Published in final edited form as:

J Am Chem Soc. 2008 June 4; 130(22): 6924–6925. doi:10.1021/ja802906k.

Rhodium(I)-Catalyzed Cycloisomerizations of Bicyclobutanes

Maciej A. A. Walczak and Peter Wipf*

Department of Chemistry, University of Pittsburgh, 219 Parkman Avenue, Pittsburgh, Pennsylvania 15260

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 precedence⁵ 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*-Bu₃P, a 6:1 mixture of **2** and **3** was formed in good overall yield (entry 1). Addition of Ph₃P (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 Ph₃P 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, CH₂ClCH₂Cl, 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}

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 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(=CHCl)₂]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 catalyst¹⁶ 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 scaffolds¹⁷ 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

This work was supported by NIGMS (NIH P50 GM067082). We thank Dr. Steve Geib for X-ray crystallographic analyses.

References

- (1). Hoz, S. The Chemistry of the Cyclopropyl Group. Rappoport, Z., editor. Wiley; New York: 1987.
(b) Wiberg KB, Lampman GM, Ciula RP, Connor DS, Schertler P, Lavanish J. Tetrahedron 1965;21:2749.
- (2). (a) Newton MD, Schulman JM. J. Am. Chem. Soc 1972;94:767. (b) Pomerantz M, Hillenbrand DF. J. Am. Chem. Soc 1973;95:5809.
- (3). Wipf P, Walczak MAA. Angew. Chem., Int. Ed 2006;45:4172.
- (4). Wender, PA.; Gamber, GG.; Williams, TJ. Modern Rhodium-Catalyzed Organic Reactions. Evans, PA., editor. Wiley-VCH; Weinheim, Germany: 2005. (b) Namyslo JC, Kaufmann DE. Chem. Rev 2003;103:1485. [PubMed: 12683789] (c) Rubin M, Rubina M, Gevorgyan V. Chem. Rev 2007;107:3117. [PubMed: 17622181]
- (5). (a) Paquette LA. Acc. Chem. Res 1971;4:280. (b) Bishop KC III. Chem. Rev 1976;76:461.
- (6). (a) Sakai M, Masamune S. J. Am. Chem. Soc 1971;93:4610. (b) Sakai M, Westberg HH, Yamaguchi H, Masmune S. J. Am. Chem. Soc 1971;93:4611.
- (7). (a) Gassman PG, Reitz RR. J. Organomet. Chem 1973;52:C51. (b) Gassman PG, Atkins TJ, Williams FJ. J. Am. Chem. Soc 1971;93:1812. (c) Gassman PG, Nakai T. J. Am. Chem. Soc 1972;94:5497.
- (8). (a) Noyori R, Suzuki T, Kumagai Y, Takaya H. J. Am. Chem. Soc 1971;93:5894. (b) Noyori R. Tetrahedron Lett 1973;14:1691. (c) Noyori R, Kawauchi H, Takaya H. Tetrahedron Lett 1974;15:1749. (d) Takaya H, Suzuki T, Kumagai Y, Hosoya M, Kawauchi H, Noyori R. J. Org. Chem 1981;46:2854.
- (9). (a) Dauben WG Jr. J. Am. Chem. Soc 1972;94:3669. (b) Dauben WG, Kielbania AJ Jr. Raymond KN. J. Am. Chem. Soc 1973;95:7166.
- (10). For recent reviews, see:(a)Davies HML, Beckwith REJ. Chem. Rev 2003;103:2861. [PubMed: 12914484](b)Merlic CA, Zechman AL. Synthesis 2003:1137.(c)Davies H. Org. React 2001;57:2. (d)Padwa A. J. Organomet. Chem 2001;617-618:3.(e)Doyle MP, Forbes DC. Chem. Rev 1998;98:911. [PubMed: 11848918]
- (11). (a) See Supporting Information for additional optimization conditions. (b) Determined by ^1H NMR analysis of a crude reaction mixture. The relative configuration was determined by NOESY (2) or X-ray analysis of the corresponding ketone (3). For details, see Supporting Information.
- (12). (a) Miyashita A, Takahashi M, Takaya H. J. Am. Chem. Soc 1981;103:6257. (b) Miyashita A, Watanabe Y, Takaya H. Tetrahedron Lett 1983;24:2595.
- (13). Isomerization of *N*-sulfonamides (no allyl substituents) under conditions favoring formation of **12** or **13** afforded only diene products.
- (14). (a) Ikto N, Takamura N, Young SD, Ganem B. Tetrahedron Lett 1981;22:4163. (b) Shi W, Xiao F, Wang J. J. Org. Chem 2005;70:4318. [PubMed: 15903306]
- (15). May JA, Stoltz BM. J. Am. Chem. Soc 2002;124:12426. [PubMed: 12381180]
- (16). Trnka TM, Grubbs RH. Acc. Chem. Res 2001;34:18. [PubMed: 11170353]
- (17). (a) Wipf P, Stephenson CRJ, Walczak MAA. Org. Lett 2004;6:3009. [PubMed: 15330670] (b) Dolle RE, Le Bourdonnec B, Morales GA, Moriarty KJ, Salvino JM. J. Comb. Chem 2006;8:597. [PubMed: 16961395]

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(=)₂Cl]₂, Ph₃P, PhMe, 110 °C then metathesis catalyst,¹⁶ 60 °C; (b) i. Na/naphthalene, THF, -78 °C; ii. PhCOCl, DMAP, Et₃N, CH₂Cl₂, 0 °C, 53%.

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

entry ^a	pre-catalyst	ligand	yield [%] ^b	
			2	3
1	[Rh(=) ₂ Cl] ₂	<i>n</i> -Bu ₃ P	78	12
2	“	Ph ₃ P	87 ^c	8
3	“	Ph ₃ P(20%)	70	2
4	“ (1 mol%)	Ph ₃ P	71	3
5	“	(4-MeOC ₆ H ₄) ₃ P	43	4
6	“	(4-FC ₆ H ₄) ₃ P	61	1
7	“	<i>t</i> -Bu ₃ P	22	5
8	“	Ph ₂ MeP	81	9
9	[Rh(coe) ₂ Cl] ₂	Ph ₃ P	38	9
10	[Rh(cod) ₂ Cl] ₂	Ph ₃ P	57	20
11	RhCl(PPh ₃) ₃ (10 mol%)	-	24	49
12	[Rh(CO) ₂ Cl] ₂	dppe	<1	83 ^d
13	“	dppp	<1	29
14	“	dppb	<1	7
15 ^e	“	dppe	<1	63
16	[Rh(=) ₂ Cl] ₂	-	11	10

^aReactions used 5% of precatalyst and 10% of phosphine ligand at 0.05 M concentration of **1** in PhMe at 110 °C.

^bNMR yields based on internal standard.

^cIsolated yield: 77%.

^dIsolated yield: 77%.

^eConcentration: 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) ₂ C ₆ H ₃	5a , 67%	6a , 87%
2	4b , R = 4-ClC ₆ H 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%

^aMethod A: [Rh(=)Cl]₂ (5 mol %), Ph₃P (10 mol %), PhMe (0.05 M), 110 °C.

^bMethod B: [Rh(CO)₂Cl]₂ (5 mol %), dppe (10 mol %), PhMe (0.05 M), 110 °C.