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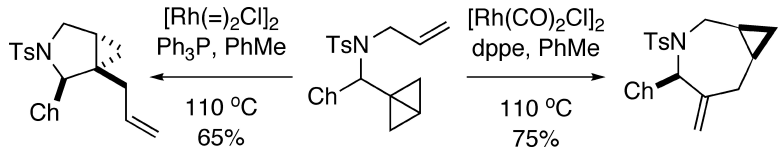

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Rhodium(I)-Catalyzed Cycloisomerizations of Bicyclobutanes

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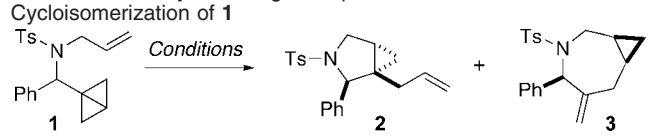
Among strained ring systems, bicyclo[1.1.0]butanes are of special significance due to their unique chemical bonding properties.[1] Cleavage of the central bond in bicyclo[1.1.0]butane, formally a $C_{sp^3}-C_{sp^3}$ σ-bond, is facilitated by the release of ~65 kcal/mol in strain energy and represents the most common reaction pathway observed for these molecules. The similarity of the σ-bond to a $C_{sp^2}=C_{sp^2}$ π-bond has often been invoked to explain the chemical behavior of bicyclo[1.1.0]butanes,[2] in particular, their participation in pericyclic, radical, and ionic reactions.[1,3] As with other strained rings,[4] metal-catalyzed isomerization reactions of bicyclo[1.1.0]butanes have been studied extensively.[5] Formation of 1,3-butadiene is a major reaction pathway, but the selectivity is strongly dependent on catalysts, reaction conditions, and substituents.[5b] For example, reactions catalyzed by Ag(I) are thought to proceed via an initial cleavage of the lateral C−C bond in bicyclo[1.1.0]butanes followed by skeletal rearrangement of a carbocation.[6] In contrast, group 9 and 10 metals have been shown to operate through a mechanistically distinct pathway.[7–9] Trapping experiments confirmed the formation of a carbene intermediate,[8] but low yields as well as limited scope in these reactions prevented a further development of general synthetic methodologies.

We have recently shown that bicyclo[1.1.0]butylalkylamines undergo highly stereoselective intramolecular cycloadditions with alkenes and alkynes under mild reaction conditions.[3] We further envisioned that a transient metal carbenoid species resulting from isomerization of the bicyclo[1.1.0]butane could be trapped intramolecularly by the *N*-allyl substituent before undergoing isomerization to a 1,3-butadiene. Mindful of literature precedence[5] as well as the similarity of the carbene-forming step to the metal-catalyzed decomposition of diazocompounds,[10] we selected Rh(I) precatalysts as potential promoters of the rearrangement reactions. Representative optimization studies for a rhodium-catalyzed cycloisomerization of bicyclobutanes are shown in Table 1.[11a] When **1** was heated with 5% $[Rh(=)_2Cl]_2$ in PhMe at 110 °C in the presence of 10% *n*-Bu_3P, a 6:1 mixture of **2** and **3** was formed in good overall yield (entry 1). Addition of Ph_3P (10%) improved the yield of pyrrolidine **2** to 87% with 8% of the azepine **3** (entry 2). The reaction was complete within 10 min and **2** was formed with excellent diastereoselectivity (>95:5).[11b] When additional Ph_3P was added, or the amount of precatalyst was reduced (entries 3 and 4), the yield of **2** dropped. Phosphines with electron-donating or -deficient aromatic substituents had a detrimental effect (entries 5 and 6), and bulkier aliphatic ligands reduced the yield of **2** dramatically (entry 7). Precatalysts bearing large alkene ligands (entries 9 and 10) also led to diminished yields and chemoselectivity.

Wilkinson's catalyst led to a 1:2 ratio of **2** to **3**, but a more striking reversal of selectivity was observed when bidentate phosphines were used in combination with $[Rh(CO)_2Cl]_2$ (entries 11−15). We found that addition of 10% dppe provided the desired azepine **3** in high yield and excellent diastereoselectivity.[11b] The combination of $[Rh(=)_2Cl]_2$ and dppe provided the azepine in 77% yield. Other bidentate phosphines furnished **3** in lower yields and selectivities, but formation of pyrrolidine **2** was completely suppressed in all cases. In the absence of ligand, both **2** and **3** were formed in low yield (entry 16). Solvents such as EtOAc, THF, CH_2ClCH_2Cl, and *t*-BuOMe did not provide improvements. In addition, we found that the best yields were obtained when the reactions were carried out at low concentration (0.05 M) (entry 15). Finally, under the optimized conditions for the formation of **2** or **3**, isomerization of **1** to the butadiene did not exceed 1%.[11a]

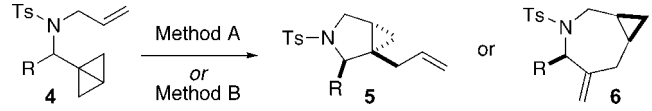
Table 1. Precatalyst and Ligand Optimizations for the Cycloisomerization of **1**



entry[a]	pre-catalyst	ligand	yield [%][b]	
			2	**3**
1	$[Rh(=)_2Cl]_2$	*n*-Bu_3P	78	12
2	"	Ph_3P	87[c]	8
3	"	Ph_3P (20%)	70	2
4	" (1 mol%)	Ph_3P	71	3
5	"	$(4\text{-}MeOC_6H_4)_3P$	43	4
6	"	$(4\text{-}FC_6H_4)_3P$	61	1
7	"	*t*-Bu_3P	22	5
8	"	Ph_2MeP	81	9
9	$[Rh(coe)_2Cl]_2$	Ph_3P	38	9
10	$[Rh(cod)_2Cl]_2$	Ph_3P	57	20
11	$RhCl(PPh_3)_3$ (10 mol%)	-	24	49
12	$[Rh(CO)_2Cl]_2$	dppe	<1	83[d]
13	"	dppp	<1	29
14	"	dppb	<1	7
15[e]	"	dppe	<1	63
16	$[Rh(=)_2Cl]_2$	-	11	10

[a] Reactions used 5% of precatalyst and 10% of phosphine ligand at 0.05 M concentration of **1** in PhMe at 110 °C. [b] NMR yields based on internal standard. [c] Isolated yield: 77%. [d] Isolated yield: 77%. [e] Concentration: 0.1 M.

Table 2. Rh(I)-Catalyzed Isomerizations of Bicyclo[1.1.0]butanes **4**



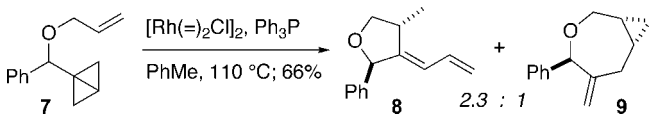
entry	substrate	method A[a]	method B[b]
1	**4a**, R = 3,5-$(MeO)_2C_6H_3$	**5a**, 67%	**6a**, 87%
2	**4b**, R = 4-ClC_6H_4	**5b**, 55%	**6b**, 80%
3	**4c**, R = 2-furyl	**5c**, 75%	**6c**, 58%
4	**4d**, R = $BnOCH_2$	**5d**, 63%	**6d**, 68%
5	**4e**, R = cyclohexyl	**5e**, 65%	**6e**, 75%

[a] Method A: $[Rh(=)_2Cl]_2$ (5 mol %), Ph_3P (10 mol %), PhMe (0.05 M), 110 °C. [b] Method B: $[Rh(CO)_2Cl]_2$ (5 mol %), dppe (10 mol %), PhMe (0.05 M), 110 °C.

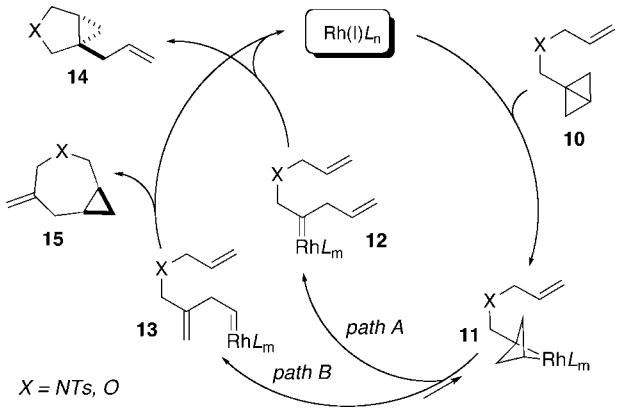
The systematic variation of precatalysts and ligands for the cycloisomerization of model system **1** provided selective access to synthetically useful pyrrolidines and azepines. The scope of this methodology was further explored using various aromatic, heteroaromatic, and functionalized aliphatic substrates (Table 2). In addition to excellent scaffold chemoselectivity (pyrrolidine **5** vs azepine **6**), all reactions proceeded in high diastereoselectivity. The

10.1021/ja802906k CCC: $40.75

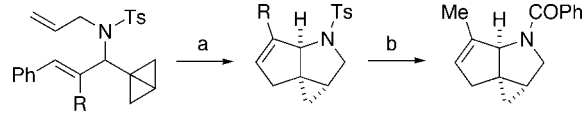
Scheme 1. Furan and Oxepane from Allylic Ether



Scheme 2. Proposed Mechanism of Cycloisomerization Reactions



Scheme 3. Synthesis of 3-Azatricyclo[6.1.0.0^{1,5}]nonanes via Tandem Isomerization−RCM[a]



[a] Reagents and conditions: (a) [Rh(=)$_2$Cl]$_2$, Ph$_3$P, PhMe, 110 °C then metathesis catalyst,[16] 60 °C; (b) i. Na/naphthalene, THF, −78 °C; ii. PhCOCl, DMAP, Et$_3$N, CH$_2$Cl$_2$, 0 °C, 53%.

degree of substitution around the bicyclo[1.1.0]butane ring appears to play a dominant role in controlling the reactivity of the transient rhodium carbene species. For example, large R groups on amide **4** considerably reduced the reaction rate, and chain-substituted allylic as well as homoallylic amides failed to give pyrrolidines or azepines in satisfactory yields.

We also briefly explored the cycloisomerization of allylic ethers (Scheme 1). With [Rh(=)$_2$Cl]$_2$ precatalyst, an NMR based yield of 66% of a 2.3:1 ratio of furanyl diene **8** and oxepane **9** was obtained. Other catalysts led to a diminished yield.

We propose that the isomerization reactions of bicyclo[1.1.0]butanes proceed via the mechanism depicted in Scheme 2. Oxidative addition of Rh(I) across the central σ-bond in bicyclo[1.1.0]butane **10** results in the formation of intermediate **11**, which subsequently undergoes rearrangement to carbenes **12** and **13**. Formation of the tricyclic intermediate **11** has been proposed for reactions of electron-deficient bicyclo[1.1.0]butanes, but it is worth noting that **11** may also exist in equilibrium with its isomers formed by insertion of the metal into the lateral bonds of bicyclo[1.1.0]butane **10**.[12] The selectivity of the rearrangement of **11** is controlled by the steric bias exerted by the phosphine ligands. Monodentate phosphines allow for the formation of internal carbene **12**, a process most likely favored by the proximity of the allyl group.[13] Alternatively, in the presence of bidentate ligands, the saturated complex **11** rearranges to carbene **13**. Although no specific mechanistic data are available, formation of carbenes **12** and **13** could also be a reversible process.[14] Subsequent cyclopropanation of the allyl group proceeds via transition states in which the α-substituent adopts a pseudoaxial orientation leading to **14** and **15**. In cases where the allyl group is not accessible for a facile reaction, carbenes **12** and **13** undergo hydride migration to afford 1,3-butadienes.[15]

In order to further extend the utility of the Rh-catalyzed isomerizations of bicyclo[1.1.0]butanes, sulfonamides **16a−c** were subjected to reaction conditions that promoted formation of pyrrolidines (Scheme 3). Upon completion of the rearrangement, Ru metathesis catalyst[16] was added and the novel tricyclic pyrrolidines **17a−c** were formed in good yields. In combination with the ligand-controlled isomerization pathways of bicyclo[1.1.0]butanes and the facile removal of the nitrogen protecting group, this synthetic strategy allows for the rapid assembly of a diverse set of molecular scaffolds[17] from a common pool of functionalized bicyclo[1.1.0]butanes.

In summary, we have developed an efficient rhodium-catalyzed cycloisomerization of N-allylated bicyclo[1.1.0]butylalkylamines. Depending on the nature of the Rh(I) phosphine ligands, these reactions provide pyrrolidines and azepines with high levels of stereo- and regiocontrol. A related transformation is also feasible for allylic ethers, providing substituted furans and oxepanes.

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Supporting Information Available: Experimental procedures, copies of ^{1}H and ^{13}C NMR spectra, and crystal information file. This material is available free of charge via the Internet at http://pubs.acs.org.

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