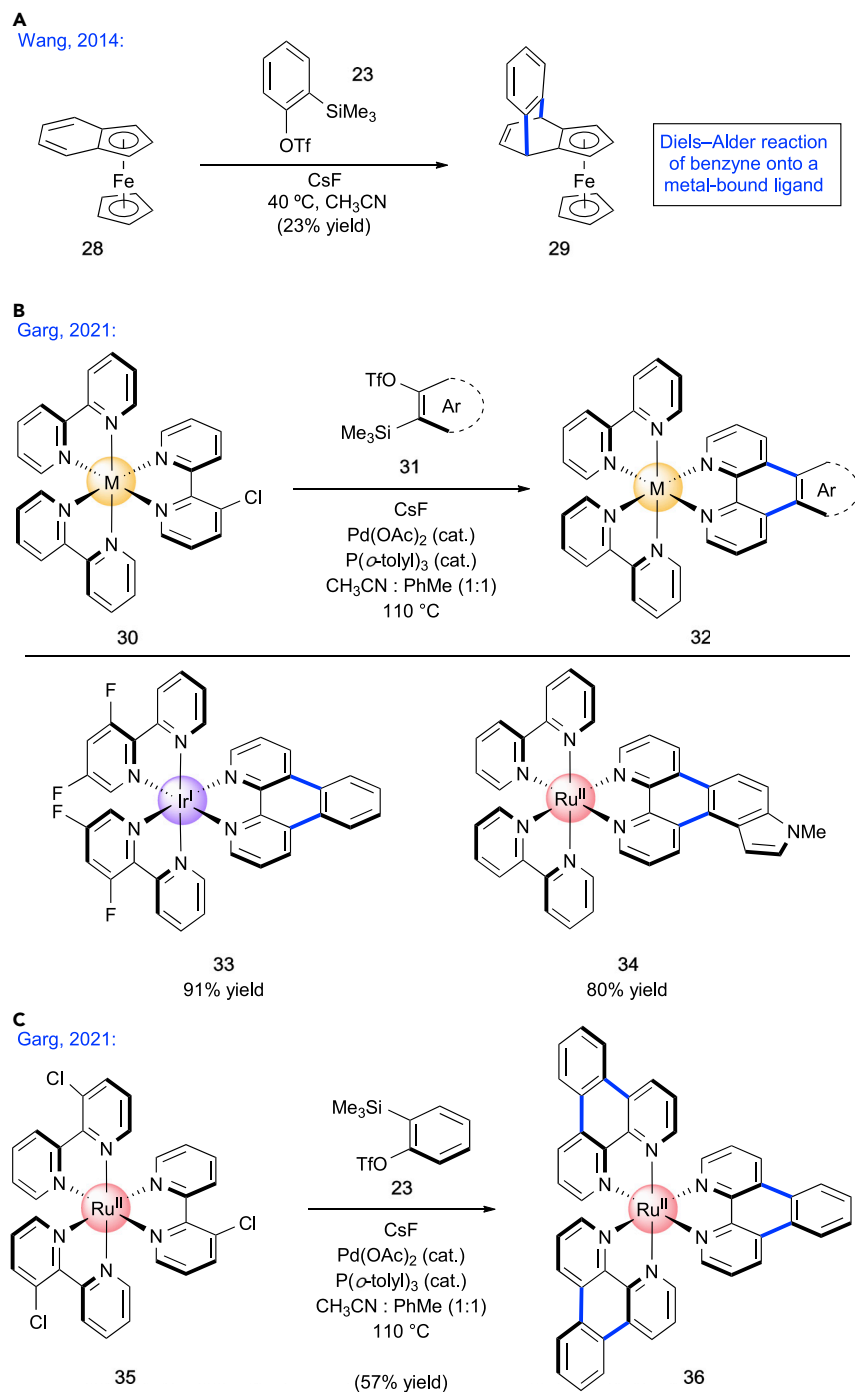


Figure 4. Arynes on the complex

(A) First reported cycloaddition of benzyne onto a metal-bound ligand.

(B) Selected palladium-catalyzed annulations of arynes with organometallic complexes.

(C) Palladium-catalyzed annulation with benzyne onto a ruthenium complex to expand the conjugation of three metal-bound ligands in a single step.

of aryne-mediated transformations of organometallic complexes continues to expand. For example,⁴⁶ studies by Inger and Polarski, where ligands are modified via the formation of aryne intermediates, are ongoing.

USE OF CYCLIC ALLENES IN ENANTIOSELECTIVE METAL-CATALYZED ANNULATIONS

Strained cyclic allenes, despite being known since the 1960s, have only recently gained significant use in chemical synthesis.^{2,47–72} Like arynes, cyclic allenes can be used to generate two new bonds, offering a means for efficiently building polycyclic scaffolds. In addition, cyclic allenes are chiral, which can allow for the generation of sp^3 centers, typically through cycloaddition reactions. Compared with arynes, strained, cyclic allenes have seen far less use in metal-catalyzed transformations. The first examples of transition-metal-mediated transformations of strained cyclic allenes were reported by Guitián in 2006 and 2009.^{47,48} Only recently have enantioselective annulations been discovered.

Two asymmetric transition metal-catalyzed annulations of strained, cyclic allenes were developed in our laboratory and are shown in Figure 5.^{50,52} Treatment of racemic cyclic allene precursors **37** and benzotriazinones **38**, in the presence of Ni and Josiphos ligand **40**, gave rise to enantioenriched tricycles **39** (Figure 5A). The transformation is thought to proceed by denitrogenation of **38**, to give an organometallic species in catalytic quantities, which, in turn, traps the fleeting cyclic allene intermediate. Formation of adducts **41–43** provide examples of compounds that were accessible using this methodology in synthetically useful yields and enantioselectivities. More recently, a palladium-catalyzed annulation involving strained, cyclic allene precursors **44** and iodoaniline pronucleophiles **45** was developed (Figure 5B). This methodology provided access to racemic compounds such as **48–50** in good to excellent yields using DavePhos ligand **47**. An enantioselective variant of this reaction, utilizing MandyPhos **54** as a ligand, was also demonstrated. In this case, racemic cyclic allene precursor **51** and iodopyridine **52** underwent palladium-catalyzed annulation to afford tricycle **53** in 64% yield and 90% ee (Figure 5C). Collectively these studies demonstrate the ability of strained, cyclic allenes to be leveraged in metal-catalyzed transformations to access heterocycles with stereocenters, including examples that proceed with high enantioselectivity.

LOOKING FORWARD

Merging strained intermediates with transition-metal catalysis can result in direct access to a variety of complex molecules. The recent studies highlighted herein specifically demonstrate that transition-metal-catalyzed transformations of strained intermediates can be leveraged to access both organometallic complexes and enantioenriched heterocycles.

Despite these recent advances, there is much room for the continued expansion of metal-mediated transformations of strained intermediates. Looking forward, methods that merge strained intermediates with transition-metal catalysis may push the boundaries on what types of molecules can be accessed synthetically. For example, new advances could allow access to chiral building blocks for the assembly of medicinal agents, materials, agrochemicals, or other compounds of importance. One area we are particularly excited about is the use of strained intermediates and metal catalysis in the total synthesis of natural products. Such efforts would not only prove useful in the preparation of target molecules but could also serve to push the limits of known methods and spawn the invention of new ones. Finally, the use of metal-catalyzed reactions of strained intermediates could be leveraged to access unique chiral molecules, with recent relevant examples reported related to axially chiral helicenenes.^{73,74} The merger

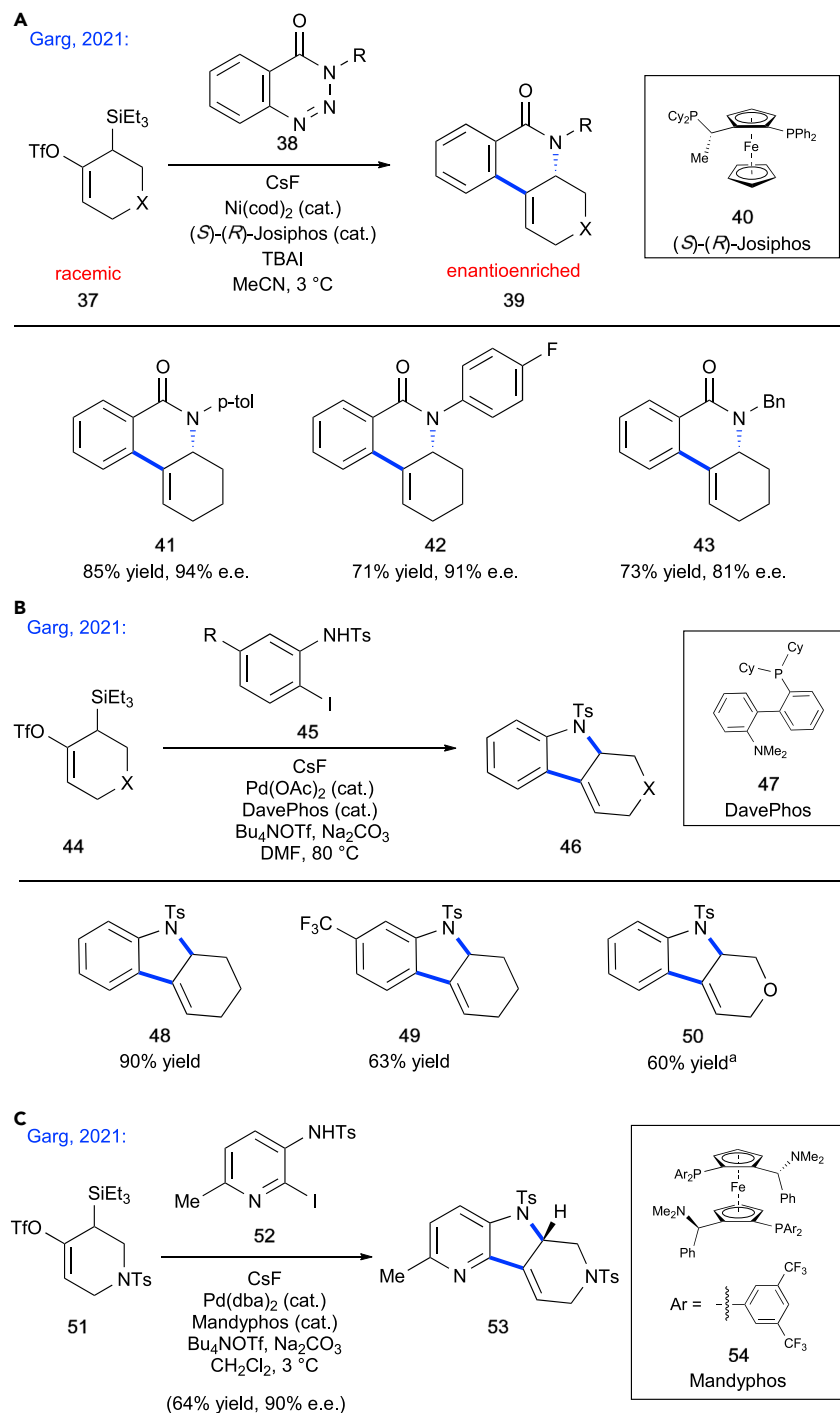


Figure 5. Transition-metal-catalyzed annulations

(A) Selected examples of enantioselective nickel-catalyzed annulations with cyclic allenes.

(B) Selected examples of palladium-catalyzed annulations of strained cyclic allenes.

(C) Enantioselective variant of the palladium-catalyzed annulation methodology.

of strained intermediates with transition-metal catalysis is likely to provide access to increasingly diverse scaffolds with unique physical, chemical, and biological properties.

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AUTHOR CONTRIBUTIONS

All authors contributed to the conceptualization, writing, and editing of the manuscript. K.A.S. and A.T.M. contributed equally.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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