Synthesis and Rhodium(I)-Catalyzed Annulative Cleavage of Bicyclo[1.1.0]butyl Dihydroquinolines and Dihydropyridines

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KEYWORDS. Rhodium, catalysis, rearrangement, intramolecular cycloaddition, bicyclo[1.1.0]butane, heterocycle, quinoline, pyridine, strain-release.

ABSTRACT: Bicyclo[1.1.0]butane (BCB)-containing compounds are a highly strained class of reagents that feature a unique chemical reactivity, triggering "strain-release" reaction cascades, and provide unique products with considerable utility in the drug discovery field. The C-C bridgehead bond of BCB's two fused cyclopropane rings holds significant π-character, allowing BCB-containing compounds to react with nucleophiles, electrophiles, radicals, π-systems, and carbenes. Herein, we reported the synthesis of new BCBs by the trapping of nucleophilic intermediates with quaternary ammonium ions derived from quinolines and pyridines. The resulting BCBs are then converted with high regioselectivity to unprecedented fused heterocycles in a rhodium(I)-catalyzed annulative rearrangement.

INTRODUCTION. The release of the molecular strain energy as driving force in chemical reactions, referred as "strain-release" reactions, has led to unprecedented chemical transformations as well as access to novel scaffolds of medicinal- and material chemistry interest.[1,2] Bicyclo[1.1.0]butanes (BCBs) are one of the most strained (60-68 kcal/mol), yet readily isolable class of carbocycles and among the most versatile strain-release reagents. In unsubstituted BCBs, the bridgehead and lateral C–C bonds have similar lengths of about 1.50 Å, spatially organized in the signature "butterfly" geometry where the two "wings" are separated by a 123° angle. As a consequence of this conformation, the hybridization of two carbon atoms of the bridgehead is dominated by a high π-character.[3] Consequently, BCBs react at the bridgehead C-C bond with a broad range of nucleophiles, electrophiles, radicals, π-systems, and carbenes, underlining the σ/π-bond ambiguity of this bond. In the last few years, the study of BCB-containing molecules has surged, and new applications in medicinal chemistry as warheads for covalent inhibition, bioisosters of *ortho*- and *meta*-substituted benzenes, and as chemical probes have been reported.[4]

BCBs can be synthesized by transannular cyclization,[5,6,7] cyclopropanation,[8,9] and side-chain cyclization which can be further divided into epoxysulfone-based[10,11,12,13] and dibromocyclopropane-based routes. In the latter method (Scheme 1A), dibromocyclopropane is used as a precursor for bromide-substituted BCB (BCB-Br) by treatment with methyllithium. The unstable and volatile BCB-Br is then treated with *t*-BuLi for a Li-Br exchange to form bicyclo[1.1.0]butyl lithium (BCB-Li).[4] This reactive organometallic reagent is then trapped with suitable electrophiles to generate BCB-containing sulfoxides,[14,15,16] esters,[17] boronates,[18] ketones,[19] amides,[19], alcohols,[20] and amines.[18,20,21] BCB-Li can be further treated with freshly prepared $MgBr_2{\cdot}Et_2O$ or $MgCl_2{\cdot}LiCl$ to form the more selective bicyclo[1.1.0]butyl magnesium bromide (BCB-MgBr) and bicyclo[1.1.0]butyl magnesium chloride-lithium chloride (BCB-MgCl·LiCl), respectively.[18] A practical method to generate BCB-Li or BCB-MgCl·LiCl consists of the treatment of the bench-stable 1-(*p*-tolylsulfinyl)bicyclo[1.1.0]butane (BCB-sulfoxide) with *t*-BuLi or *i*-PrMgCl·LiCl, respectively (Figure 1A).[18] Herein ,we report the trapping of BCB anions with quaternary ammonium salts derived from quinoline, pyridine, and their surrogate heterocycles to generate BCB-containing dihydroquinolines and dihydropyridines, respectively. We then performed a rhodium(I)-catalyzed rearrangement using phosphine ligands that allowed us to access the novel 1-methylene-2,2*a*,2*a*1,2*b*,5,5*a*-hexahydro-5-azacyclopropa[*cd*]indene scaffold (Figure 1B). This approach suitably extends our previous rhodium(I)-catalyzed cycloisomerizations of *N*-allylated bicyclo[1.1.0]butylalkylamines and ethers to synthesize cyclopropane-fused pyrrolidines, azepines, furans and oxepanes, respectively, with high stereo- and regiocontrol.[20,22]

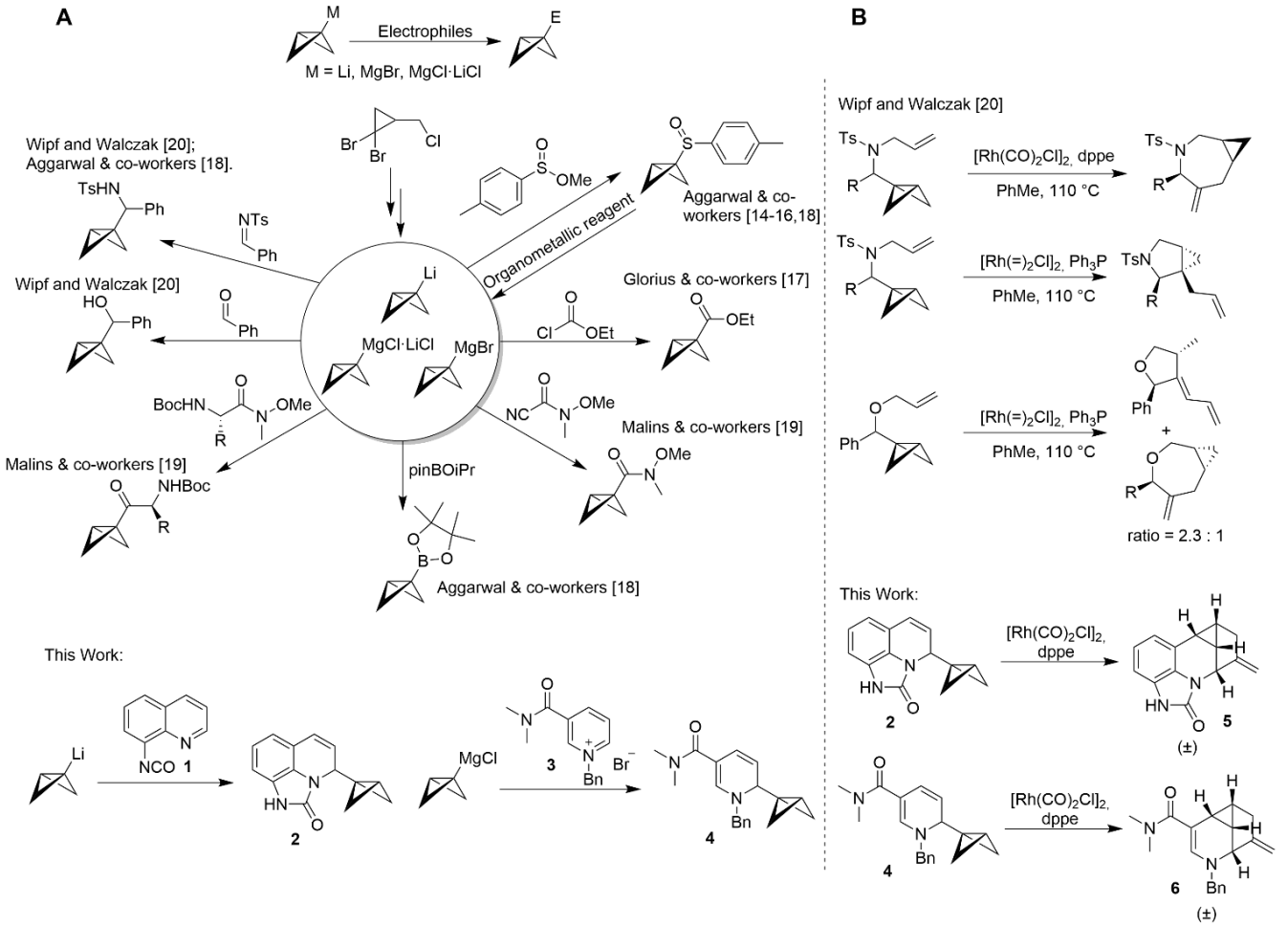
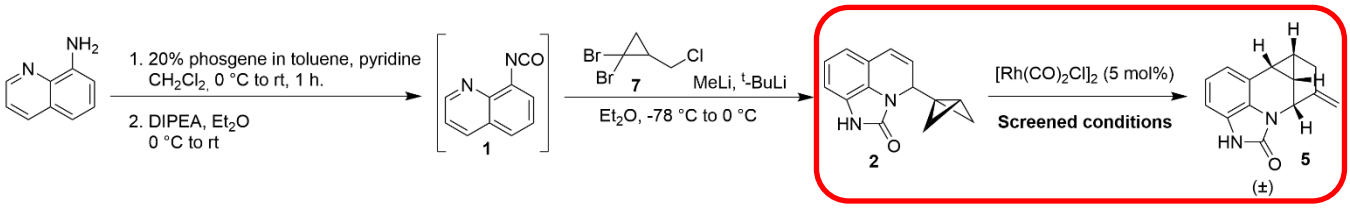


Figure 1. A: Preparation of BCB-containing reagents via nucleophilic addition of *in situ* formed BCB-organometallics to electrophiles. B: Examples of rhodium(I) catalyzed rearrangements of BCBs.

RESULTS AND DISCUSSION.

Reaction Optimization. The rhodium(I)-catalyzed rearrangement step was optimized using the bench-stable BCB **2**, synthesized from 8-aminoquinoline via the corresponding isocyanate which was then free-based using diisopropylethylamine and used for trapping BCB-Li (Scheme 1). For the conversion of **2** into **5** we screened reaction conditions, mainly focusing on ligand and solvent optimization (Table 1, See SI table for the complete set of conditions). Interestingly, dppe demonstrated to be the most effective ligand among the screened phosphines. Similar results were obtained with toluene and 1,4-dioxane (Entries 1 and 2). In order to go to completion, the reaction required a temperature of 120 °C since lower temperatures failed to improve yields even with prolonged reaction times (Entries 5 and 6). Accordingly, we selected conditions of Entry 2 for the investigation of substrate scope.

Table 1. Screening of reaction conditions to convert **2** to **5**.



Entry	Ligand (10 mol%)	Solvent [0.05 M]	Temperature	Time	NMR yield
1	dppe	Toluene[a]	120 °C	30 min	69%
2	dppe	1,4-dioxane	120 °C	30 min	80% (77%)[b]
3	dppp	Toluene[a]	120 °C	30 min	19%
4	PPh_3	Toluene[a]	120 °C	30 min	18%
5	dppe	1,4-dioxane	90 °C	30 min	46%
6	dppe	1,4-dioxane	80 °C	60 min	53%
7	dfppe	1,4-dioxane	120 °C	30 min	51%
8	tribenzylphosphine	1,4-dioxane	120 °C	30 min	36%
9	dcpe	1,4-dioxane	120 °C	30 min	39%
10	dppb	1,4-dioxane	120 °C	30 min	24%

Reactions were performed in a microwave vial sealed with a PTFE crimp cap before heating. (a) The reaction mixture was degassed before heating; (b) Isolated yield. dppe = 1,2-bis(diphenylphosphino)ethane; dppp = 1,3-bis(diphenylphosphino)propane; dfppe = 1,2-ethanediylbis[bis(pentafluorophenyl)phosphine]; dcpe = bis(dicyclohexylphosphino)ethane; dppb = 1,4-bis(diphenylphosphino)butane.

Substrate scope. We next explored the rhodium(I)-catalyzed rearrangement of BCBs-containing dihydroquinolines and dihydropyridines, obtained from the nucleophilic addition of bicyclo[1.1.0]butyl magnesium chloride (BCB-MgCl) to quaternary ammonium salts of quinoline and pyridine heterocycles. Although compound **2** did not showed any stability issue during purification and storage, its non-acylated analogs appeared to undergo decomposition during purification, suggesting the use of a one-pot/ two-step process. We first screened quinolinium ions as electrophiles with different substituents at the *N*-positions. The two-step sequence was tolerant of alkyl and benzyl substituents, as shown for compounds **8** and **9**, obtained in 43% and 52% yields, respectively. Electron-withdrawing and -donating groups on the benzyl moiety did not have a significant effect on the reaction yield, consistently providing ca. 50% product, with the exception of **13** and **14** (22% and 34% yield, respectively) due to the formation of byproducts during the purification step. We then screened quinolinium ions with substituents at the quinoline scaffold. Surprisingly, the two-step reaction worked well in the presence of reactive groups such as a hydroxy group at the C-8 position and a methyl ester at C-5, providing the desired products **15** and **16** in 33% and 38% yield, respectively. Interestingly, the presence of electron-withdrawing substituents facilitated the regioselective addition of BCB-MgCl to α-carbon of the quinolinium ion and providing significant electronic stabilization of the adduct, such as the case of compound **17** obtained in 50% yield. Electron-donating substituents such as 5-methyl and 7-methoxy groups, in contrary, gave the desired products in lower yields, probably due to corresponding destabilization effects. We then screened non-quinoline like compounds using phenanthrolinium and pyridinium ions as electrophiles. The two-step reaction gave excellent results to afford derivatives bearing amide or nitrile groups in conjugation with the basic nitrogen, such as compounds **6** (66% yield) and **21** (64% yield), respectively. Moreover, when 1-benzyl-3-cyanopyridin-1-ium bromide was used as the electrophile, the regioisomer **22** was obtained in 16% yield as minor component, resulting from the BCB addition at C-4 of the pyridinium ring.

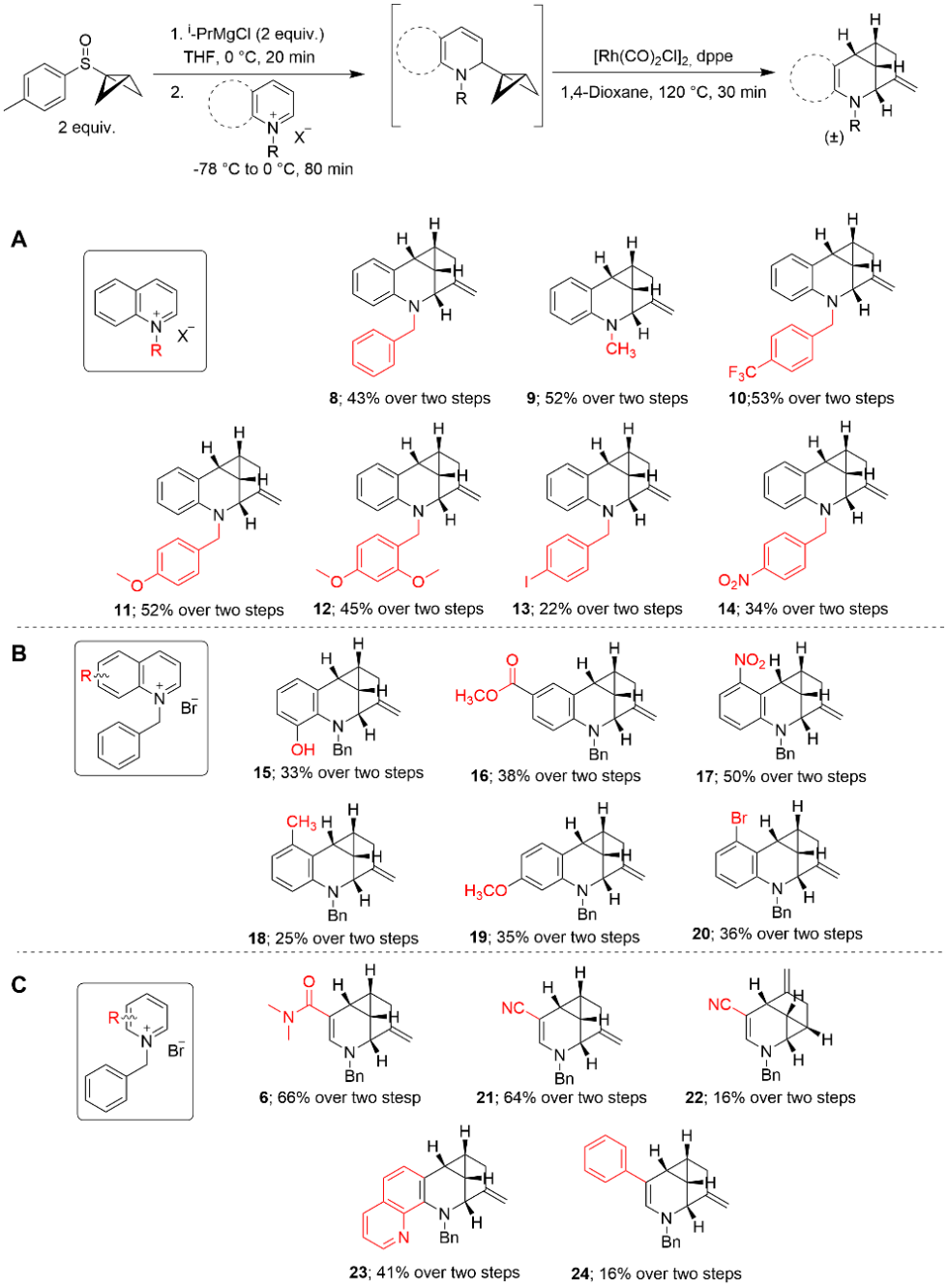
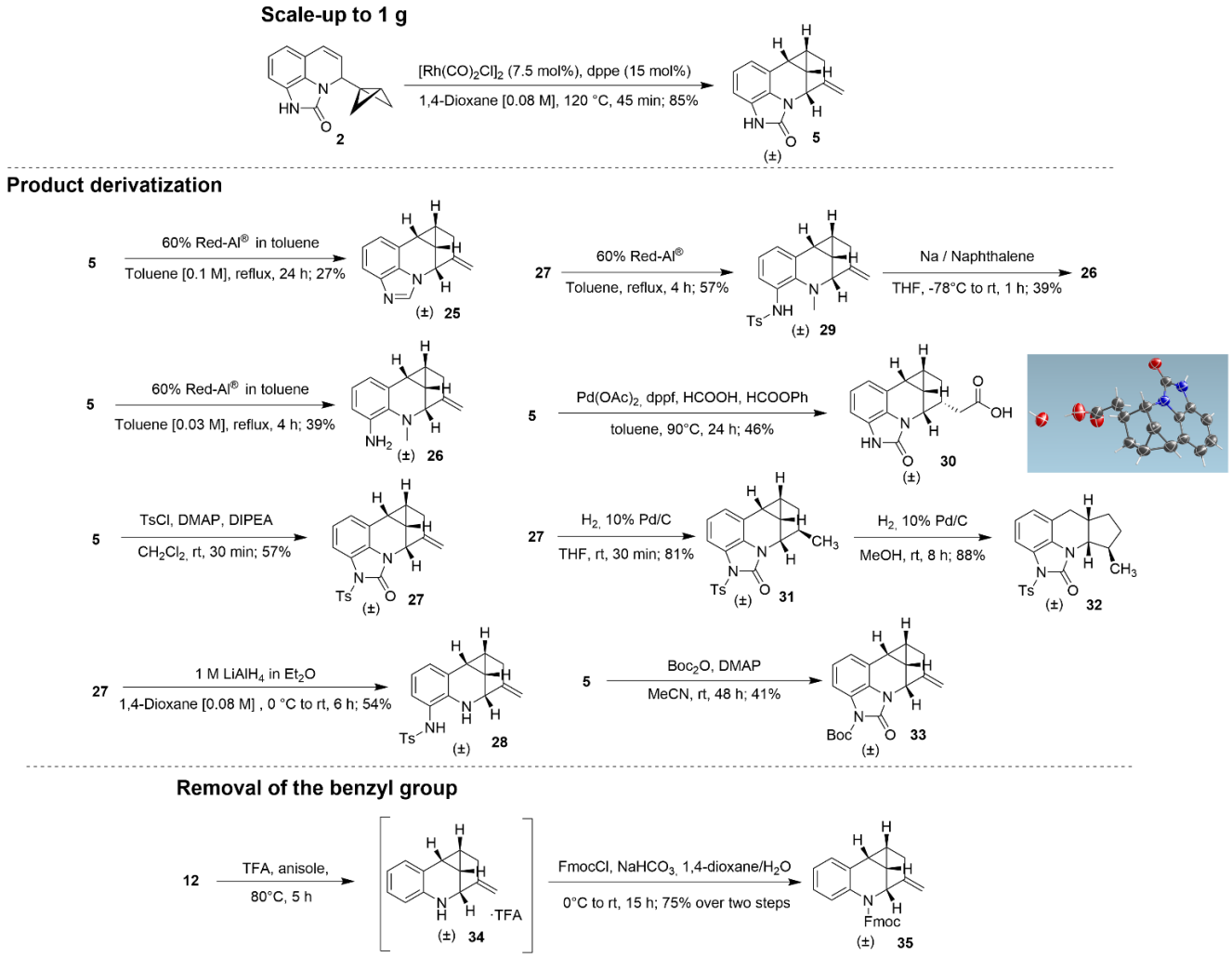


Figure 2. Addition of BCB-MgCl followed by rhodium(I)-catalyzed annulative cleavage of (A) quinolinium ions substituted at the *N*-position; (B) quinolinium ions substituted at the benzene ring; and (C) pyridinium and phenanthrolinium ions.

Synthetic applications. The Rh(I)-catalyzed rearrangement can be performed on gram-scale without compromising reaction yield. Compound **2** was used as model substrate to give product **5** in 85% yield using 7.5 mol% of catalyst and 15 mol% of ligand (Figure 3). We then performed chemical transformations at the cyclic urea moiety of **5** using 60% Red-Al® as a reducing agent, which gave benzimidazole **25** and aniline **26** in 27% and 39%, yield, respectively, based on their concentration in the reaction mixture. Under reductive cleavage conditions, the two tosyl-protected derivatives **28** and **29** can be obtained from the precursor **27**, and then further converted to **30** in 39% yield after tosyl deprotection of **26** using sodium naphthalenide. The hydrocarboxylation at the *exo*-olefin moiety in **5** provided the desired carboxylic acid **30** in 46% yield in a regioselective fashion. The olefin moiety can be reduced using hydrogen with Pd/C to give the regioisomeric **31** in 81% yield when THF was used as a solvent. Resubjecting compound **31** to the the hydrogenation conditions using a protic solvent like MeOH afforded compound **32** in 88% yield by opening the strained cyclopropane ring. We then focused our attention on finding optimal conditions for the removal of the dimethoxybenzyl group from **12** using trifluoroacetic acid and anisole to obtain the corresponding aniline, which could be further

converted to the corresponding Fmoc-protected derivative **35** in 75% yield over two steps.

Scheme 1. Scale-up of Rh(I)-catalyzed rearrangement and further derivatization of rearranged products. X-ray structure of 30.



Proposed mechanism. Based on our previous computational analyses of the Rh(I)-catalyzed rearrangement of BCBs using $[Rh(CO)_2Cl]_2$ as catalyst and 1,2-bis(diphenylphosphino)ethane as ligand,[23] we suggest that the reaction initiates with the coordination of Rh(I) to the *endo*-olefin to form the Rh(I)-π-complex **36** (Figure 3). Subsequently, attack of the rhodium catalyst at the external carbon of the BCB via double σ-bond insertion produces a Rh-carbenoid species **37**. The irreversibility of the concerted C-C bond cleavage and Rh-carbenoid formation is thought to be important for the overall regioselectivity of the reaction. At this point, the rhodium catalyst can coordinate with the *endo*-olefin to give **38** which is then converted to the metallacycle intermediate **39** by olefin insertion. Product **5** results after C–C bond formation and reductive elimination, regenerating the active rhodium(I) catalyst for the next catalytic cycle. In support of the proposed mechanism, we synthesized BCBs **41** and **44** with disubstitution at the bridgehead carbons, by performing the nucleophilic addition of BCBs **40** and **43** to the isocyanate **1**, and then subjected them to the Rh(I)-catalyzed rearrangement conditions. As expected, both **41** and **44** did not show any reactivity under these conditions, probably due to the lack of ready access to the rhodium carbenoid species.

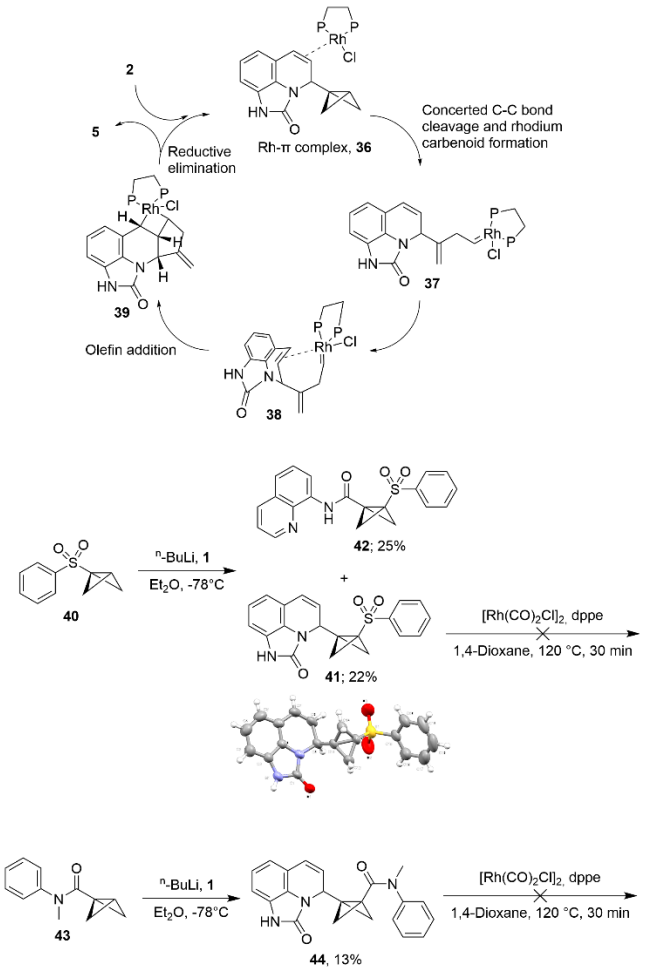


Figure 3. Proposed mechanism for the Rh(I)-catalyzed rearrangement reaction and mechanistic control experiments. X-ray structure of **41**.

CONCLUSION. In summary, we have developed a general method for the synthesis of BCB-containing dihydroquinolines and dihydropyridines through the addition of BCB-MgCl to the α-carbon of the quaternary ammonium ions of quinoline and pyridine heterocycles. The resulting BCB-containing intermediates allowed us to further expand the rhodium(I)-catalyzed rearrangement to give the novel, highly strained 1-methylene-2,2*a*,2*a*1,2*b*,5,5*a*-hexahydro-5-azacyclopropa[*cd*]indene scaffold. In order for the rearrangement to proceed, one of the two bridgehead carbons needs to be unsubstituted. The regiospecificity of the reaction originates from the formation of rhodium cyclobutene **39**. Both the BCB-addition and the rearrangement steps tolerate a wide variety of functionalities, showing high regioselectivity for the desired transformations. To the best of our knowledge, scaffolds **5** and **6** are unprecedented,[24] opening unique opportunities for future explorations as synthetic building blocks and pharmaceutical components.

ASSOCIATED CONTENT

Supporting Information. Experimental details and spectral data.

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Funding Sources

We are grateful to the National Science Foundation (CHE-0910560 to P.W.) for financial support of this research.

ACKNOWLEDGMENT

The authors thank Steven Geib (Pittsburgh) for x-ray structure analyses.

ABBREVIATIONS

DIPEA, N,N-diisopropylethylamine; dppe, 1,2-bis(diphenylphosphino)ethane ; THF, tetrahydrofurane; DMAP, 4-dimethylaminopyridine; TFA, trifluoroacetic acid.

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Graphical Abstract