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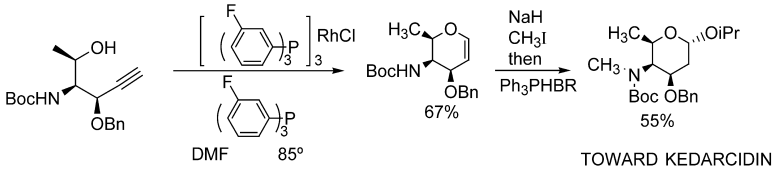

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A Rh(I)-Catalyzed Cycloisomerization of Homo- and Bis-homopropargylic Alcohols

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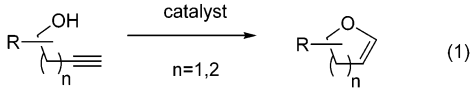
While organometallic vinylidene complexes generated from terminal alkynes have been examined from the point of view of preparation and properties, catalytic processes have been slow to develop until recently.[1] Only very few metals capable of forming such complexes have led to useful catalytic processes. The first example involved the Ru-catalyzed addition of terminal alkynes and allyl alcohols to generate β,γ-unsaturated ketones.[2] Subsequently, a number of other processes involving Ru catalysis have emerged.[3] The formation of oxygen heterocycles mediated/catalyzed by carbonyl complexes of molybdenum and tungsten[4] as well as catalyzed by phosphine ruthenium complexes[5] illustrated in eq 1 represents a particularly useful synthetic reaction given the biological importance of many such compounds. The limitations posed by the existing catalysts make the discovery of new catalysts that might be more chemoselective and give higher turnover desirable.



(1)

The wide utility of Rh in catalytic synthetic organic chemistry combined with the ability of Rh to form vinylidene complexes from terminal alkynes[6] makes its complexes natural targets for the evaluation for cycloisomerizations as shown in eq 1. Little is known about catalytic reactions involving Rh(I)-vinylidene complexes as reactive intermediates.[7] In the course of our continuing study in this field, we uncovered a cycloisomerization of homo- and bis-homopropargylic alcohols catalyzed by Rh(I) complexes that has excellent chemoselectivity.

Initial attempts to use **1** as a model substrate in the presence of the Rh complex **3a** in toluene led to the formation of dimeric as well as unidentified oligomeric compounds.[8] Surprisingly, employing a polar solvent such as DMF gave dihydrofuran **5** in moderate yield, as shown in Table 1, entry 1. Because the dimeric compound (~15%) was still obtained, we reasoned that the undesirable processes could be suppressed by excess phosphines. Indeed, the addition of ligand **2a** (60%) significantly improved the yield (entry 3). To explore the electronic effect of the phosphine, we employed complex **4**. Although electron-rich phosphines such as triisopropylphosphine have been often used for stoichiometric preparation of Rh(I)-vinylidene complexes (Figure 1), using such ligands in the catalytic process slowed the reaction. Placing an electron-donating substituent on the aryl rings of triphenyl phosphine, as in ligand **2b**, also harmed the yield of the cycloisomerization (entry 6). On the other hand, a significant improvement arises by employing electron-poor ligands **2c**, **2d**, and **2e** (entries 7−9). In the best case, using 55 mol % ligand **2e** with precatalyst **4** (2.5 mol %) in DMF provided the dihydrofuran in 69% isolated yield (entry 9). Under this condition, only trace amounts of dimeric compounds were detected. On the other hand, using **2f** (entry 6), a more electron-poor and smaller ligand, significantly slowed the reaction. Addition of triethylamine (0.5−2 equiv) had no effect. Thus, the reaction is performed under totally neutral conditions. The optimized conditions employ pregenerated[9] catalyst **3d** (5%) in the presence of the ligand **2e** (30%), which provided **5** in 68% yield (entry 11).[10]

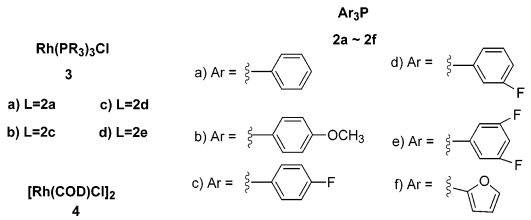
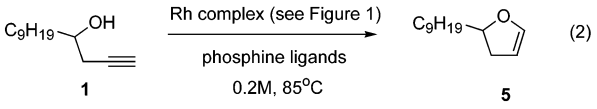


Figure 1. List of Rh(I) complexes and phosphine ligands.

Table 1. Optimization of Cycloisomerization

entry	Rh complex	ligand	time (h)	conv	yield[a]
1	**3a** (10%)		2	100%	25%
2	**3a** (10%)	**2a** (40%)	2	100%	46%
3	**3a** (10%)	**2a** (60%)	2	100%	53%
4	**3a** (10%)	**2a** (80%)	2	100%	51%
5	**4** (2.5%)	**2a** (55%)	2	100%	55%
6	**4** (2.5%)	**2b** (55%)	2	100%	42%
7	**4** (2.5%)	**2c** (55%)	2	100%	61%
8	**4** (2.5%)	**2d** (55%)	2	100%	69%
9	**4** (2.5%)	**2e** (55%)	2	100%	75% (69%)[b]
10	**4** (2.5%)	**2f** (55%)	4	40%	29%
11	**3d** (5%)	**2e** (30%)	1	100%	73% (68%)[b]
12	**3d** (3%)	**2e** (20%)	2	83%	55%

[a] GC yield. [b] Isolated yield.



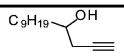
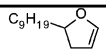
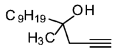
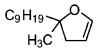
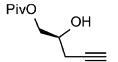
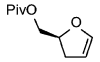
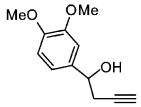
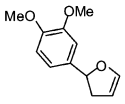
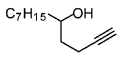
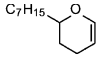
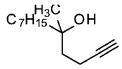
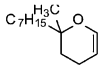
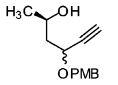
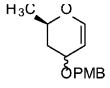
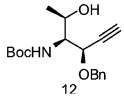
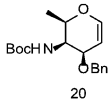
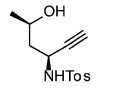
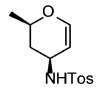
(2)

With the optimized conditions in hand, a number of homopropargylic alcohols were tested in DMF at 85 °C. As summarized in Table 2, secondary (entries 1, 3, and 4) as well as tertiary alcohols (entry 2) gave the products in good yields. The catalyst loading for the cyclization is considerably lower than that of related cycloisomerizations.[4,5] In the case of substrate **8** (entry 4), only 3 mol % catalyst loading was needed for complete conversion to give **16** in 67% yield.

Under the same conditions, bis-homopropargylic alcohols are also successfully converted into dihydropyrans. Remarkably, the scope of the substrate is much broader than that of related metal-catalyzed cycloisomerizations. For example, tertiary alcohol **10** (entry 6) and propargylic ether **11** (entry 7) were converted into dihydropyrans in good yields. Unlike molybdenum-mediated cycloisomerizations, a pyrrole derivative was not formed in the case of substrate **12** (entry 8).[11] Interestingly, using a less electron-poor

10.1021/ja0344258 CCC: $25.00

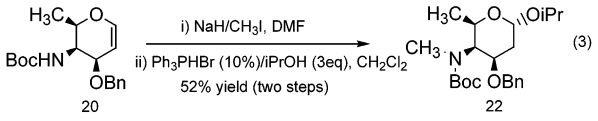
Table 2. Syntheses of Dihydrofurans and Dihydropyrans by Cycloisomerization

Entry	Substrate	Product	Method[a]	Conv	Yield[b]
1	 1	 5	A B C	100% 85% 100%	69% 52% 68%
2	 6	 14	A	90%	62%
3	 7	 15	A C	100% 100%	71% 68%
4	 8	 16	A B	100% >98%	74% 67%
5	 9	 17	A	100%	61%
6	 10	 18	C	100%	61%
7	 11	 19	C D	100% >98%	58% 70%
8	 12	 20	C D	>95% >95%	54% 67%
9	 13	 21	A	94%	52%

[a] Method A: catalyst **4** (2.5%), ligand **2e** (55%) were used. Method B: catalyst **4** (1.5%), ligand **2e** (33%) were used. Method C: catalyst **3d** (5%), ligand **2e** (30%) were used. Method D: catalyst **3c** (7.5%), ligand **2d** (45%) were used. [b] Isolated yield.

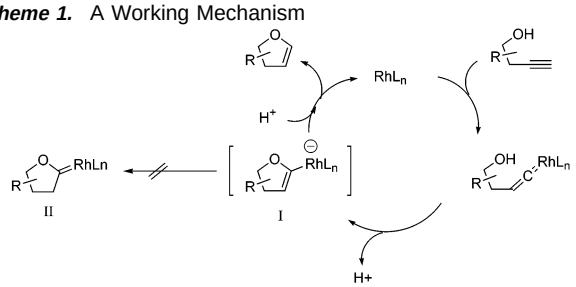
ligand **2d** significantly improved the yield for propargylic ethers **11** and **12** (method C vs method D for entries 7, 8).

To illustrate the synthetic utility of the Rh-catalyzed process, the glycosylation of the dihydroyran **20** which cannot be made by the other catalytic systems was pursued as an approach to amino sugars. Methylation followed by $Ph_3P{\cdot}HBr$-catalyzed glycosylation gives β-anomer **22** predominantly.[12] This type of deoxyaminoglycoside is present in several bioactive natural products, such as kedarcidin.[13]



Although the exact mechanism awaits further study, we suggest Scheme 1 as a working hypothesis. It appears that the protonation of intermediate I occurs exclusively at the metal to liberate the product and that the Rh-oxacarbene complex II is not formed in the cycloisomerization. In fact, all attempts to generate lactones

Scheme 1. A Working Mechanism



by using *N*-hydroxysuccinimide[3b] only led to cycloisomerization. To the best of our knowledge, such Rh(I)-complexed oxacarbenes remain unknown.[14]

In summary, we demonstrated that the ease of generating rhodium-vinylidene complexes from terminal alkynes in situ can lead to a useful catalytic process. The cycloisomerization proceeds under nonbasic conditions. The rhodium catalysts demonstrate the best chemoselectivity and turnover numbers to date. Thus, the effectiveness of this new catalyst enhances the generality and contributes to making this useful approach to five- and six-membered ring heterocyles a powerful tool in organic synthesis. Investigation of the mechanism as well as applications in synthesis are underway.

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Supporting Information Available: Detailed experimental procedure and characterization data for compounds **5**, **14**−**21**, and **22** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews, see: Bruce, M. I.; Swincer, A. G. *Adv. Organomet. Chem.* **1983**, *22*, 59. Bruce, M. I. *Chem. Rev.* **1991**, *91*, 197. Bruneau, C.; Dixneuf, P. H. *Acc. Chem. Res.* **1999**, *32*, 311. See also: Weyerhausen, B.; Dotz, K. H. *Eur. J. Inorg. Chem.* **1999**, 1057.
(2) Trost, B. M.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1992**, *114*, 5579. Trost, B. M.; Dyker, G.; Kulawiec, R. J. *J. Am. Chem.* **1990**, *112*, 7809.
(3) (a) Merlic, A. A.; Pauly, M. E. *J. Am. Chem. Soc.* **1996**, *118*, 11319. (b) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **1999**, *121*, 11680. (c) For catalytic processes involving other metals, see: Ohe, K.; Yokoi, T.; Miki, K.; Nishino, F.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 526. Miura, T.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 518.
(4) (a) For a review, see: McDonald, F. E. *Chem.-Eur. J.* **1999**, *5*, 3103. (b) McDonald, F. E.; Reddy, K. S.; Diaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304.
(5) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 2528.
(6) (a) Wolf, J.; Werner, H.; Serhadli, O.; Ziegler, M. L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 414. (b) Alonso, F. J.; Hohn, A.; Wolf, J.; Otto, H.; Werner, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 406.
(7) Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc.* **2000**, *122*, 4990.
(8) For Rh(I)-catalyzed dimerization of terminal alkynes, see: Schmit, H. J.; Singer, H. *J. Organomet. Chem.* **1978**, *153*, 165.
(9) Richter, B. D.; Spek, A. L.; van Koten, G.; Deelman, B. J. *J. Am. Chem. Soc.* **2000**, *122*, 3945.
(10) Employing bidentate ligands (BINAP, dppf) resulted in significant conversion problems.
(11) McDonald, F. E.; Zhu, Y. H. *Tetrahedron* **1997**, *53*, 11061.
(12) Bolitt, V.; Mioskowski, C.; Lee, S.-G.; Falck, J. R. *J. Org. Chem.* **1990**, *55*, 5812.
(13) Myers, A. G.; Hogan, P. C.; Hurd, A. R. Goldberg, S. D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1062.
(14) Stang, P. J.; Huang, Y. H. *J. Organomet. Chem.* **1992**, *432*, 247.

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