Synthesis P. Sihag, M. Jeganmohan Special Topic

Recent Advances in Transition-Metal-Catalyzed C–H Functionalization Reactions Involving Aza/Oxabicyclic Alkenes

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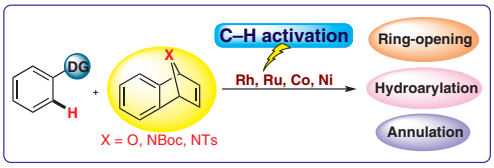

Dedicated to Prof. Shinji Mura for his outstanding contributions to organic synthesis using transition-metal catalysis.

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Abstract Bicyclic alkenes, including oxa- and azabicyclic alkenes, readily undergo activation with facial selectivity in the presence of transition-metal complexes. This is due to the intrinsic angle strain on the carbon–carbon double bonds in such unsymmetrical bicyclic systems. During the past decades considerable progress has been made in the area of ring opening of bicyclic strained rings by employing the concept of C–H activation. This short review comprehensively compiles the various C–H bond activation assisted reactions of oxa- and azabicyclic alkenes, viz., ring-opening reactions, hydroarylation, and annulation reactions.

Key words C–H activation, bicyclic alkenes, 7-oxabenzonorbornadienes, 7-azabenzonorbornadienes, ring-opening, hydroarylation, annulation

Masilmani Jeganmohan was born in Vazhapattampalayam, Tamilnadu, India, in 1978. He received his master's degree in organic chemistry from the University of Madras in 2001. He earned his Ph.D. in 2005 from the National Tsing Hua University, Taiwan, under the guidance of Prof. Chien-Hong Cheng, and then pursued postdoctoral work in the same laboratory (2005–2009). He subsequently moved to Ludwig-Maximilians-Universität, Munich, Germany, to undertake postdoctoral studies, supported by the Alexander von Humboldt Foundation, with Prof. Paul Knochel (2009 to 2010). He started his independent research career in November 2010 at IISER Pune as an assistant professor. In April 2016, he was promoted to associate professor at IISER Pune. Since October 2016, he has been working as an associate professor at the Indian Institute of Technology Madras. He is the recipient of the DAE Young Scientist Research Award (2011), the Science Academy Medal for a Young Associate, Indian Academy of Sciences (2012–2015), the Science Academy Medal for Young Scientists, Indian National Science Academy (2013), the Alkyl Amines – ICT Young Scientist Award from the Institute of Chemical Technology Mumbai (2013), the ISCB Award of Appreciation for Chemical Science, CSIR-CDRI, India (2014), and is a Fellow of the Royal Society of Chemistry (2019). His research interests include the development of new synthetic methods using metal complexes as catalysts, asymmetric synthesis and natural product synthesis.

1 Introduction

Heterobicyclic olefins are versatile synthons for constructing biologically and medicinally significant compounds containing multiple stereocenters.[1a] Of these, 7-oxa/azabenzonorbornadienes are extremely important and reactive synthetic intermediates. The presence of a free alkene, bridged heteroatoms (for the coordination of electrophiles, Lewis acids, and metals), and ring strain contributes to the reactivity of these compounds. They are the crucial precursors for synthesizing medicinally relevant molecules such as benzocarbazoles, sertraline, dihydrexidine, and aphanorphine.[1b] E. J. Corey proposed an asymmetric method for synthesizing such strained oxabenzonorbornadienes via the Diels–Alder reaction between 2,5-dimethylfuran and diverse dienophiles.[2a] In addition, Suzuki report-

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ed the Diels–Alder reaction of in situ generated benzyne precursors (using *n*-BuLi) with furan.[2b] Another method to synthesize these bicyclic systems is to employ in situ generated benzyne (formed by the reaction between anthranilic acid and isoamyl nitrite) and furan/*N*-Boc-pyrrole in DME as the solvent.

These bicyclic strained systems undergo a variety of ring-opening,[3] hydrofunctionalization,[4] cycloaddition,[5] and C–H activation reactions. The ring-opening reaction has received more attention because various natural products and biologically active molecules have been synthesized by employing this methodology. Numerous research groups have reported transition-metal-catalyzed ring-opening desymmetrization reactions of oxo- and azabicyclic alkenes with nucleophiles in the past two decades. Different nucleophiles, including hydrides, carbanions, alcohols, amines, and carboxylates, have been employed in these reactions.[6] This transformation results in the generation of two new stereogenic centers in a highly diastereoselective manner.

Two activation modes have been employed for the ring opening of these heterobicyclic olefins: Lewis acid activation and transition-metal activation. In the former, the Lewis acid coordinates to the heteroatom followed by the generation of an allyl-type cation leading to reactions with nucleophiles to form the corresponding products. In the latter case, after the *exo*-coordination of the metal complex, three reaction pathways are possible: (1) carbometalation followed by β-heteroatom elimination leading to the *cis*-product, (2) oxidative insertion followed by S_N2 nucleophilic attack resulting in a product with *trans*-geometry, and (3) formation of a π-allyl intermediate followed by reductive elimination to form a *cis*-product (Figure 1). The type of metal and nucleophile determine which pathway is followed.[7]

In 2013, Li reported pioneering research employing the concept of transition-metal-assisted C–H activation for the ring-opening/coupling with the oxa/azabenzonorbornadienes.[8] For the first time, an Rh(III) catalyst was employed for the ring opening of strained bicyclic systems leading to a naphthylated product. Since then, other transition-metal catalysts such as ruthenium and cobalt have also been explored. In this case, the initially cyclometalated arene intermediates, produced via chelation with the directing group, further coordinate with the heterobicyclic alkene. Subsequently, migratory insertion occurs, which is the enantiodetermining step. Additionally, β-heteroatom elimination can give the ring-opened product; alternatively, direct reductive elimination occurs, incorporating the bicyclic core into the final product.

In the case of the ring-opening reaction, it is challenging to control elimination of the hydroxy or amine group from the ring-opening product. It has been found that this can be achieved by controlling the reaction conditions used for a particular aryl substrate. In general, the presence of excess silver salt in the reaction mixture favors elimination, leading to a naphthylated product. Apart from ring-opening-type reactions, hydroarylation and oxidative cyclization of bicyclic alkenes with substituted aromatics catalyzed by rhodium or ruthenium have also been well explored.

In this short review, we discuss the various literature reports on the concept of C–H bond activation assisted ring-opening reactions of these strained bicyclic systems. In addition, reports on hydroarylation and annulation reactions employing 7-oxa/azabenzonorbornadienes have been included.

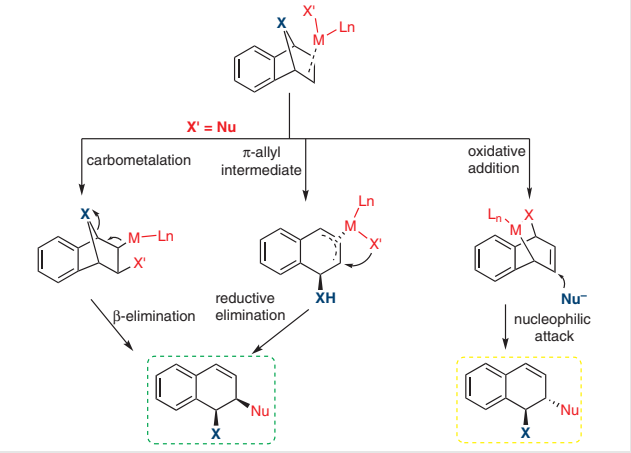


Figure 1 Transition-metal-activated ring-opening pathways

2 Reactions of Heterobicyclic Ring Systems

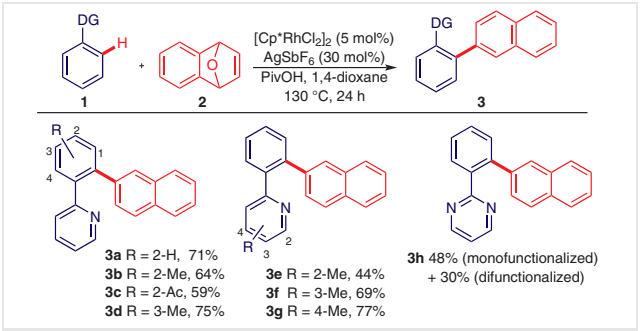
2.1 Ring-Opening Reactions of Oxa- and Azabenzonorbornadienes

2.1.1 Reactions Using 7-Oxabenzonorbornadienes

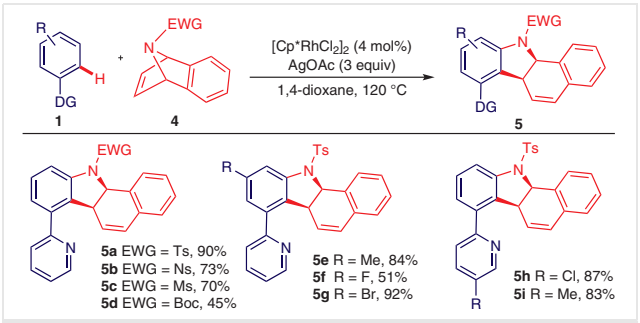
In 2013, Li and Qi reported their work utilizing norbornadiene systems for C–H activation and subsequent (ring-opening) coupling with other cyclic structures possessing different directing groups.[8] The reaction involves the generation of a Rh(III)–C bond via C–H activation, followed by insertion into the strain-activated C=C bond in 7-oxa/azabenzonorbornadienes and subsequent ring opening. The coupling of 7-oxa/azabenzonorbornadienes occurs under redox-neutral and oxidative conditions, respectively. In this reaction, mono- and difunctionalized products have been observed, depending on the directing group employed. The reaction of 2-phenylpyridine **1** with 7-oxabenzonorbornadiene (**2**) in the presence of $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (30 mol%) and PivOH (2.0 equiv) in 1,4-dioxane at 130 °C resulted in naphthylated product **3** in 71% yield. It has been

observed that substrates containing electron-donating and electron-withdrawing groups at different positions on the phenyl and pyridine rings all coupled smoothly with **2** to give the naphthylation products **3a–h** in 59–77% yields (Scheme 1). However, the coupling of 2-phenylpyridine with 7-azabenzonorbornadiene **4** did not occur under the above redox-neutral conditions; instead, the reaction follows an oxidative pathway as product formation requires a stoichiometric amount of AgOAc as the oxidant (Scheme 2). Similar to the 2-naphthylation reaction, in this case, a broad scope of directing groups was tolerated. Also, substrates with different substituents on the phenyl and pyridine rings resulted in the cyclization products **5a–i** in good to high yields. Mechanistic studies revealed that this reaction with azabenzonorbornadiene proceeds via a double C–H activation pathway, which involves a seven-membered rhodacycle complex as a key intermediate. The *cis* insertion of the Rh–C(aryl) bond into the olefin unit has been confirmed from the X-ray structure of the rhodacycle intermediate.

A plausible mechanism for this reaction is shown in Scheme 3. Once intermediate **A** has formed, there are two possible reaction pathways. In pathway 1, β-nitrogen elimination occurs to give the amidate **B**, which undergoes cyclometalation to afford the six-membered rhodacycle **D**. Subsequent reductive elimination gives the product along with a rhodium(I) intermediate that is reoxidized to Rh(III) to complete the catalytic cycle. In the case of pathway 2, **A** undergoes cyclometalation before β-nitrogen elimination to result in the same intermediate **D**. The pathway followed directly depends on the relative rate of the cyclometalation versus the β-nitrogen elimination. Also, NMR analyses gave

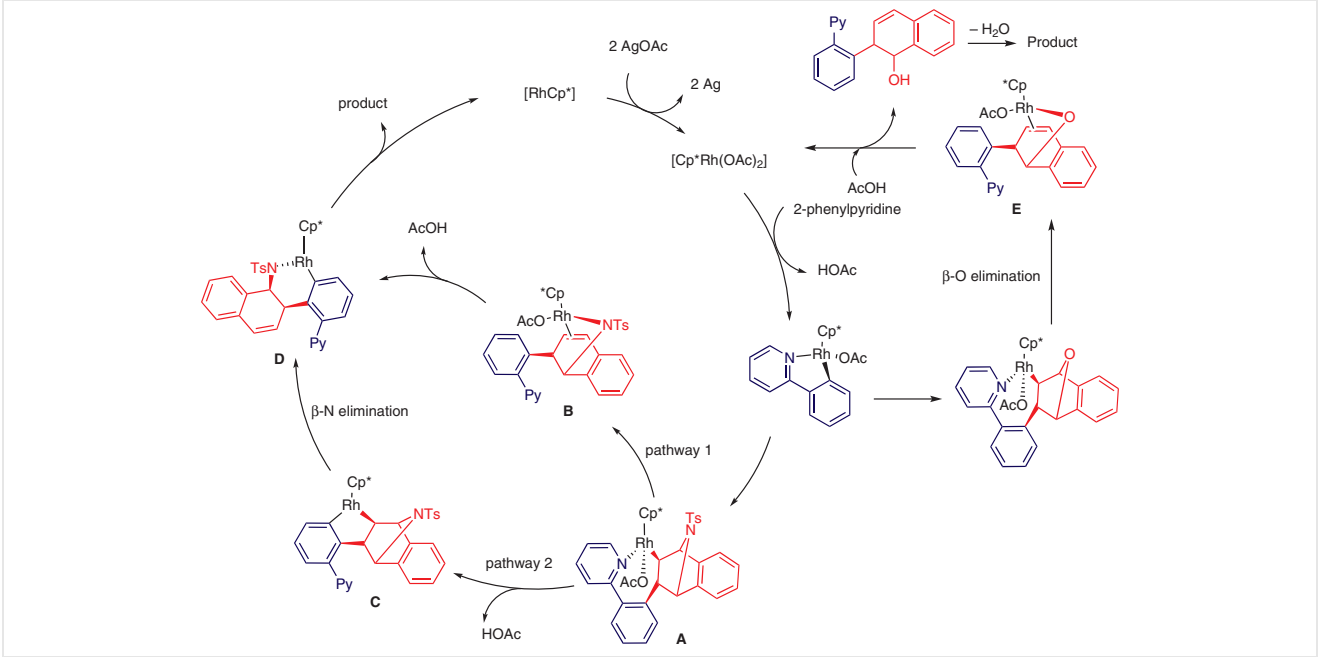


Scheme 1 Dehydrative coupling with 7-oxabenzonorbornadienes[8]



Scheme 2 Oxidative coupling with 7-azabenzonorbornadienes[8]

indicated that essentially no C–N coupling occurred, and it was thus concluded that pathway 1 was less likely, and that pathway 2 was strongly preferred. In the case of the coupling of 7-oxabenzonorbornadiene, it has been proposed

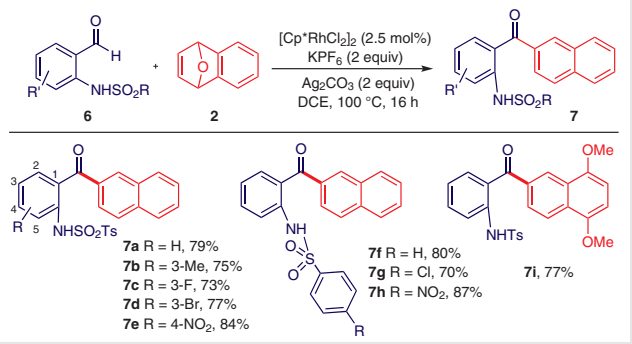


Scheme 3 A plausible mechanism for dehydrative and oxidative coupling

that β-oxygen elimination occurs preferentially resulting in intermediate **E** after olefin insertion. Further, protonolysis of the Rh–O bond by an acid releases the dihydronaphthol intermediate, which is then dehydrated to give the product.

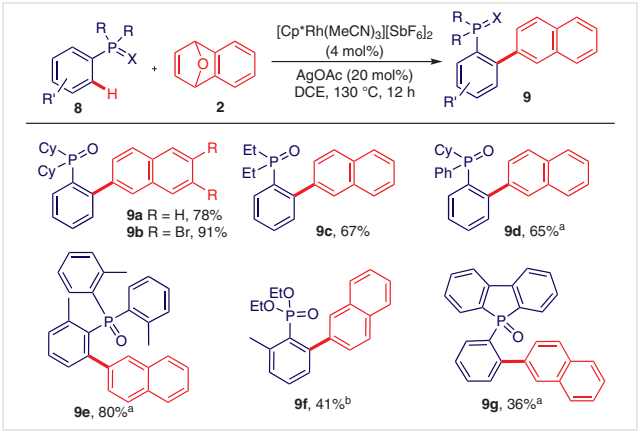
Later, Li's group demonstrated a Rh(III)-catalyzed redox-neutral coupling of *N*-sulfonyl 2-aminobenzaldehydes with oxygenated allylic olefins such as 7-oxabenzonorbornadienes and allyl carbonate (Scheme 4).[9] In this case, C–H activation is proposed to occur via an oxidative addition pathway. The dehydrative coupling reaction of N-Ts 2-aminobenzaldehyde **6** with 7-oxabenzonorbornadiene (**2**) was carried out using $[Cp^*RhCl_2]_2$ (2.5 mol%) as the catalyst and Ag_2CO_3 (2 equiv) as the base in the presence of KPF_6 and DCE as the solvent. During optimization, it was observed that when Ag_2CO_3 was omitted or switched to K_2CO_3, the coupling occurred with lower efficiency. This attests to the unique role of Ag_2CO_3 as a base, although it is a typical oxidant in coupling reactions. This methodology is also compatible with substrates with differently substituted N-Ts 2-aminobenzaldehydes, yielding products **7a–i** in good to moderate yields.

The rhodium-catalyzed redox-neutral direct *ortho*-arylation of aryl phosphine derivatives **8** with heterobicyclic alkene **2** has been reported by Miura et al. (Scheme 5).[10] Several biaryl phosphine derivatives **9a–g** have been obtained from various substituted aryl phosphine oxides. During optimization, it was found that the cationic rhodium species generated in situ was less effective than $[Cp^*Rh(MeCN)_3(SbF_6)_2]$. Furthermore, a one-pot synthesis of dibenzophosphole derivatives from the combination of rhodium-catalyzed *ortho*-arylation and acid-mediated intramolecular phospha-Friedel–Crafts reaction was possible from readily available diarylphosphinothionic amides.



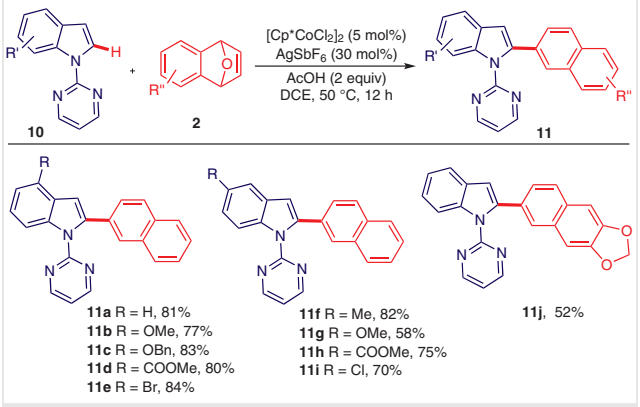
Scheme 4 Dehydrative coupling with 7-oxabenzonorbornadienes[9]

Further, in 2016, Li's group demonstrated a Co(III)-catalyzed C–H arylation of *N*-pyrimidinylindoles **10** with 7-oxabenzonorbornadienes **2** as the naphthylating reagents. They employed $[Cp^*CoCl_2]_2$ (5 mol%) as the catalyst, $AgSbF_6$ (30 mol%), AcOH (2 equiv) and DCE as the solvent at 50 °C for 12 hours (Scheme 6).[11a] The amount of silver additive present



Scheme 5 Reactions of arylphosphine derivatives **8** with heterobicyclic alkene **2**.[10] [a] Substrates **8** (0.5 mmol) and **2** (0.25 mmol) were used. [b] AgOAc (0.5 mmol) was used.

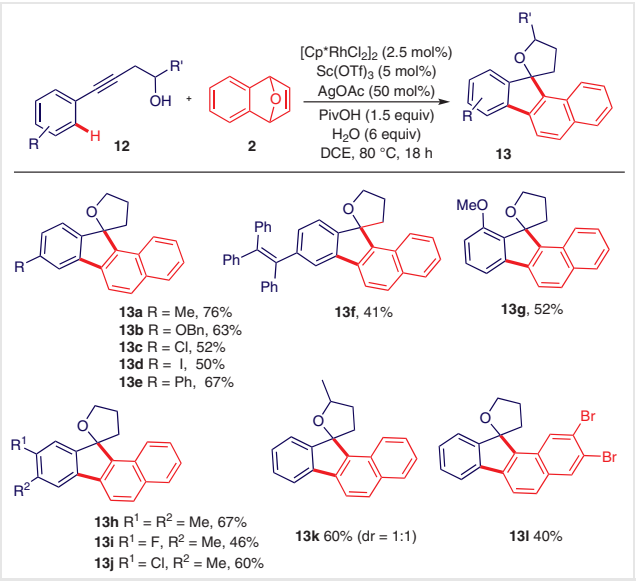
in the reaction had a drastic effect on the reaction yield. It is expected that the presence of excess silver likely activates the 7-oxabenzonorbornadiene substrate as a Lewis acid. This reaction shows good compatibility with *N*-pyrimidinylindoles and 7-oxabenzonorbornadienes substituted with different electron-withdrawing and electron-donating groups, resulting in naphthylated products **11a–j** in good to moderate yields.



Scheme 6 Dehydrative coupling of indoles **10** with 7-oxabenzonorbornadienes **2**[11a]

The presence of substituents at the 3- and 7-positions of the indole and on the pyrimidine ring had minimal influence indicating a tolerance towards steric effects. Further, based on a competition experiment, it has been suggested that the C–H activation probably occurs via a concerted metalation–deprotonation (CMD) mechanism. Cheng's group reported similar methodology in 2017 utilizing a cobalt catalyst for the arylation of various aromatic systems, e.g., *N*-pyrimidinylindoles and 2-arylpyridines, with oxygen-containing bicyclic ring systems.[11b]

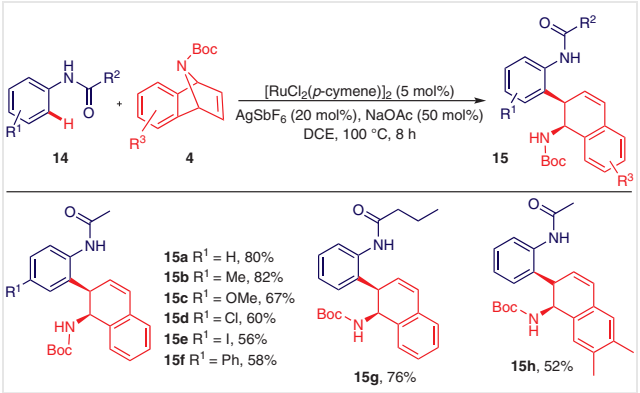
A synergic bimetallic-catalyzed cascade reaction of alkynols **12** and 7-oxabenzonorbornadienes **2** was reported by Liu et al. in 2016 (Scheme 7).[12] This methodology provided spirocyclic dihydrobenzo[*a*]fluorenefurans **13** with excellent regioselectivity and in good yields. This methodology has been proposed to involve three main steps, viz., transient hemiketal group directed C–H activation, dehydrative naphthylation, and intramolecular Prins-type cyclization.



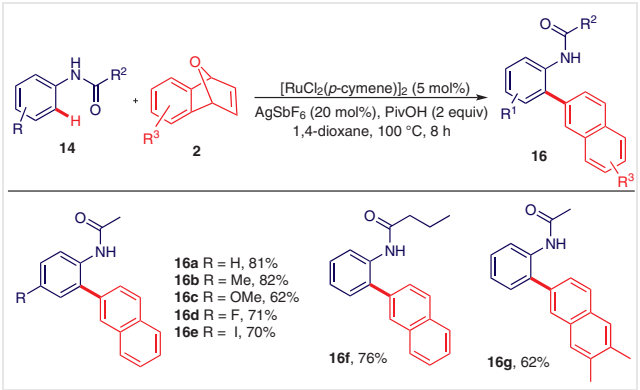
Scheme 7 Synergic bimetallic cascade reactions of alkynols **12** and 7-oxabenzonorbornadienes **2**[12]

Treatment of alkynol **12** with 7-oxabenzonorbornadiene (**2**) in the presence of $[Cp^*RhCl_2]_2$ (2.5 mol%) and $Sc(OTf)_3$ (5 mol%) as the catalysts and AgOAc (0.5 equiv), PivOH (1.5 equiv) and H_2O (6 equiv) as additives in DCE at 80 °C for 18 hours resulted in the spirocyclic product. In this methodology, various alkynols substituted with different functional groups and possessing a secondary hydroxy group were compatible, providing products **13a–l** in good to moderate yields. Further, mechanistic studies and density functional theory calculations indicated that C–H bond cleavage was the rate-determining step and provided evidence for the key roles of both the transient hemiketal and synergistic Rh(III)/Sc(III) catalysis.

In 2018, Zhang's group reported a ruthenium-catalyzed redox-neutral ring-opening reaction for the assembly of valuable hydronaphthylamines **15** from anilides **14** and 7-azabenzonornadienes **4**.[13] Treatment of the anilides with 7-azabenzonornadienes in the presence of $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $AgSbF_6$ (30 mol%) and NaOAc (50 mol%) in 1,2-dichloroethane (DCE) at 100 °C for 8 hours provided functionalized products **15a–h** in good to moderate yields (Scheme 8). The transformation exhibited high stereoselectivity to afford *cis*-configured products. 7-Oxabenzonornadienes **2** were also compatible with this catalytic system and gave functionalized naphthalenes **16a–g** under modified reaction conditions (Scheme 9). Mechanistic studies suggested the occurrence of C–H activation via a concerted metalation–deprotonation mechanism.



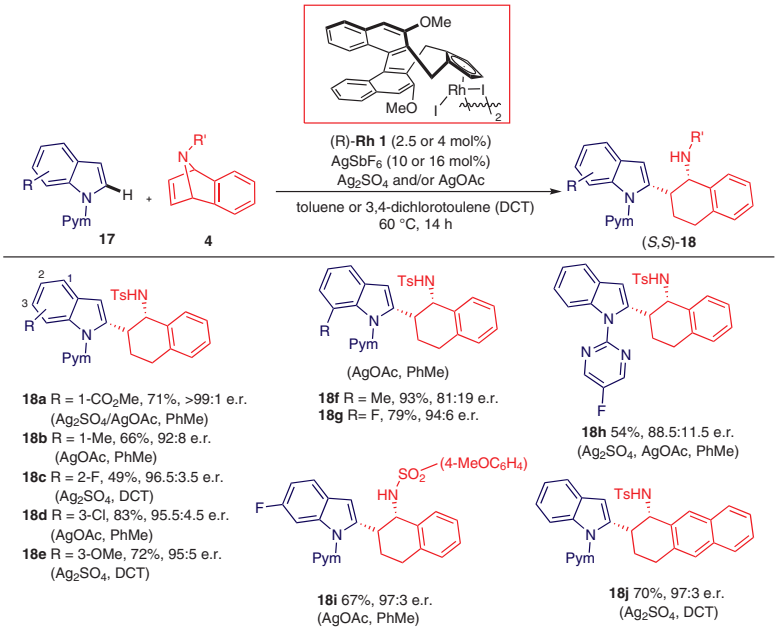
Scheme 8 Redox-neutral ring-opening reactions of anilides **14** and 7-azabenzonornadienes **4**[13]



Scheme 9 Direct ring-opening reactions of 7-oxabenzonorbornadienes **2** with anilides **14**[13]

2.1.2 Reactions Using 7-Azabenzonorbornadienes

Li's group described asymmetric ring openings of bicyclic systems with good to excellent enantioselectivities by combination of a Cramer-type $Cp^XRh(III)$ catalyst and silver additives (Scheme 10).[14] This methodology was designed to overcome the challenges of unwanted elimination leading to naphthylated products and to the control the enantioselectivity of the reaction by sufficient steric bias between the directing group and the arene ring. This was made possible by carrying out the enantioselective C–C coupling of N-substituted indoles **17** with azabenzonorbornadienes **4** using (*R*)-Rh **1**/$AgSbF_6$ to afford the dihydronaphthylamines (*S*,*S*)-**18a–j** in moderate yields and good enantioselectivities. Solvent screening revealed that combinations of AgOAc/3,4-dichlorotoluene (DCT) and Ag_2SO_4/toluene were optimal. While extending the substrate scope of this

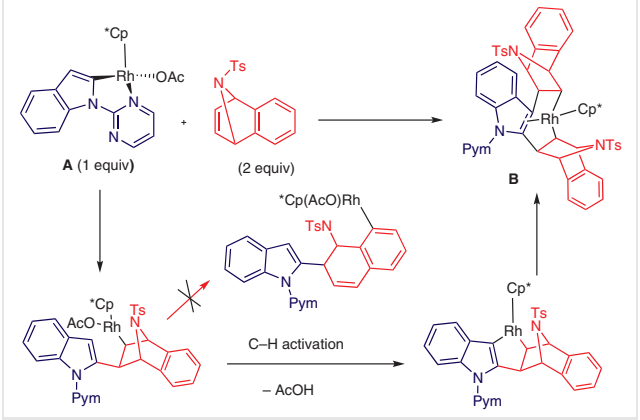


Scheme 10 Asymmetric ring opening of bicyclic systems[14]

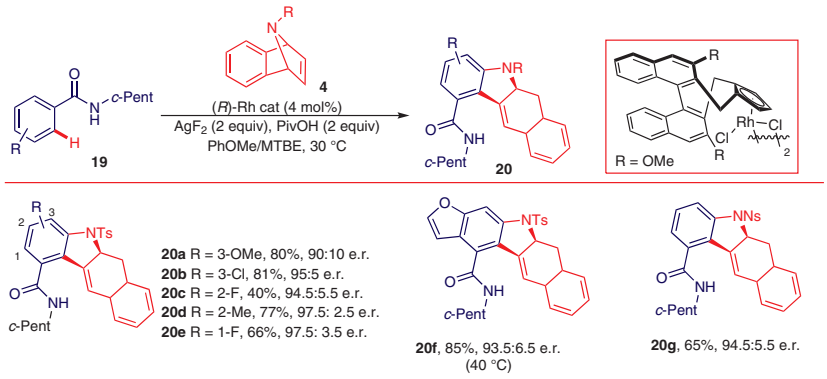
methodology, it was observed that the reaction outcomes were strongly dependent on the nature of the indole substrate and the azabenzonorbornadienes; hence, for a particular substrate, a particular silver salt/solvent combination provided a better yield and enantioselectivity. A significant impact of the C7-substituent on the enantioselectivity was also observed.

It has been proposed that the reaction follows a sequence of olefin migratory insertion, acetate-assisted C3-H activation and a second migratory insertion (Scheme 11), leading to the formation of a complex which is isolated and characterized by single-crystal X-ray diffraction (XRD). It has also been inferred that neither **A** nor **B** is catalytically active during the reaction. Further, mechanistic studies confirmed the role of $AgSbF_6$ in preventing the undesired C3-H activation as the reaction of the rhodium complex **A** in the presence of $AgSbF_6$ results in the desired monofunctionalized product.

Subsequently, Li's group reported the [3+2] annulation of *N*-cyclopentylbenzamides **19** with 7-azabenzonorbornadienes **4** using a similar Cramer-type Rh catalyst for the enantioselective synthesis of *cis*-fused dihydrocarbazoles **20a–g** (Scheme 12).[15] Different arenes and azabenzonorbornadienes were examined and all were smoothly converted into the desired products **20a–g** in good yields and enantiomeric ratios. During solvent optimization, it was found that anisole provided a high yields, whereas methyl *tert*-butyl ether (MTBE) was favorable for high enantioselectivities but reduced the yields. Hence, using a combination of MTBE/PhOMe allowed isolation of the desired products in high yields and enantioselectivities. Mechanistically, it has been proposed that the arene ring is oriented toward the rear, so when an olefin approaches with the NTs group pointed upward to minimize steric interactions with the ligated arene, *cis* insertion occurs *syn* to the NTs group, leading to the observed enantioselectivity. In addition, under slightly modified reaction conditions, a variety of aryl ethers also proved to be viable substrates, where a (4-methyl)-1-isoquinolyl moiety acted as a directing group.

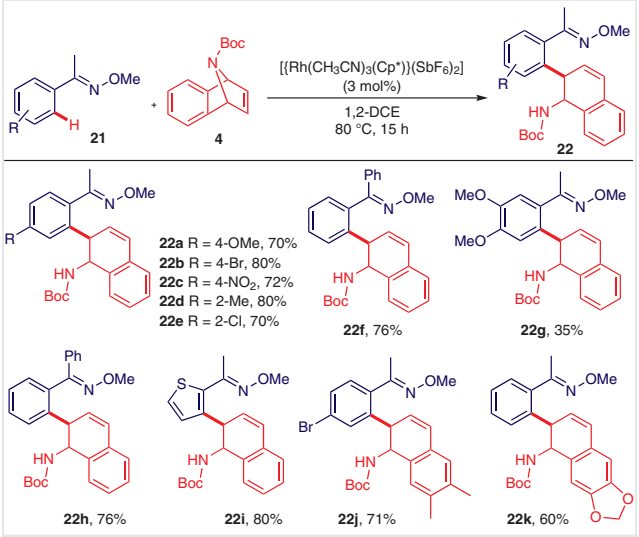


Scheme 11 Mechanistic studies: a stochiometric-scale reaction



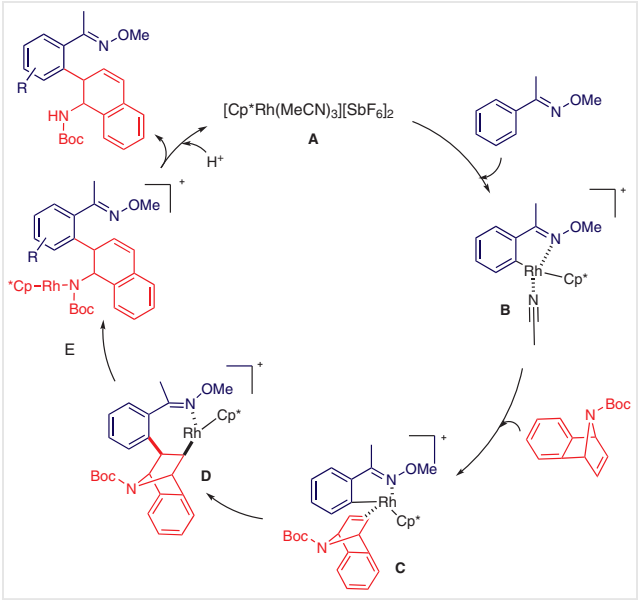
Scheme 12 [3+2] Annulations of *N*-cyclopentylbenzamides **19** with 7-azabenzonorbornadienes **4**[15]

Our group has also reported the rhodium(III)-catalyzed redox-neutral ring opening of 7-azabenzonorbornadienes with aromatic ketoximes **21** to afford 2-arylated hydronaphthylamines **22a–k** in a highly diastereoselective manner (Scheme 13).[16] This protocol is suitable for different substituted ketoximes and bicyclic ring systems, resulting in good to moderate product yields. Further, the products have been converted into fused tetracyclic benzophenanthridine derivatives by acid hydrolysis followed by aromatization in the presence of DDQ.



Scheme 13 Redox-neutral ring opening of 7-azabenzonorbornadienes **4** with aromatic ketoximes **21**[16]

A plausible mechanism for this ring opening is shown in Scheme 14. Initially, the rhodium species **A** is obtained by coordination of the lone pair of the nitrogen atom of the ketoxime, which is followed by C–H activation leading to the five-membered rhodacycle intermediate **B** along with loss of a proton. Further, the *exo* face coordination of the alkene π-bond of 7-azabenzonorbornadiene to the rhodium intermediate **B** forms intermediate **C**. Subsequently, the double bond is inserted into the Rh–C bond of the intermediate **C** to provide the seven-membered rhodacycle intermediate **D**. β-N elimination of the intermediate **D** affords the ring-opened intermediate. Finally, protonation of intermediate **E** yields the product and regenerates the active catalyst.

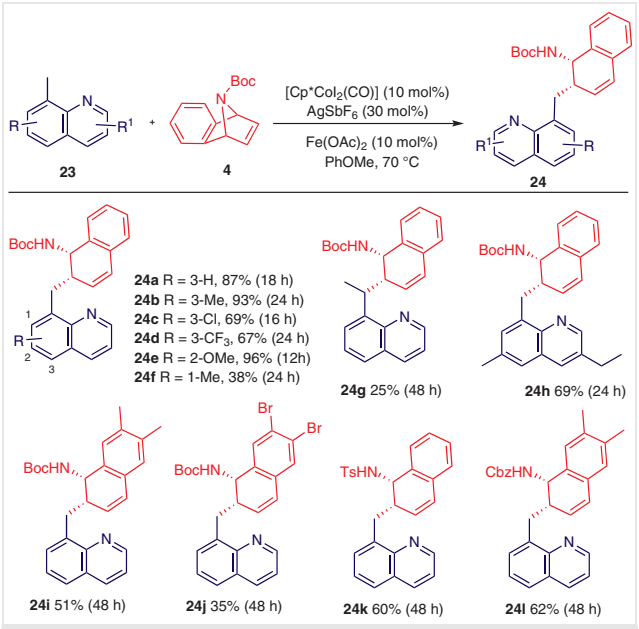


Scheme 14 A plausible mechanism for the ring opening of 7-azabenzonorbornadienes

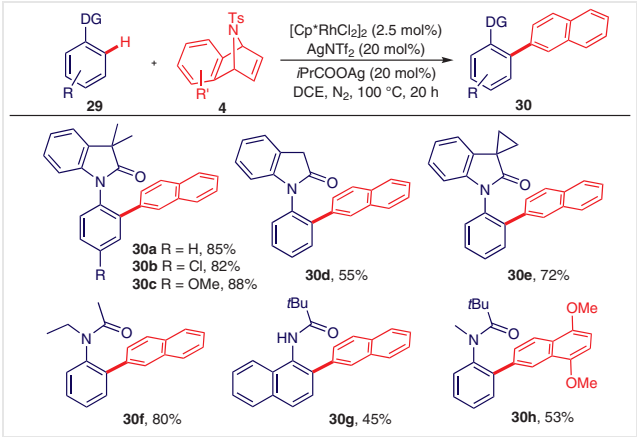
A pioneering report on the addition of C(sp^3)–H bonds to azabenzonorbornadienes using a cobalt catalyst was reported by Fan's group (Scheme 15).[17] The reactions of 8-methylquinolines **23** with azabenzonorbornadienes **4** using a catalytic system consisting of [Cp*CoI_2(CO)] (10 mol%), $AgSbF_6$ (30 mol%) and $Fe(OAc)_2$ (10 mol%) in PhOMe yielded the ring-opened C–H addition products. This methodology was compatible with various electron-donating and electron-withdrawing substituted 8-methylquinolines and azabenzonorbornadienes, resulting in functionalized deriva-

tives **24a–l** in good to excellent yields. Single-crystal XRD confirmed the *cis*-configuration of the products. Mechanistic studies demonstrated that a reversible C–H activation step was the rate-determining step.

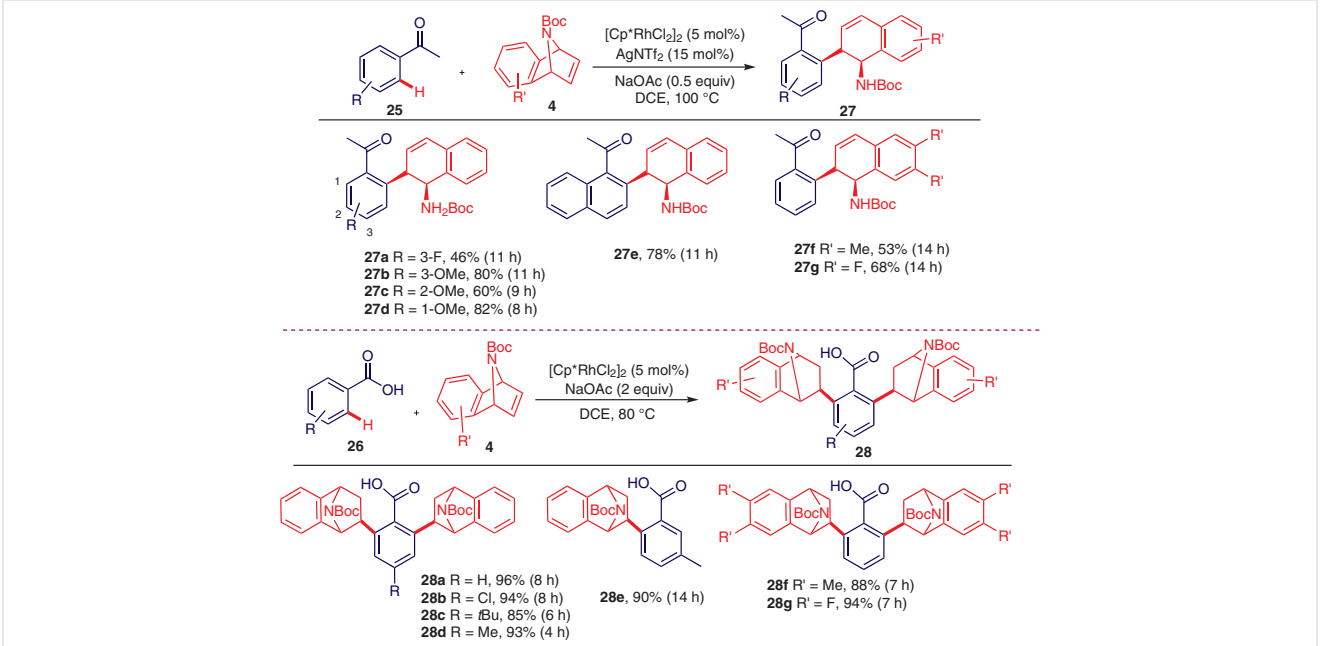
An efficient regioselective Rh-catalyzed addition reaction between weakly coordinating directing groups like ketones **25** and carboxylate arenes **26** with oxa/azabicyclic alkenes has been reported by Fan (Scheme 16).[18] The ketones and benzoic acids afforded different addition products **27** or **28** when reacted with oxa/azabicyclic alkenes. In the case of ketones, regioselective ring-opening addition occurred at the *ortho*-position of the ketone. In contrast, in the case of benzoic acids, 1:2 hydroarylation occurred at both *ortho* positions in the absence of a silver additive. This protocol is favorable for different substituted ketones and azabicyclic alkenes, giving mono-substituted products in good yields. It was observed that substitution at different positions of the benzoic acid affected the type of product formed. *para*-Substituted benzoic acids resulted in disubsti-



Scheme 15 Addition of C(sp^3)–H bonds to azabenzonorbornadienes[17]



Scheme 17 Naphthylation of anilides and benzamides **29** with 7-azabenzonorbornadienes[19]



Scheme 16 Addition reactions of weakly coordinating ketones **25** and carboxylate arenes **26** with oxa/azabicyclic alkenes[18]

tuted products. In contrast, *meta*- or *ortho*-methyl-substituted benzoic acids resulted in the corresponding monosubstituted products.

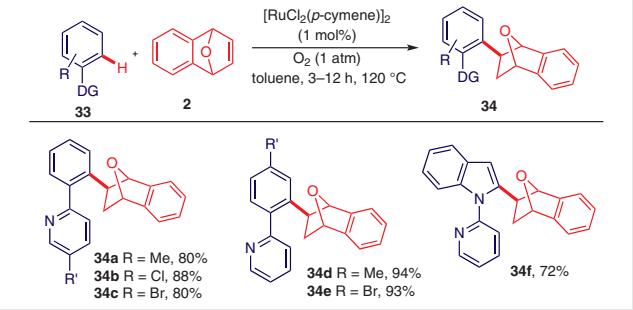
Recently, the Wang group reported the use of 7-azabenzonorbornadienes **4** as naphthylation reagents for the functionalization of anilides and benzamides **29** catalyzed by a Rh(III) catalyst (Scheme 17).[19] This methodology has broad substrate scope. In mechanistic studies, the role of the excess $AgNTf_2$ additive was identified as enabling the elimination of the NTs group leading to naphthylated products **30a–h**. It has been inferred that the reaction of the ring-opening product, which is expected to be that of the intermediate with $AgNTf_2$, resulted in the naphthylated products in good yields.

2.2 Hydroarylation Reactions

Another type of reaction is possible with these bicyclic systems that retains the heterobicyclic system core, i.e., hydroarylation-type reactions. The hydroarylation reaction allows keeping the backbone of the unsaturated starting material intact.

The Bolm group were the first to report the formation of hydroarylation products from a bicyclic alkene. It has been observed that the reactions of NH-sulfoximines **31** and benzo-substituted heterobicyclic olefins **2** in the presence of $[Cp^*Rh(MeCN)_3][BF_4]_2$ (2.5 mol%), $Fe(OAc)_2$ (20 mol%), and dioxygen (1 atm) in toluene at 120 °C resulted in saturated benzo-fused 7-oxanorbornane products **32a–g** instead of the oxidative olefination products (Scheme 18).[20] Various diversely substituted sulfoximines were reacted efficiently with alkenes **2** to give good to excellent product yields. Further, the hydroarylated product obtained on treatment with the methylsulfonic acid in chloroform under reflux conditions resulted in the *ortho*-naphthylated product. Also, aryl-fused thiazines were obtained by the palladium-catalyzed oxidative ring closure catalyzed by a combination of $Pd(OAc)_2$ and $PhI(OAc)_2$.

In 2015, the same group reported a ruthenium-catalyzed C–H bond activation leading to additions of (hetero)arenes **33** to bicyclic olefins **2** (Scheme 19).[21] The synthetically useful functionalized 7-oxa- and 7-azabenzonorbornane derivatives **34a–f** were obtained. In this report, no metal additives were required for catalyst activation. Instead, the presence of additives had a detrimental effect on product formation. It was observed that dioxygen played a decisive role in product formation, but its exact role remains unclear.



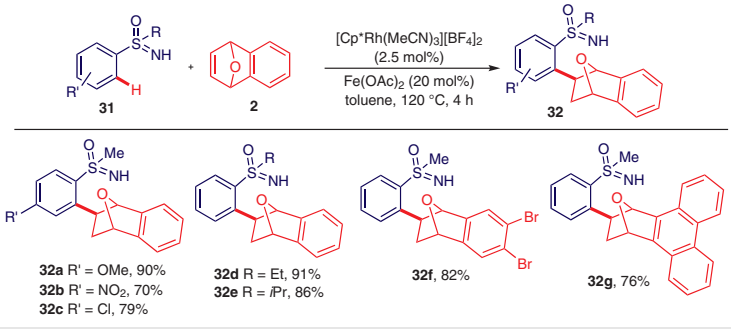
Scheme 19 Hydroarylation reactions of heteroarenes **33**[21]

The intermolecular carboaminations of bicyclic alkenes catalyzed by Cp*Co(III) via non-annulative redox-neutral couplings were reported by the Zhao group in 2019 (Scheme 20).[22] A range of substrates was explored under these carboamination conditions. Various substituted *N*-phenoxyacetamides **35** and bicyclic alkenes **36** were competent substrates, resulting in carboamination products **37a–o** in good to excellent yields and enantioselectivities. Further, this methodology has been extended for the diversification of various natural scaffolds such as estrone, tyramine, etc.

2.3 Annulation Reactions

Various annulations have been described using bicyclic systems as π-components. These reactions have been mostly reported using Co, Rh, and Ni catalysts.

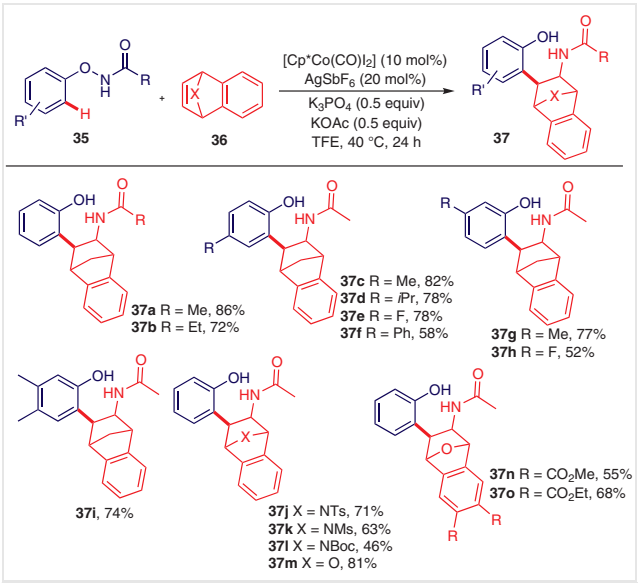
In 2017, Cheng's group reported unusual [3+2] cycloadditions of bicyclic ring systems with secondary amides.



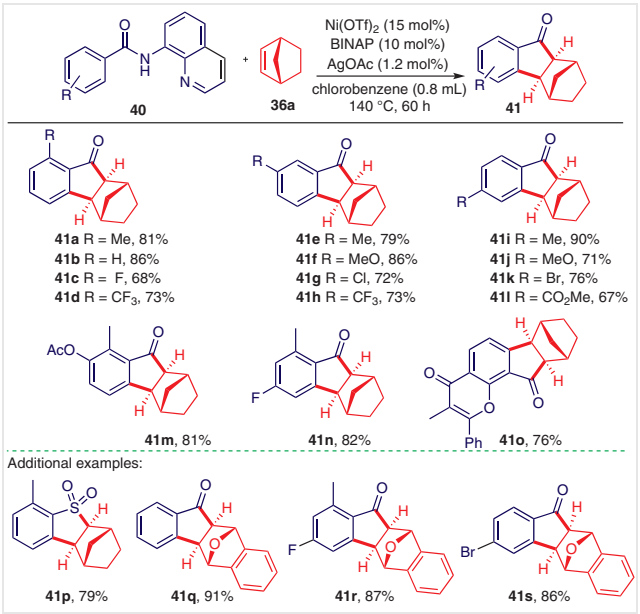
Scheme 18 Hydroarylation reactions of NH-sulfoximines **31** and benzo-substituted heterobicyclic olefin **2**[20]

This represented pioneering work on [3+2] annulations because transition-metal-catalyzed C–H activation reactions of secondary amides with alkenes usually lead to [4+2] or [4+1] annulations (Scheme 21).[23] The Co-catalyzed amide C(sp^2)–H bond activation/[3+2] annulation reaction with substituted *N*-(quinolin-8-yl)benzamides **38** and 7-oxabenzonorbornadiene **2** as well as other bicyclic systems **36** in the presence of $Co(OAc)_2$, Ag_2CO_3 and K_2CO_3 in 2,2,2-trifluoroethanol (TFE) as the solvent at 80 °C for 20 hours resulted in substituted dihydroepoxybenzofluorenone products **39a–m**. It was found that the reaction did not work when the quinolyl (Q) unit was replaced with an 8-aminoquinoline moiety. It has been inferred that the 8-aminoquinoline (AQ) released during the reaction coordinates to the metal, which probably reduces the catalytic activity of the Co catalyst. Mechanistic investigations indicated that the reaction might be catalyzed by a Co(III) species formed in situ from Co(II) by oxidation with Ag^+. It has also been found that the stereochemistry observed occurs due to *exo*-face insertion of the bicyclic system into a metalacyclic intermediate.

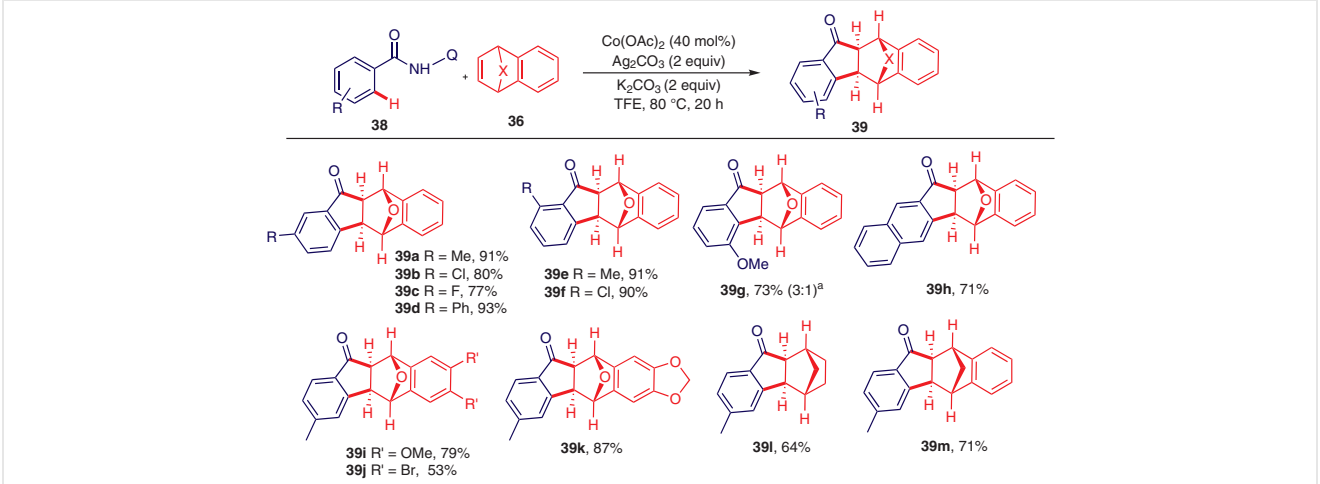
Later Chatani and Skhiri reported [3+2] annulation reactions of benzamides **40**, possessing an 8-aminoquinoline directing group, and norbornene (**36a**) using $Ni(OTf)_2$ as the catalyst, BINAP as an efficient ligand and AgOAc as an additive (Scheme 22).[24]



Scheme 20 Redox-neutral carboamination reactions of *N*-phenoxyacetamides and bicyclic alkenes[22]

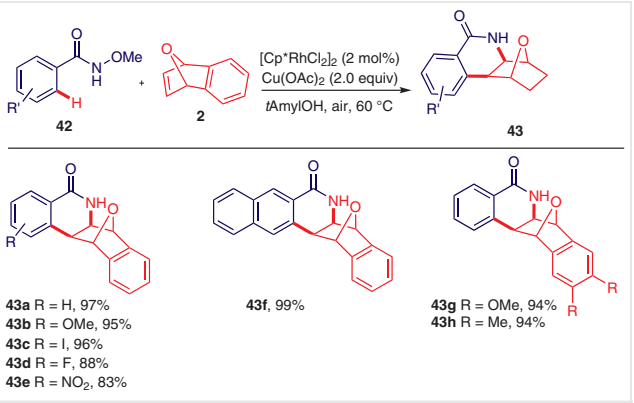


Scheme 22 Ni-catalyzed [3+2] annulation reactions[24]



Scheme 21 [3+2] Cycloadditions of bicyclic ring systems with secondary amides[23]

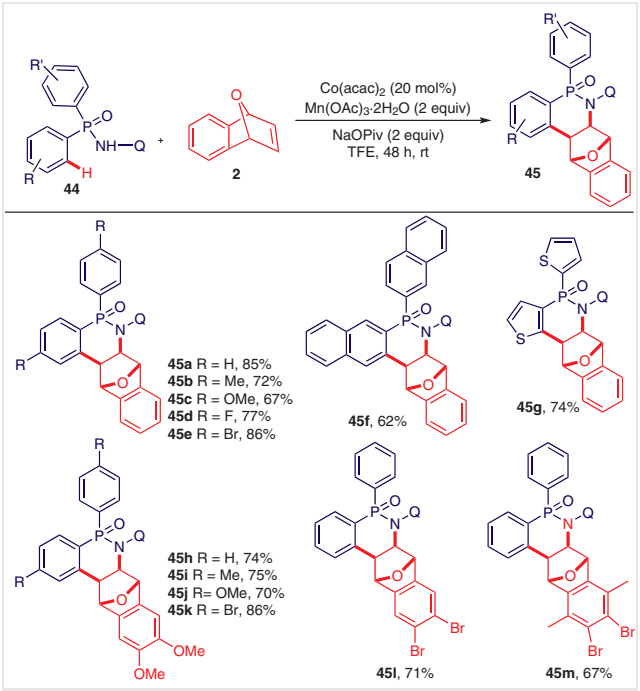
In 2017, the Bolm group developed the rhodium(III)-catalyzed annulation of *N*-methoxybenzamides **42** with 7-oxabenzonorbornadienes **2**, leading to synthetically relevant benzo[*b*]phenanthridinones **43a–h** (Scheme 23).[25a] *N*-Methoxybenzamides bearing both electron-donating and electron-withdrawing groups at various positions on the arene ring reacted smoothly with 7-oxabenzonorbornadiene to afford the corresponding annulated products in yields of 83–99%. Benzo[*b*]phenanthridinones have been prepared by the elimination reactions of annulation products in acidic medium. Further functionalization of the NH group leads to the synthesis of an anti-hepatitis C virus (HCV) active product.[25b] Similarly, the Co(III)-catalyzed [4+2] redox annulation reaction of *N*-methoxybenzamides with 7-oxa/azabenzonorbornadienes without any external oxidant has been reported by Volla's group using CsOAc as an additive and TFE as the solvent.[25c] Further, an acid-mediated ring-opening/aromatization of a product benzophenanthridinone has also been described.[25c]



Scheme 23 Annulations of *N*-methoxybenzamides **42** with 7-oxabenzonorbornadiene (**2**)[25a]

Volla's group has also reported an annulation reaction of diphenylphosphinamides **44** with the readily available bicyclic olefin **2** using $Co(acac)_2$ as the catalyst, $Mn(OAc)_3{\cdot}2H_2O$ as the oxidant, and NaOPiv as the base (Scheme 24).[26] It was found that the formed annulation products **45a–m** were the thermodynamically more favorable *exo*-isomers, as confirmed by single-crystal XRD studies. This methodology shows compatibility with differently substituted phoshinamides and bicyclic olefins, resulting in the desired substituted products in moderate to good yields.

Recently, annulations using sulfoxonium ylides as directing groups were reported by Li et al. (Scheme 25).[27] The sulfoxonium ylide also functions as an oxidizing carbene-type directing group. In this report, under different reaction conditions, [4+2] annulation and C–H (di)alkylation occurred. It was found that the introduction of PivOH shifted the selectivity to ring-retentive alkylation. Various sulfoxonium ylides bearing electron-donating and electron-withdrawing groups at the *ortho*, *meta* and *para* positions of the benzene ring all reacted smoothly with substituted 7-oxa/azabenzonorbornadiene to afford products **47a–r** in good to excellent yields. To demonstrate the synthetic utility of the products, a polycyclic aromatic hydrocarbon was obtained via oxidative dimerization on treatment with *p*-TSA.



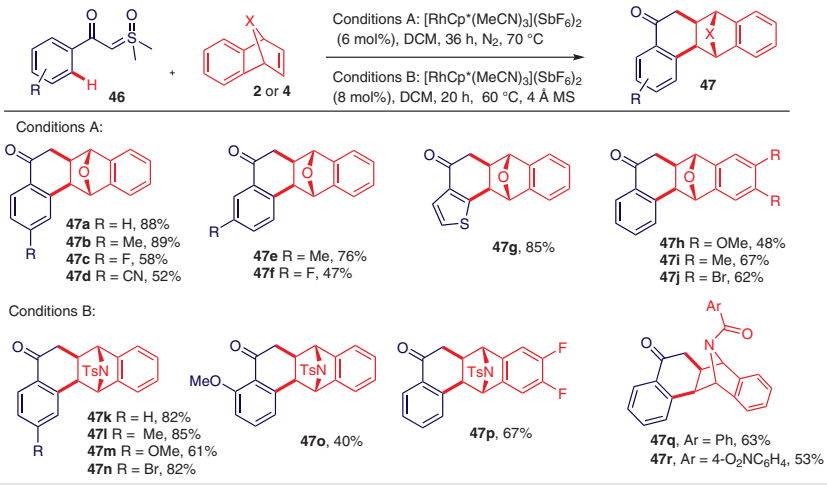
Scheme 24 Annulation reactions of diphenylphosphinamides and bicyclic olefin **2**[26]

Some other examples of annulation reactions using oxa/azabenzonorbornadienes catalyzed by chiral rhodium and cobalt complexes have also been reported.[28]

2.4 Other Reactions

Glorius reported an efficient Rh(III)-catalyzed combined C–H activation/Wagner–Meerwein-type rearrangement in the reaction of *N*-phenoxyacetamides **48** with azabenzonorbornadienes **4**, leading to bridged polycyclic molecules **49** (Scheme 26).[29] In this context, the oxidative directing group acts as both an internal oxidant and an intramolecular nucleophile after O–N bond cleavage. This methodology required a lower catalyst loading and was tolerated various substituents on the N-phenoxyacetamides and 7-azabenzonorbornadienes, leading to substituted polycyclic products **49a–l**.

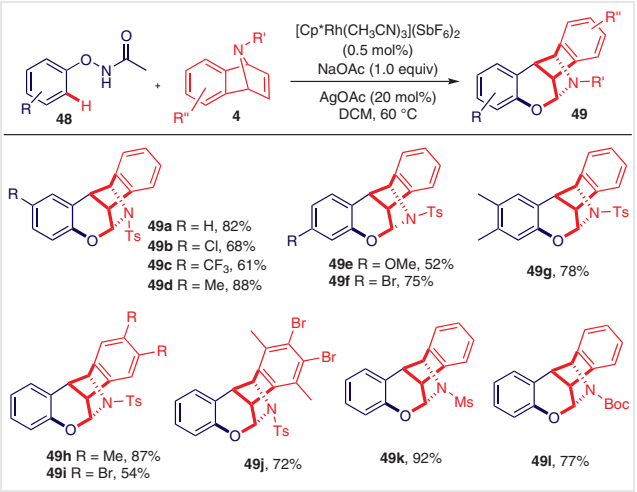
The two possible pathways proposed for this reaction are shown in Scheme 27. Initially, C–H activation occurs. This is followed by the generation of rhodacycle **A** and then



Scheme 25 Annulation reactions of sulfoxonium ylides **46** with bicyclic systems[27]

olefin insertion forms the seven-membered rhodacycle **B**. In the presence of acetic acid, protonation of **B** occurs, leading to the Rh(V) nitrene complex **C** (pathway a). Coordination of AcOH to the Rh(V) nitrene intermediate then generates the intermediate **D**. The Rh(V) intermediate **D** then undergoes rearrangement to form intermediate **E**, which finally gives the product and regenerates the catalyst via ligand exchange. In another possible pathway, a Wagner–Meerwein-type rearrangement occurs directly from the Rh(III) species **B** to afford the rearranged Rh(I) intermediate **G** (pathway b). This is followed by oxidative addition of Rh(I) in the presence of AcOH to produce **E**.

Very recently, Ellman's group reported a modular three-component reaction to access 1,2-disubstituted [2.2.1]-bridged bicycles via the Rh(III)-catalyzed 1,2-addition of C–H bonds and amidating reagents to bridged bicyclic alkenes



Scheme 26 Wagner–Meerwein-type rearrangements in reactions of *N*-phenoxyacetamides **48** with 7-azabenzonorbornadienes[29]

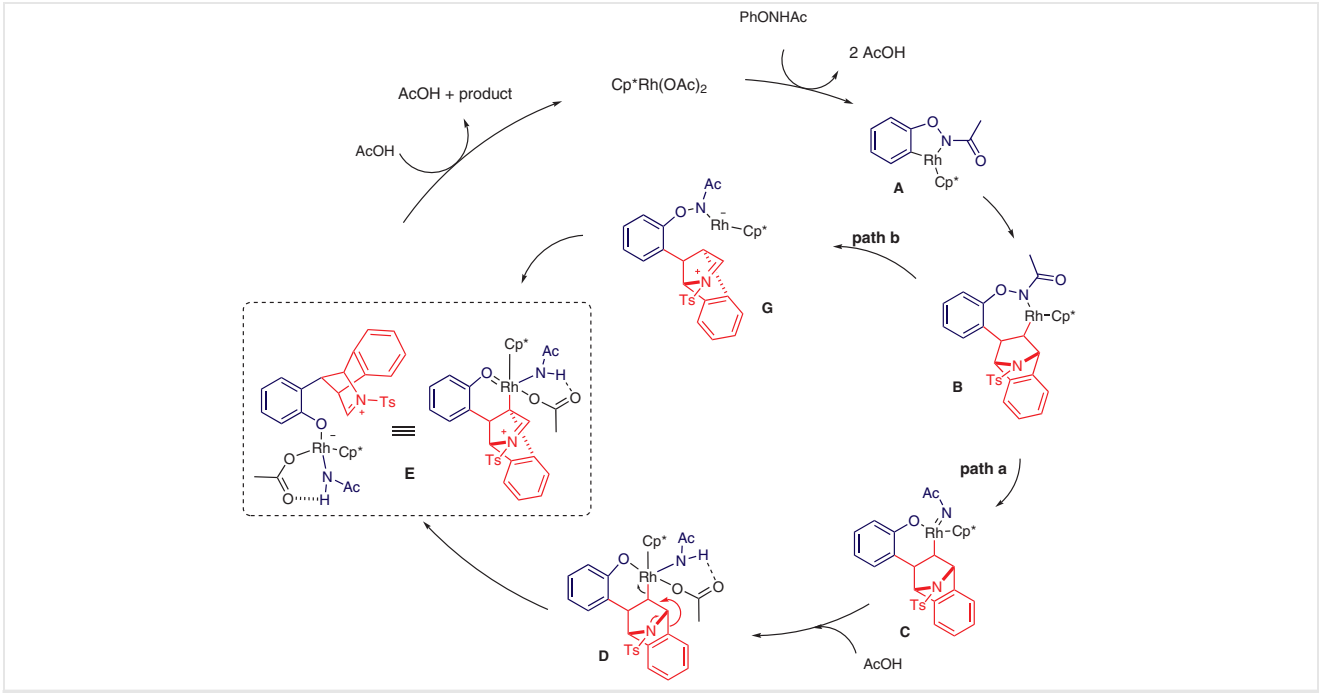
(Scheme 28).[30] Different types of arene substrates **50**, aliphatic and aromatic amidating reagents **51**, and a variety of bridged bicyclic alkenes **52** reacted to afford a broad range of 1,2-disubstituted products **53a–j**. Cramer designed a chiral ligand. Asymmetric catalysis is achieved using the chiral Rh(III) catalyst. During optimization studies, it was found that the addition of sodium acetate as an additive was essential in facilitating the initial C–H activation step leading to product formation in good yields.

3 Conclusion

In this short review, recent reports on C–H activation ring-opening reactions of bicyclic rings assisted by high-valent metal complexes have been discussed. Due to the intrinsic angle strain on the carbon–carbon double bonds of these unsymmetrical bicyclic systems, including oxa- and azabicyclic alkenes, they can be readily activated with facial selectivity using transition-metal complexes. In the literature, the use of such strained systems have led to remarkable advancements. Additionally, ring-opening reactions of bicyclic heteroalkenes via activation of a Lewis acid or transition metal in the presence of nucleophiles is well-known chemistry.

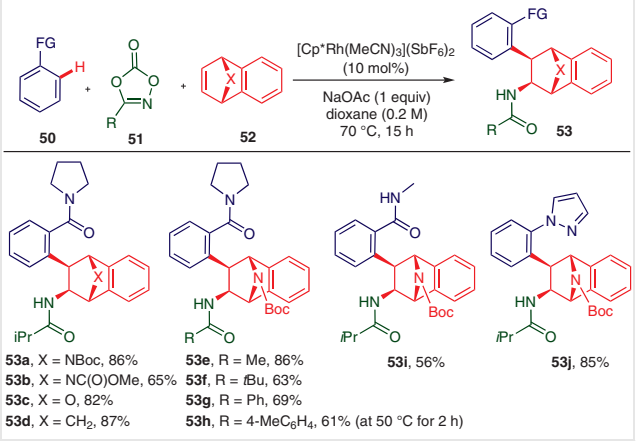
The utilization of high-valent transition-metal complexes for the ring opening of such bicyclic systems via C–H activation represents a growing field. Various directing groups, including aldehydes, amides, acids, ketoximes, alkynols, and many others, have been employed. Apart from ring-opening reactions, several hydroarylation, as well as other annulation reactions, have also been reported.

Since this is a growing area of chemistry, there is room for the extension of this field. Bicyclic systems are important synthons for the synthesis of biologically and naturally relevant molecules, and such compounds can be obtained



Scheme 27 Proposed mechanism of the Wagner–Meerwein-type rearrangement

by employing the concept C–H activation. Moreover, this chemistry could be explored by utilizing alternative strong and weak directing groups, whilst the development of asymmetric C–H activation using strained bicyclic systems needs to be further explored with other directing groups. This may represent crucial steps for the enantioselective synthesis of natural products.



Scheme 28 Three-component reactions of bicyclic alkenes[30]

Conflict of Interest

The authors declare no conflict of interest.

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