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Ring-Strain-Enabled Reaction Discovery: New Heterocycles from Bicyclo[1.1.0]butanes

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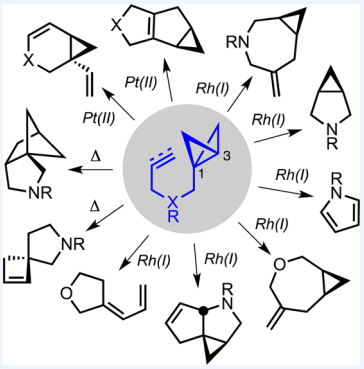
CONSPECTUS: Mechanistically as well as synthetically, bicyclo[1.1.0]butanes represent one of the most fascinating classes of organic compounds. They offer a unique blend of compact size (four carbon atoms), high reactivity (strain energy of 66 kcal/mol), and mechanistic pathway diversity that can be harvested for the rapid assembly of complex scaffolds. The C(1)−C(3) bond combines the electronic features of both σ and π bonds with facile homolytic and heterolytic bond dissociation properties and thereby readily engages pericyclic, transition-metal-mediated, nucleophilic, and electrophilic pathways as well as radical acceptor and donor substrates.



Despite this multifaceted reaction profile and recent advances in the preparation of bicylo[1.1.0]butanes, the current portfolio of synthetic applications is still limited compared with those of cyclopropanes and cyclobutanes. In this Account, we describe our work over the past decade on the exploration of substituent effects on the ring strain and the reactivity of bicyclo[1.1.0]butanes, particularly in the context of metal-mediated processes. We first describe Rh(I)-catalyzed cycloisomerization reactions of *N*-allyl amines to give pyrrolidine and azepine heterocycles. The regioselectivity of the C,C-bond insertion/ring-opening step in these reactions is controlled by the phosphine ligand. After metal carbene formation, an intramolecular cyclopropanation adds a second fused ring system. A proposed mechanism rationalizes why rhodium(I) complexes with monodentate ligands favor five-membered heterocycles, as opposed to Rh(I)−bidentate ligand catalysts, which rearrange *N*-allyl amines to seven-membered heterocycles. The scope of Rh(I)-catalyzed cycloisomerization reactions was extended to allyl ethers, which provide a mixture of five- and seven-membered cyclic ethers regardless of the nature of the phosphine additive and Rh(I) precatalyst. The chemical diversity of these cycloisomerization products was further expanded by a consecutive one-pot metathesis reaction.

Rh(I)-catalyzed cycloisomerizations of propargyl amides, ethers, and electron-deficient bicyclo[1.1.0]butanes diverged mechanistically and often led to a significant number of decomposition products. In these cases, Pt(II) emerged as a superior, more alkynophilic late transition metal with its own mechanistic peculiarities. While monosubstituted bicyclo[1.1.0]butanes led to the formation of tetrahydropyridines, 1,3-disubstituted and electron-deficient bicyclo[1.1.0]butanes reacted distinctly differently with Pt(II) and ultimately provided a complementary set of nitrogen- and oxygen-containing cyclic scaffolds.

The metal-catalyzed ring transformations of bicyclo[1.1.0]butanes presented herein suggest additional strategies for new reaction discoveries that can access a wide variety of novel cyclic frameworks from relatively simple starting materials. In addition, these case studies highlight the considerable potential for future applications in natural products, medicinal, and diversity-oriented synthesis based on the wealth of mechanistic pathways available to these strained small-ring carbocycles.

INTRODUCTION

A significant part of our work over the past two decades has been influenced by explorations of the synthetic, mechanistic, structural, and biological consequences of ring strain.[1] Bond angle and bond length distortions, torsional interactions, and transannular and nonbonded steric clashes significantly alter the chemical and physiological properties of organic molecules. For example, we have explored the conformational effects influencing metal ion chelation of five-membered heterocycles embedded in the macrocyclic ring system of *Lissoclinum* peptides.[2] We have also taken advantage of the reactivity of a fused tricyclic substructure in furanosteroids toward aza-Michael additions to generate a potent anticancer agent that has moved to phase-II clinical trials.[3] Furthermore, several of our natural product target molecules have inspired us to develop new synthetic strategies and tactics in order to overcome the substantial ring strain present in their polycyclic frameworks.[4] However, the exquisite ring strain in bicyclo[1.1.0]butanes has been the single richest source of serendipity-driven discovery of novel reaction pathways and unique heterocyclic scaffolds in our research.[5] We have studied thermal pericyclic[6] as well as transition-metal-catalyzed

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conversions of nitrogen- and oxygen-tethered bicyclo[1.1.0]-butanes,[7] including applications in natural product synthesis.[8]

In 1959, Wiberg and Ciula[9] synthesized ethyl bicyclo[1.1.0]-butane-1-carboxylate, a compound more highly strained than cyclopropane for which "*no authentic derivative has* [previously] *been reported*" and thus opened a new chapter in the chemistry of strained carbocycles. Bicyclo[1.1.0]butanes distinguish themselves by a unique combination of intrinsic reactivity and high kinetic barriers for C,C-bond cleavage. Strain release is clearly a major driving force for a frequently observed isomerization to 1,3-butadienes and the formation of cyclobutanes by electrophilic or nucleophilic attack. The unique molecular orbital configuration of bicyclobutanes and the ability to selectively activate core bonds by transition-metal insertions provided strong incentives for both theoretical and experimental chemists to study this compact bicyclic system.[10−14] However, unlike cyclopropanes or cyclobutanes and their derivatives, which rank among the most useful synthetic building blocks,[15−18] bicyclo[1.1.0]butanes have yet to gain significant attention as synthetic tool compounds. This discrepancy can be attributed to several factors, including, until recently, a dearth of versatile synthetic procedures for the synthesis of functionalized bicyclo[1.1.0]butanes and the absence of biologically relevant compounds containing this moiety.[19,20] Traditional synthetic methods, including intramolecular displacement of a leaving group and most commonly the insertion of cyclopropylidene into a C−H bond,[21,22] provide simple bicyclobutanes in high yields, but the lack of functionalization significantly limits their utility. While the addition of methylene carbenes to alkynes offers the broadest access to functionalized bicyclo[1.1.0]butanes,[23] a main disadvantage is the mixture of endo and exo stereoisomers obtained with unsymmetrically substituted carbenes. In 2013, the groups of Fox[24] and Davies[25] independently reported a rhodium-catalyzed intramolecular cyclopropanation of readily available 2-diazo-5-enoates that affords enantiomerically enriched bicyclobutanes in good yields. Furthermore, the development of transition-metal-mediated protocols that suppress undesired side reactions (e.g., butadiene formation) in the further conversions of functionalized bicyclo[1.1.0]-butanes has recently gained considerable traction. In this Account, we will focus on metal-catalyzed conversions that provide high-yielding access to ring-expanded products and illustrate the opportunities for new reaction discoveries starting from this spring-loaded four-carbon building block.

STRAIN EFFECTS IN BICYCLO[1.1.0]BUTANES

An immediately apparent feature of bicyclo[1.1.0]butanes is their high ring strain energy (RSE). The experimental RSE of the unsubstituted parent bicycle has been calculated at 66.3 kcal mol^{-1}, which exceeds the sum of the strain energies of two cyclopropanes by ca. 8.3 kcal mol^{-1} (Figure 1).[1,26,27] The origin of this additional strain was attributed to 1,3-carbon−carbon interactions[28] derived from the puckered structure (Dunitz−Schomaker hypothesis).[29] Recently, this interpretation was challenged by Barić and Maksić,[30] who suggested that the increased strain originates from angle deformations at the terminal carbon atoms (Baeyer strain).

The orbital perturbations in bicyclo[1.1.0]butanes also play a critical role in determining the strain energies of the entire bicyclic system as well as its reactivity. Pertinent experimental and calculated RSEs of substituted bicyclo[1.1.0]butanes and related carbocycles are listed in Figure 1. Alkyl or aryl

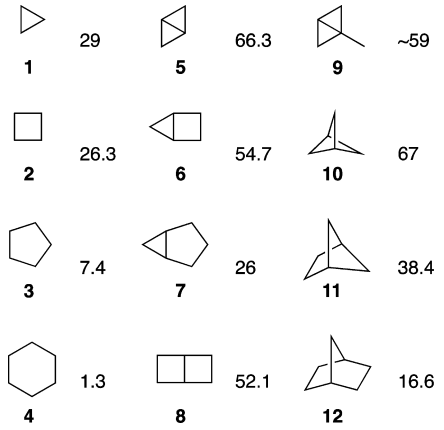

Figure 1. Experimental (**1**−**8**) and calculated (**9**−**12**) ring strain energies (in kcal mol^{-1}) for selected mono- and bicyclic carbocycles.[27,31]

substitution decreases the strain energy, and conjugation to a phenyl group also causes an elongation of the central C(1)−C(3) bond by ca. 4%.[27]

Bicyclo[1.1.0]butanes fold into puckered, butterfly-like structures, adopting an angle of ca. 122° between the two cyclopropane rings.[32] C(1) and C(3) possess an umbrella-like inverted geometry[33] (all four substituents lie in the same hemisphere), allowing π systems, radicals, electrophiles, and nucleophiles ready access to this central bond.[10]

Because of the RSE of bicyclo[1.1.0]butanes, diminished thermal stability and difficulties in their isolation may be expected. Many bicyclo[1.1.0]butanes, however, can be purified by conventional chromatographic methods and stored over prolonged periods of time. This surprising level of chemical inertia originates from the relatively high kinetic barrier for ring-opening processes.[34,35] A major general reactivity pattern, especially for bicyclo[1.1.0]butanes conjugated to electron-deficient groups (e.g., ester, aldehyde, amide), is radical addition, and this property is useful for the preparation of organic polymers.[36−38] Typically, 1,3-disubstituted and sterically shielded bicyclo[1.1.0]butanes are more robust than less-substituted analogues, and neat samples can be stored at −20 °C for several months with minimal decomposition. Small amounts of radical inhibitors (e.g., BHT) can provide additional stabilization. In light of the kinetic barriers for ring opening, accessing the high strain energy of bicyclo[1.1.0]-butanes for selective product formation without initiating uncontrollable side and decomposition processes has emerged as the major challenge in the synthetic chemistry of these molecules.

METAL-CATALYZED ISOMERIZATION REACTIONS OF BICYCLOBUTANES TO GIVE DIENES AND CARBOCYCLES

In a serendipitous discovery, we found that a hydrozirconation/transmetalation/imine addition/Simmons−Smith cascade reaction[39] of internal alkyne **13** and alkynyl imine **14** led to highly substituted bicyclo[1.1.0]butane **18** (Scheme 1).[7] After 1,2-addition of the alkenylzinc intermediate to imine **14**, cyclopropation with a zinc carbenoid leads to cyclopropene **17** via cyclopropane **16**. A third and final cyclopropanation provides bicyclo[1.1.0]butane **18** in 51% yield. The steric congestion of the internal ethyl substituent appears to prevent further C,C-σ-bond insertion and cyclopropanation to give dicyclopropyl

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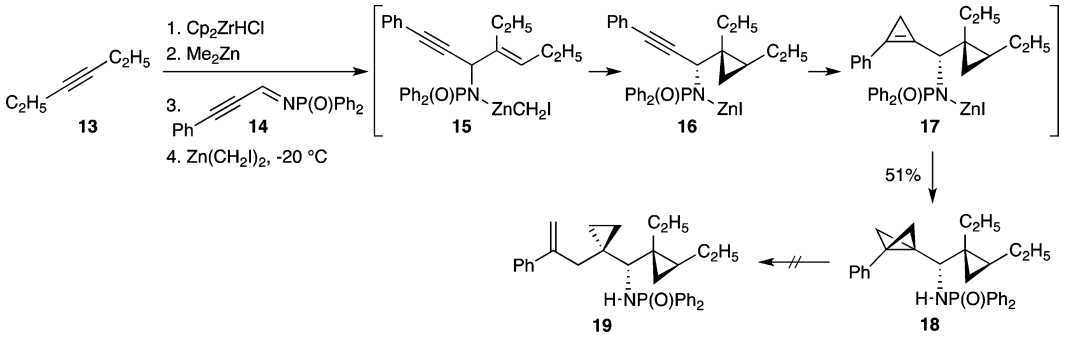
Acc. Chem. Res. 2015, 48, 1149−1158

Scheme 1. Cascade Reaction Leading to Bicyclo[1.1.0]butylcyclopropylalkylamine 18



alkylamine **19**, the expected product formed exclusively from terminal alkynes. Overall, a total of seven new C,C-bonds are formed in the conversion of **13** to **18**. An X-ray structure of this product is shown in Figure 2, illustrating the peculiar geometric features of bicyclobutanes.

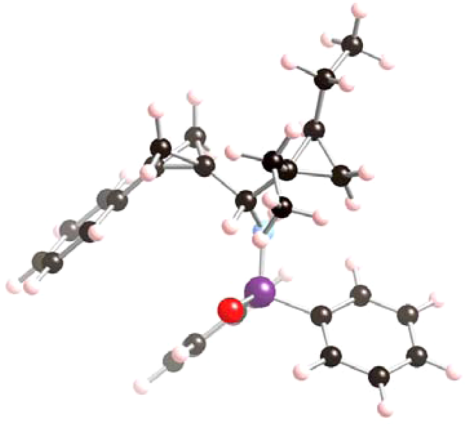
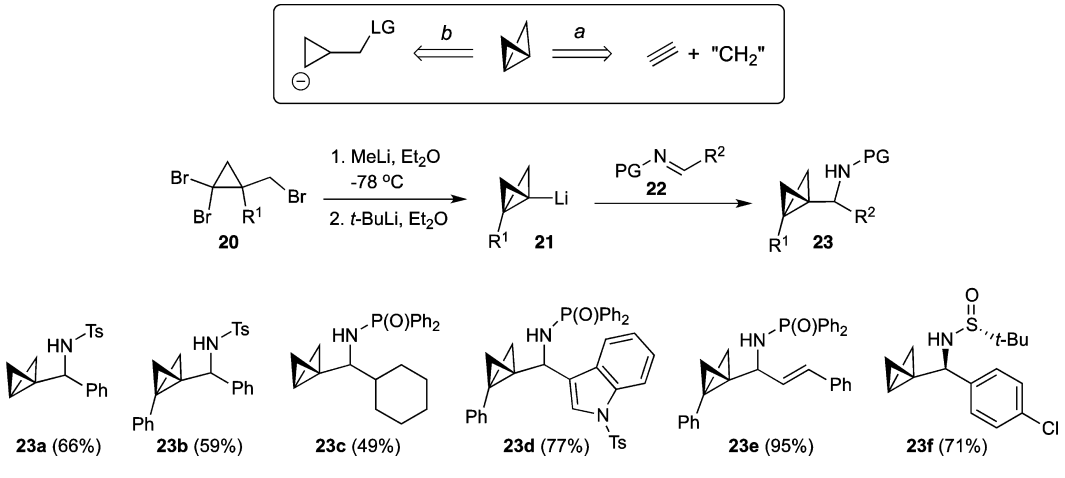


Figure 2. X-ray structure of **18**.

In an attempt to identify an alternative, more general synthetic pathway to the Simmons–Smith route "*a*", bicyclobutanes were subsequently accessed by an intramolecular displacement of a leaving group by a cyclopropyl anion derived from lithium–halogen exchange, e.g., route "*b*" (Scheme 2).[19] A two-step sequence involving treatment of dibromocyclopropylmethyl bromides **20** with MeLi followed by transmetalation with *t*-BuLi to give the versatile lithium reagents **21** and subsequent in situ addition to N-protected (PG) imines **22** afforded bicyclo[1.1.0]butanes **23** in moderate to high yields.[6] The intermediate lithiobicyclobutanes **21** are valuable precursors for a broad range of bicyclobutyl alkylamines, including *N*-tosyl, *N*-diphenylphosphinoyl, and chiral sulfinyl derivatives **23a–f**.[6,40]

Our initial investigations focused on thermal conversions of amine-substituted bicyclo[1.1.0]butanes such as **25**, which upon reaction with an unsubstituted allyl bromide such as **24a** led to the formation of pyrrolidine **26** in what represents an intramolecular variant of the Alder-ene mechanism (Scheme 3). When instead a conjugated allyl bromide such as **24b** was used, the tricyclic pyrrolidine **27** was obtained; the latter compound is a unique structure that has not been previously prepared. In addition, we noticed that substrates with hydrogen or alkyl substitutions at both C(1) and C(3), i.e., those lacking an aromatic substituent on the bicyclobutane, did not undergo the expected formal ene or [2 + 2] reactions even under forcing conditions and irrespective of the nature of the N-tethered alkene or alkyne moiety. For example, neither alkene **28** nor alkyne **29** underwent the expected intramolecular cycloaddition at temperatures of up to 150 °C (Scheme 4).[8] Only allyl moieties attached to strongly electron-withdrawing groups (aldehydes, esters) had sufficiently low LUMO energies to allow the cycloaddition process to proceed under regular thermal conditions.[8] Accordingly, we became interested in exploring transition-metal catalysts to reduce the high kinetic barrier in stable bicyclo[1.1.0]butane derivatives such as **28** and

Scheme 2. Retrosynthetic Routes to Bicyclo[1.1.0]butanes



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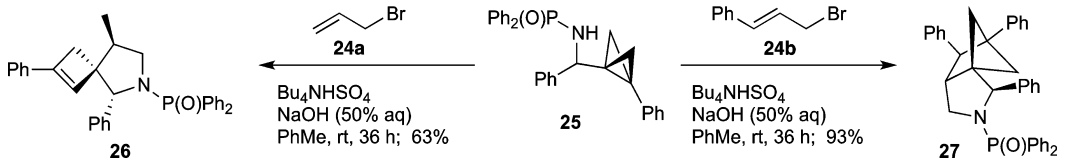
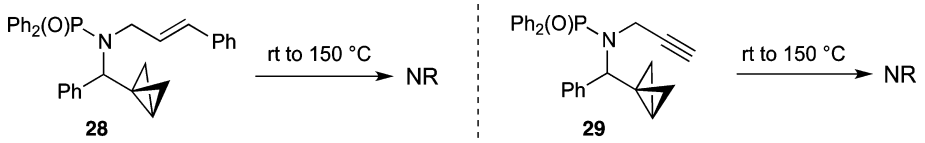
Acc. Chem. Res. 2015, 48, 1149–1158

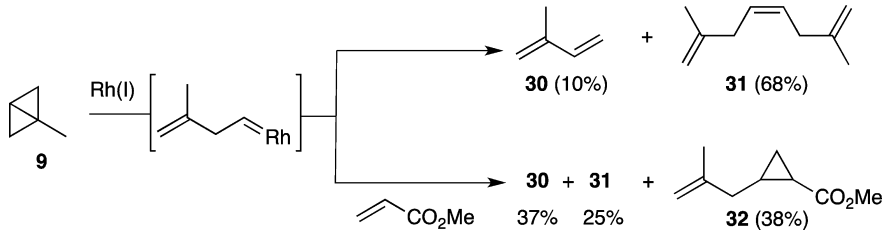
Scheme 3. Tandem N-Allylation Intramolecular Ene (26) or [2 + 2] Cycloaddition (27) Reaction of 25; These Intramolecular Pericyclic Reactions Occur at Room Temperature Because of the High RSE of the Bicyclo[1.1.0]butane, and the Reaction Pathway Depends on the Substituent on the Allyl Moiety



Scheme 4. Heating of Alkene 28 and Alkyne 29 Results in Recovery of Starting Material



Scheme 5. Isomerization Reactions of Bicyclo[1.1.0]butane 9



29, in particular also since pertinent literature precedent[41] was supportive of this hypothesis.

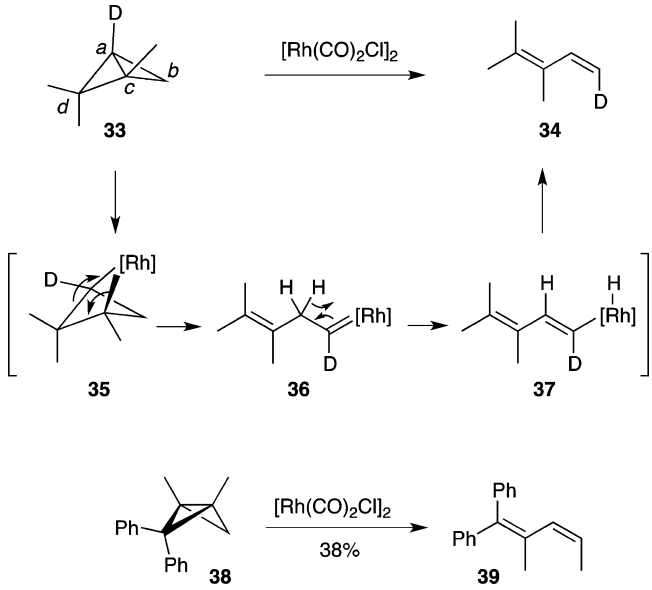
RHODIUM-CATALYZED CONVERSIONS OF BICYCLOBUTANES TO DIENES

Rhodium(I) complexes have frequently been used for the metal-catalyzed isomerization of strained molecules.[41] Their utility in the synthesis of natural and unnatural target molecules has been demonstrated, and a plethora of mechanistic information has been collected.[42] The value of rhodium for valence isomerization reactions has also been recognized in the chemistry of bicyclo[1.1.0]butanes.[43−47] Rhodium and nickel have played key roles in the determination of reaction mechanisms.[48−50] Silver(I) ions can also efficiently catalyze the rearrangement of bicyclo[1.1.0]butanes, albeit via a different mechanism.[51−53]

The first isomerization reaction involving bicyclo[1.1.0]-butanes was reported by Gassman and Williams.[43] They demonstrated that simple bicyclo[1.1.0]butanes such as **9** rearrange to 1,3-butadienes **30** in the presence of a rhodium catalyst (Scheme 5). After isolating triene **31** from a reaction of **9** with rhodium norbornadiene−rhodium chloride dimer, they postulated that the triene could arise from the dimerization of two metallocarbene intermediates. This hypothesis was later confirmed by trapping of the reactive carbene intermediate with methyl acrylate, which also afforded cyclopropane **32**.

The mechanism of the ring-opening process was further investigated using deuterated bicyclo[1.1.0]butanes (Scheme 6). The rhodium-catalyzed isomerization of **33** afforded the cis product **34** stereospecifically. This experiment demonstrated that the isomerization occurs via cleavage of two geminal σ bonds (bonds *ac* and *ad*) and the formation of carbene **36**. The selectivity of these reactions is complementary to the thermal opening of bicyclo[1.1.0]butanes, which follows a molecular-orbital-allowed concerted process and proceeds via cleavage of

Scheme 6. Stereospecific Rearrangement of Substituted Bicyclobutanes 33 and 38



two vicinal σ bonds (*ab* and *cd* or *ad* and *bc*).[43−45] Carbene isomerization was also observed in the Rh(I)-catalyzed reactions of diazo compounds.[54,55] Analogous to the deuterated bicyclobutane **33**, **38** rearranged to diene **39** as a major product.[44b] In spite of significant efforts, however, these early studies of metal-mediated rearrangements were of limited synthetic relevance, in part because of continued mechanistic ambiguities that led one researcher to conclude in 1976 that "*no class of transition metal catalyzed rearrangements has been the subject of more controversy than those of bicyclobutane*".[41]

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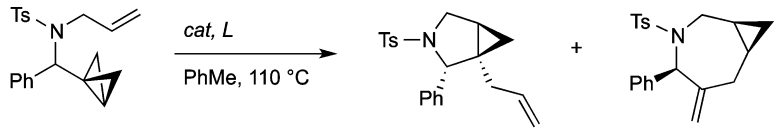
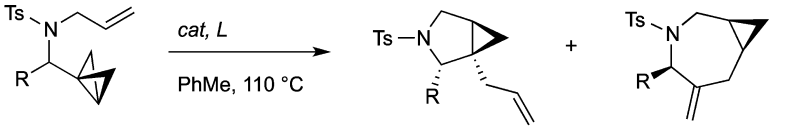
Acc. Chem. Res. 2015, 48, 1149−1158

Scheme 7. Ligand-Dependent Rh(I)-Catalyzed Cycloisomerization Reactions



(1) **40**, *cat* = $[Rh(=)_2Cl]_2$; *L* = Ph_3P — **41** (87%), **42** (8%)
(2) **40**, *cat* = $[Rh(CO)_2Cl]_2$; *L* = dppe — **41** (<1%), **42** (83%)

Scheme 8. Rh(I)-Catalyzed Isomerization of Bicyclo[1.1.0]butanes



	cat = $[Rh(=)_2Cl]_2$, *L* = Ph_3P	*cat* = $[Rh(CO)_2Cl]_2$, *L* = dppe
43 (R = 3,5-$(MeO)_2C_6H_3$)	**46** (67%)	**47** (87%)
44 (R = 2-furyl)	**48** (75%)	**49** (57%)
45 (R = 4-ClC_6H_4)	**50** (53%)	**51** (80%)

The formation of the metal carbenes resembles the decomposition reactions of diazo compounds,[56,57] and the carbenoid character of bicyclo[1.1.0]butane could be utilized analogously in intramolecular processes. The metal carbene intermediate usually forms at the less-substituted position of the bicyclo[1.1.0]butane, but the specific formation of a carbenoid controlled by tunable reaction conditions (i.e., ligands, additives, temperature, etc.) and suitably positioned intramolecular trapping moieties would deliver an attractive synthetic manifold.

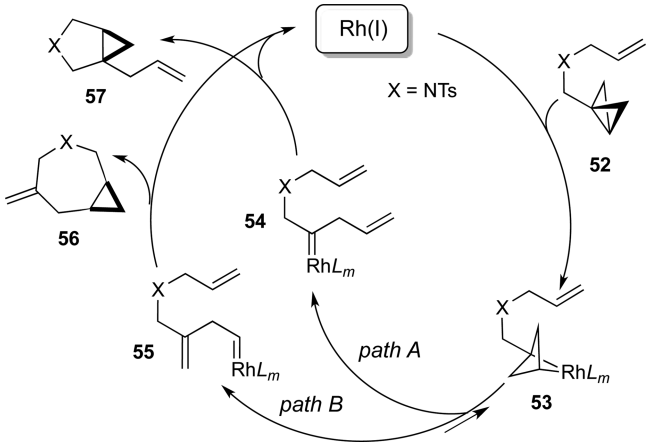
RHODIUM-CATALYZED CYCLOISOMERIZATION OF *N*-ALLYL AMINES

We used the thermally relatively unreactive *N*-allyl amide **40** to test the use of rhodium ligands for an intramolecular cycloaddition (Scheme 7).[40] Generally, Rh(I) precatalysts stabilized by an alkene ligand in combination with monodentate phosphines favor the formation of an internal carbene, which subsequently could undergo cyclopropanation with the allyl group to furnish pyrrolidine **41**. Alternatively, bidentate phosphine ligands in combination with $[Rh(CO)_2Cl]_2$ favor the formation of a terminal carbene followed by trapping with the alkene to give azepine **42**. The influence of the ligand on the regioselectivity of the reaction was reflected by various ratios of **41** and **42**.[40] The yield for the formation of the azepine correlated with the bite angle of the bidentate phosphine.[58,59] Although all of the bidentate ligands suppressed the formation of pyrrolidine **41**, 1,2-bis(diphenylphosphino)ethane (dppe) with a bite angle of 85° was the optimal additive, providing **42** in 83% yield with only traces of **41** formed. Other metals ($Ni(cod)_2$, $Pd(PPh_3)_4$) did not catalyze the rearrangement of **40** into **41** and **42** in synthetically useful yields. From these studies[31,40] it became clear that metal-catalyzed intramolecular cycloadditions of bicyclo[1.1.0]butanes were not only feasible but ligand-tunable and therefore offered a very attractive alternative to the thermal processes.

In subsequent investigations of the scope of Rh(I)-catalyzed cycloisomerization reactions, we were able to demonstrate highly chemo- and diastereoselective conversions of **43**–**45** to pyrrolidines or azepines **46**–**51** as a function of the reaction conditions (Scheme 8).[40] Furthermore, the steric environment of the allyl group and its ability to coordinate to the metal played a critical role in determining the outcome of these reactions. For instance, substrates with *N*-prenyl and *N*-benzyl substituents provided only 1,3-butadienes after exposure of the bicyclo[1.1.0]butane to the rhodium catalyst.[31]

Mechanistically, we envisioned that cleavage of the central bond in bicyclo[1.1.0]butane **52** would lead to intermediate **53** (Scheme 9). Subsequent rearrangement to **54** or **55** would be

Scheme 9. Proposed Mechanism for the Cycloisomerization Reactions in the Presence of Monodentate (Path A) and Bidentate (Path B) Phosphines



controlled by the π donation of the alkene group as well as the steric bulk of the phosphine ligands. It is also possible that the conversion of **52** to the corresponding carbenes is reversible, allowing for thermodynamic equilibration. This possibility is supported by earlier studies on the synthesis of bicyclo[1.1.0]-butanes from diazo compounds in the presence of catalytic $Rh_2(OAc)_4$.[60] The vinyl group may undergo a competitive 1,2-shift as in the reactions of β-amino-α-diazocarbonyl compounds.[61] The final step in the catalytic cycle would be the release of the metal complex through an intramolecular cyclopropanation, furnishing **56** or **57**.

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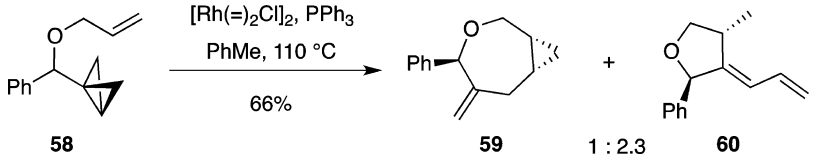
Acc. Chem. Res. 2015, 48, 1149–1158

Scheme 10. Cycloisomerization of *O*-Allyl Ether 58

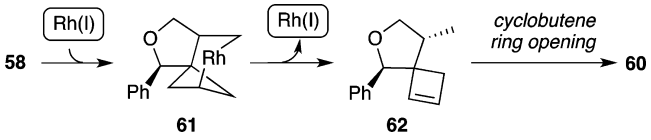


RHODIUM-CATALYZED CYCLOISOMERIZATIONS OF *O*-ALLYL ETHERS

Interestingly, the cycloisomerization reactions of *O*-allyl ether **58** diverged from the reactions of the corresponding *N*-allyl compounds (Scheme 10). Both mono- and bidentate phosphine ligands afforded a mixture of oxepane **59** and furan **60**. The ratio of these two compounds was dependent on the nature of the phosphine ligand as well as on the rhodium precatalyst.[31]

Although more data are needed to support a mechanistic proposal, furan **60** may arise from a rhodium-catalyzed intramolecular ene reaction of the allyl group with the bicyclo[1.1.0]butane ring (Scheme 11). The resulting intermediate **61** would undergo a reductive elimination to give **62** and a (metal-catalyzed) opening of the cyclobutene to afford **60**. Alternatively, the tricyclic intermediate **61** may undergo a direct isomerization to the product.

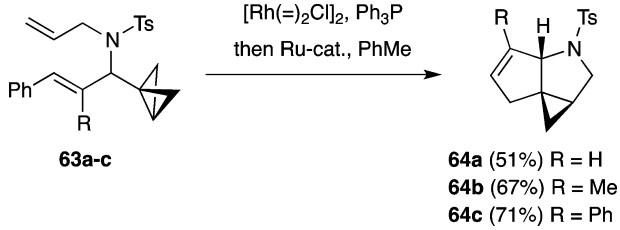
Scheme 11. Mechanism Hypothesis for Isomerization of 58



RHODIUM/RUTHENIUM-CATALYZED TANDEM CYCLOISOMERIZATION/METATHESIS REACTIONS OF *N*-ALLYL AMINES

The utility of the metal-catalyzed rearrangement reactions of bicyclo[1.1.0]butanes was further expanded by subjecting the products from the cycloisomerization reactions to a metathesis process (Scheme 12). We were able to demonstrate that this one-pot transformation afforded the novel tricyclic scaffolds **64** in good yields.[40] The core structure of pyrrolidines **64** was unique and had not previously been prepared. Although the isomerization reactions were carried out only with nonchelating *N*-tosyl amides, this PG was readily removed under standard reductive conditions (Na/naphthalene).

Scheme 12. Tandem Isomerization/Ring-Closing Metathesis Reaction of *N*-Allyl Bicyclo[1.1.0]butanes 63a–c



RHODIUM-CATALYZED FORMATION OF PYRROLES AND FURANS

The majority of our exploratory studies on the metal-catalyzed cycloisomerizations of bicyclo[1.1.0]butanes were focused on C–C bond-forming processes. Inspired by reports on stereoselective carbene insertion reactions of diazo compounds with nitrogen[62−65] and oxygen[66] nucleophiles, we extended our methodology toward the insertion into heteroatom–hydrogen bonds (Scheme 13). *N*-Tosyl amides and alcohols **65** were treated with a Rh(I) precatalyst, resulting in the formation of pyrroles **66** and methylenetetrahydrofurans **67**, respectively.[31] Elimination of the tosyl group, also observed in other studies,[67,68] is followed by tautomerizaton to give the pyrrole.

In view of the wealth of reaction pathways and novel product formations discovered in these model studies with catalytic rhodium complexes, this chemistry shows great promise for future reaction exploration. The use of Rh(I) complexes often leads to high chemo- and regioselectivity. Moreover, applications of chiral ligands and the use of more highly substituted bicyclo[1.1.0]butanes will be natural extensions of this methodology.

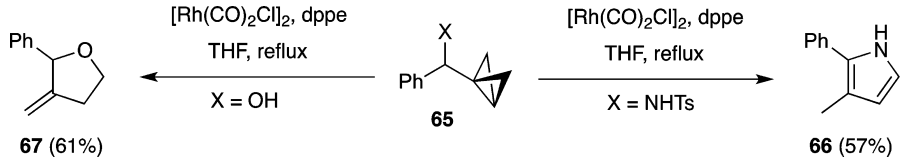
PLATINUM-CATALYZED FORMATION OF TETRAHYDROPYRIDINES

While subjecting N-propargylated bicyclo[1.1.0]butanes to preformed Rh(I) catalysts did not lead to the expected cycloisomerization reactions, the use of late transition metals such as Pt(II), which demonstrate increased alkynophilic character,[69] met with greater success and turned out to involve yet a different mechanistic pathway.

When amide **68a** was treated with 10 mol % $PtCl_2$ in PhMe at 110 °C, cyclopropane **69a** was isolated in modest yield (Scheme 14). Interestingly, an analogous rearrangement reaction of ether **68b** proceeded smoothly at 50 °C with $PtCl_2$ to give vinyl ether **69b**.

This transformation can be rationalized by the mechanism depicted in Scheme 15. By analogy to the formation of the homoallylic Rh carbene **55** (shown in Scheme 9), the formation of terminal Pt carbene **71** is postulated. This intermediate

Scheme 13. Rh(I)-Catalyzed Isomerization of *N*-Tosyl Amides and Alcohols



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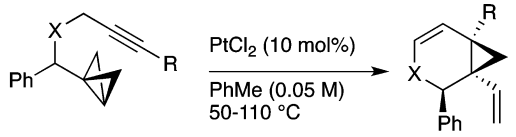
Acc. Chem. Res. 2015, 48, 1149–1158

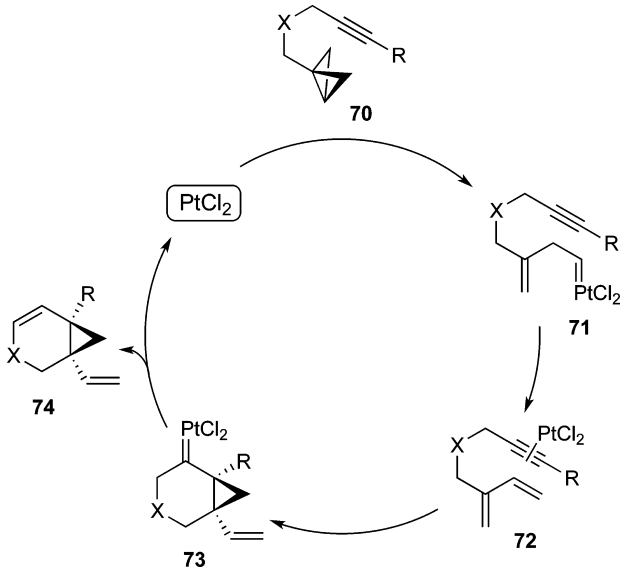
Scheme 14. $PtCl_2$-Catalyzed Isomerization Reactions of Bicyclo[1.1.0]butanes



68a, X = NTs, R = Me
68b, X = O, R = H

69a (21%)
69b (61%)

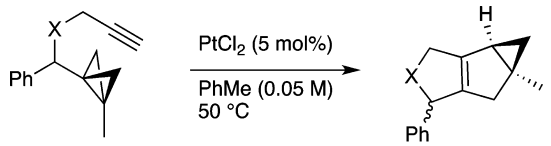
Scheme 15. Proposed Mechanism for the Rearrangement of Monosubstituted Bicyclo[1.1.0]butanes with $PtCl_2$



would undergo a rearrangement to give butadiene **72**. Fürstner suggested that Pt complexes of certain allyl propargyl amides or ethers may undergo an ene−yne metathesis;[70−72] thus, the formation of diene **72** may be followed by conversion to Pt(IV) carbene **73**. This intermediate could then collapse via a hydride shift to give the observed product **74**. The selectivity in these pathways is controlled by a facile insertion of $PtCl_2$ into the less-hindered C(1)−C(3) bond of the bicyclo[1.1.0]butane, which is a more reactive site compared with the alkyne tether.

Steric hindrance clearly plays a significant role in the site selectivity of $PtCl_2$ insertion. With 1,3-disubstituted bicyclo[1.1.0]butanes, the selectivity of Pt insertion apparently switches to the alkyne tether. Both propargyl sulfonamide **75a** and propargyl ether **75b** afforded the corresponding tricyclic products **76a** and **76b** in the presence of 5 mol % of $PtCl_2$ in good yields as mixtures of diastereomers (Scheme 16).[31] This suggests that the steric hindrance at the methylated bicyclo[1.1.0]butane prevents the insertion of Pt(II) into the strained ring bond and directs the metal to the alkyne tether. Adding additional substituents to the substrate diminished the diastereoselectivity in the cycloisomerization reaction, but changing the temperature did not significantly perturb it. The diastereomeric ratio was improved, however, for a substrate in which the directing group was located at a position closer to the reacting carbene. Substitution at the propargyl site was not tolerated.[31]

Scheme 16. Cycloisomerization Reactions of 1,3-Disubstituted Bicyclo[1.1.0]butanes

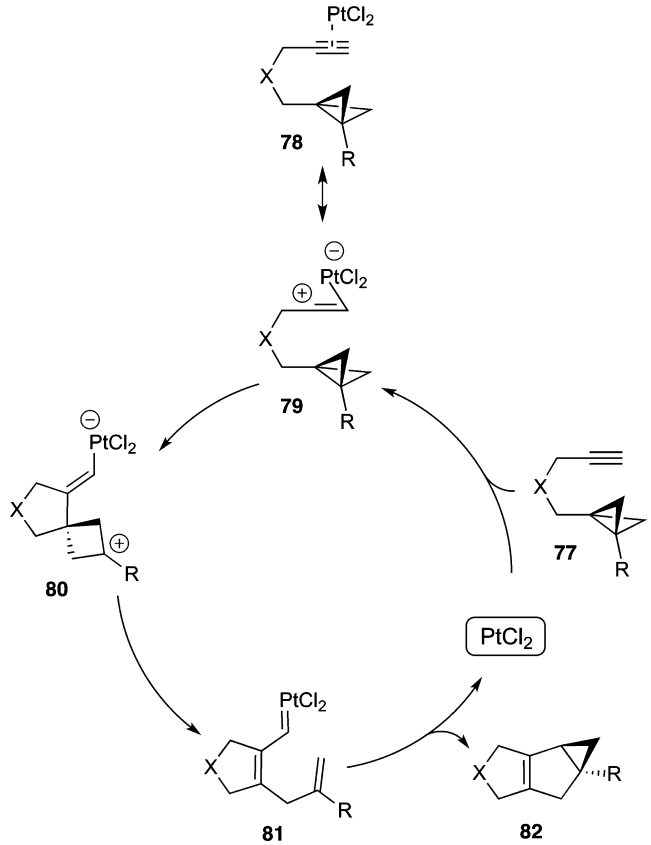


75a, X = NTs
75b, X = O

76a (71%)
76b (52%)

A mechanism for the rearrangement of 1,3-disubstituted bicyclo[1.1.0]butanes **77** is proposed in Scheme 17. Alkyne

Scheme 17. Proposed Mechanism for Rearrangement of 1,3-Disubstituted Bicyclo[1.1.0]butanes Catalyzed by $PtCl_2$



complexation leads to **78**, which can be depicted as an alternative resonance structure **79**. Electrophilic attack on the bicyclo[1.1.0]butane generates cyclobutyl carbocation **80**, which is stabilized by the R substituent and rearranges to give metal carbenoid **81**. At this stage, an intramolecular cyclopropanation yields the observed product **82**.

In addition to amine- and ether-tethered compounds, amide **83a** and ketone **83b** were also suitable substrates for the Pt(II)-catalyzed cycloisomerization, and internal alkynes were well-tolerated (Scheme 18).[31] The yield was generally highest when the reaction was performed at 150 °C under microwave heating in the presence of 10 mol % $PtCl_2$.

The outcome of the conversion of **83** to **84** can be rationalized by the mechanism depicted in Scheme 19. Conjugation with the carbonyl groups lowers the HOMO energy in electron-deficient bicyclo[1.1.0]butane **83**, decreasing the steric hindrance at that site and stabilizing the complexation to Pt(II). Therefore, it is feasible that these reactions proceed via the internal carbene intermediate **86** (in contrast to **71** in

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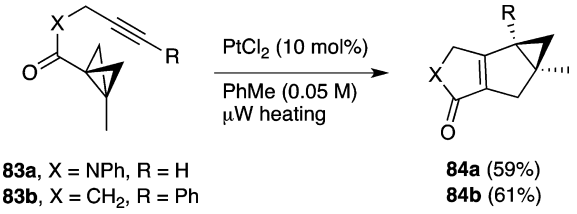
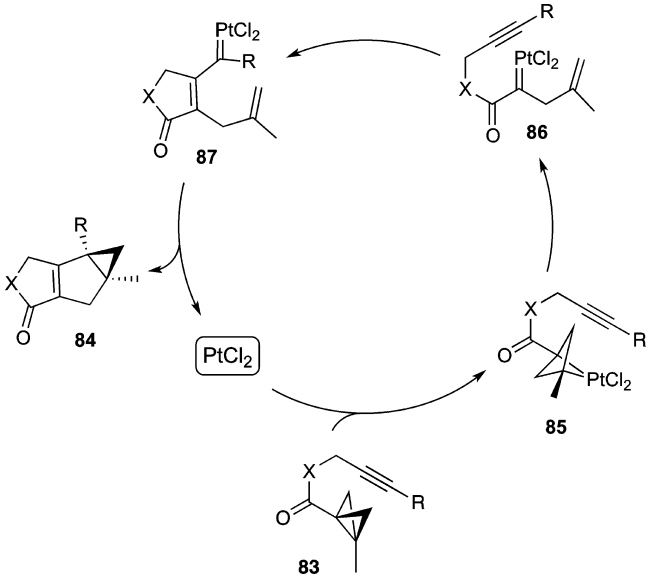
Scheme 18. $PtCl_2$-Catalyzed Isomerization of Electron-Deficient Bicyclo[1.1.0]butanes



83a, X = NPh, R = H
83b, X = CH_2, R = Ph

84a (59%)
84b (61%)

Scheme 19. Proposed Alternative Mechanism for Ene−Yne Metathesis of Bicyclo[1.1.0]butanes Catalyzed by $PtCl_2$



Scheme 15). After rearrangement of this intermediate via ene−yne metathesis to give carbene **87**, an intramolecular cyclopropanation of the allyl group gives **84**. Irrespective of the initial mechanism for the opening of the bicyclo[1.1.0]butane, the pathways pictured in Schemes 17 and 19 converge at the vinyl carbene **81**/**87**, which subsequently reacts with the neighboring alkene. The core scaffolds of tricycles **76** and **84** are unique and were not prepared previously.

CONCLUDING REMARKS AND PROSPECTS

Shortly after becoming synthetically accessible in 1959, bicyclo[1.1.0]butanes attracted major attention in the physical organic chemistry community because of their unique bonding features, very high strain energy, and mechanistically diverse reaction patterns. However, compared with cyclopropanes and cyclobutanes, the synthetic chemistry of bicyclo[1.1.0]butanes has remained relatively unexplored. Recently, a large body of mechanistic studies on organometallic and pericyclic transformations combined with the availability of highly functionalized bicyclo[1.1.0]butanes place these highly strained, versatile reagents back onto center stage for new reaction development in organic synthesis. They enable not only the mild and selective construction of quaternary carbon centers but also provide opportunities to promote intra- and intermolecular coupling reactions of increasing complexity, allowing surprisingly straightforward access to unique new heterocyclic scaffolds. Bicyclo[1.1.0]butanes are therefore truly privileged tools for new reaction discoveries.

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Notes

The authors declare no competing financial interest.

Biographies

Maciej A. A. Walczak was born in Poland and received his undergraduate degree from Adam Mickiewicz University in Poznań. In 2003, he moved to the University of Pittsburgh and obtained his Ph.D. in 2009 in the Wipf group. He then became a Terrie Brodeur Foundation postdoctoral associate with Professor Samuel J. Danishefsky at the Memorial Sloan-Kettering Cancer Center in New York. In 2013, he embarked on his independent career at the University of Colorado, Boulder, as an Assistant Professor of Chemistry and Biochemistry.

Tanja Krainz was born in Austria and received her Dipl. Ing. from the Vienna University of Technology. In 2010, she moved to the University of Queensland, Australia, and obtained her Ph.D. in 2014 under the supervision of Associate Professor Craig M. Williams in the field of natural product synthesis. She since has joined the Wipf group as a postdoctoral research fellow.

Peter Wipf was born in Switzerland and received his Dipl. Chem. in 1984 and his Ph.D. in 1987 from the University of Zürich under the direction of Professor Heinz Heimgartner. After a Swiss NSF postdoctoral fellowship with Professor Robert E. Ireland at the University of Virginia, he began his appointment at the University of Pittsburgh in 1990 and was named Distinguished University Professor of Chemistry in 2004. He is also a Professor of Pharmaceutical Sciences and of Bioengineering

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ABBREVIATIONS

BHT, 2,6-di-*tert*-butyl-4-methylphenol; cod, cyclooctadiene; dppe, 1,2-bis(diphenylphosphino)ethane; PG, protective group; NR, no reaction; RSE, ring strain energy

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