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Cycloisomerization of Aromatic Homo- and Bis-homopropargylic Alcohols via Catalytic Ru Vinylidenes: Formation of Benzofurans and Isochromenes

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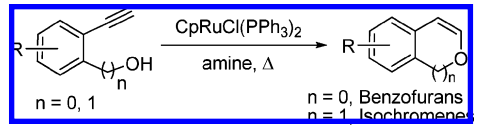
ABSTRACT



Ru-catalyzed cycloisomerizations of aromatic homo- and bis-homopropargylic alcohols effectively afford benzofurans and isochromenes. These processes proved to be chemo- and regioselective (5-, and 6-*endo* cyclizations) derived from key Ru vinylidene intermediates. The presence of an amine/ammonium base−acid pair is crucial for the catalytic cycle.

The development of effective strategies for the synthesis of a large structural diversity of heterocyclic compounds is a very important challenge for modern organic synthesis.[1] Convenient synthetic approaches involving heterocyclizations of functionalized alkynes have been developed in which catalytic metal vinylidenes have been invoked as key intermediates.[2] Pioneer work using Mo and W vinylidenes has been developed by McDonald when homo- and bis-homopropargylic alcohols cycloisomerized to dihydrofurans and dihydropyrans, respectively, in moderate to good yields.[3] Other seminal studies were carried out by Trost using cationic Ru vinylidenes as catalytic species (from $CpRuCl(PAr_3)_2$/*N*-hydroxysuccinimide/*n*-Bu_4NPF_6, and $NaHCO_3$) in oxidative cyclizations of homo- and bis-homopropargylic alcohols to γ-butyro- and δ-valerolactones[4] and cycloisomerizations of bis-homopropargylic alcohols to dihydropyrans,[5] but no Ru-catalyzed cycloisomerization of homopropargylic alcohols to dihydrofurans has been described under these conditions (Scheme 1, eq 1). However, cycloisomerizations of both alcohols with catalytic Rh vinylidenes (from $[Rh(cod)Cl]_2/PAr_3$) showed better chemoselectivities and turnovers than Ru vinylidenes.[6] More recently, successful cycloisomerizations of 2-(ethynyl)anilines and phenols (aromatic homopropargylic alcohols) to indoles and benzofurans, respectively, have been achieved under the same Rh conditions that require relatively large amounts of phosphine ligands.[7] Herein, we now describe a fruitful simple combina-

(1) *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K. , Eds.; Elsevier: New York, 2008.

(2) For reviews of metal vinylidenes in catalysis, see: (a) Bruce, M. I. *Chem. Rev.* **1991**, *91*, 197. (b) Bruneau, C.; Dixneuf, P. H. *Acc. Chem. Res.* **1999**, *32*, 311. (c) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695. (d) Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 2176. (e) Trost, B. M.; McClory, A. *Chem. Asian J.* **2008**, *3*, 164.

(3) (a) McDonald, F. E.; Connolly, C. B.; Gleason, M. M.; Towne, T. B.; Treiber, K. D. *J. Org. Chem.* **1993**, *58*, 695. (b) McDonald, F. E.; Schultz, C. C. *J. Am. Chem. Soc.* **1994**, *116*, 9363. (c) McDonald, F. E.; Bowman, J. L. *Tetrahedron Lett.* **1996**, *37*, 4675. (d) McDonald, F. E.; Gleason, M. M. *J. Am. Chem. Soc.* **1996**, *118*, 6648. (e) McDonald, F. E.; Zhu, H. Y. H. *Tetrahedron* **1997**, *53*, 11061. (f) McDonald, F. E.; Zhu, H. Y. H. *J. Am. Chem. Soc.* **1998**, *120*, 4246. (g) McDonald, F. E.; Reddy, K. S.; Diaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304.

(4) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **1999**, *121*, 11680.
(5) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 2528.
(6) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2003**, *125*, 7482.
(7) Trost, B. M.; McClory, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 2074.

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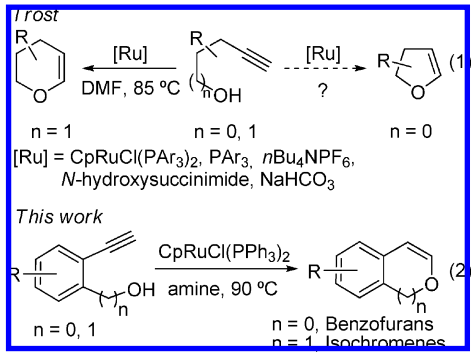
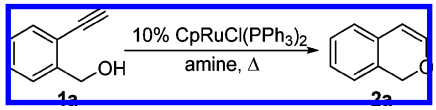
Scheme 1. Ru-Catalyzed Cycloisomerization of Aliphatic and Aromatic Homo- and Bis-homopropargylic Alcohols



tion of $CpRuCl(PPh_3)_2$[8] and amines (n-$BuNH_2$ or Py) to accomplish new cycloisomerizations of aromatic homo- and bis-homopropargylic alcohols to benzofurans and isochromenes,[9] respectively, through formation of cationic Ru vinylidenes as key catalytic intermediates (Scheme 1, eq 2).[10]

First, the amine solvent and other reaction parameters of the ruthenium-catalyzed cycloisomerization (6-*endo* cyclization) of aromatic bis-homopropargylic alcohol **1a** was optimized (Table 1). Heating an *n*-butylamine solution of **1a** (0.15 M) in a sealed

Table 1. Optimization of Ru-Catalyzed Cycloisomerization of Bis-homopropargylic Alcohol **1a**



entry	amine	time (h)	temp (°C)	yield[a] (%)
1	n-$BuNH_2$	6	90	86
2	Py	3	90	42
3	Py	4	130	60
4[b]	n-$BuNH_2$	48	90	
5[c]		24	90	
6[d]		24	90	dec

[a] [**1a**] = 0,15 M. [b] Without Ru catalyst. [c] DMF as solvent. [d] DMF/$NaHCO_3$ (2 equiv).

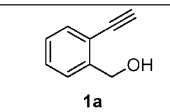
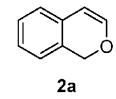
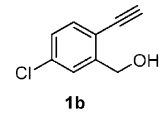
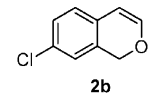
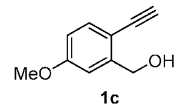
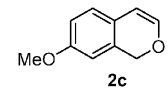
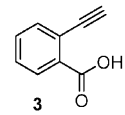
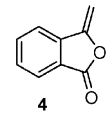
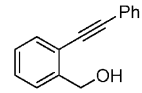
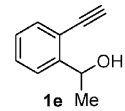
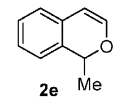
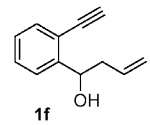
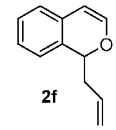
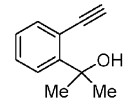
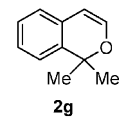
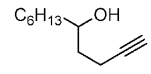
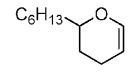
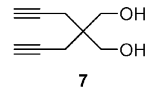
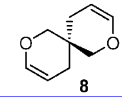
tube at 90 °C in the presence of 10% $CpRuCl(PPh_3)_2$ as catalyst gave an excellent 86% yield of isochromene **2a** (entry 1), whereas in pyridine it gave only a 42% yield (entry 2). Heating at a higher temperature in pyridine (130 °C) gave an improved 60% yield (entry 3). Control experiments showed that both Ru catalyst and amine solvent were essential (entries 4 and 5) as well as the use of amine as organic base (entry 6).[11,12]

(8) $CpRuCl(PPh_3)_2$ has been previously used in stoichiometric reactions with homo- and bis-homopropargylic alcohols to give stable cyclic oxacarbene Ru complexes: Bruce, M. I.; Swincer, A. G.; Thomson, B. J.; Wallis, R. C. *Aust. J. Chem.* **1980**, *33*, 2605.

(9) For isochromenes with interesting biological properties, see: (a) Biber, B.; Muske, J.; Ritzan, M.; Graft, U. *J. Antibiot.* **1998**, *51*, 381. (b) Maruse, N.; Goto, M. *J. Antibiot.* **1998**, *51*, 545. (c) Wang, W.; Breining, T.; Li, T.; Milbum, R.; Attardo, G. *Tetrahedron Lett.* **1998**, *39*, 2459, and references cited therein.

A variety of aromatic bis-homopropargylic alcohols **1** were converted into the corresponding isochromenes **2** in good yields using the optimized conditions for both amine solvents (Table 2). Both electron-poor and electron-rich substrates

Table 2. Cycloisomerization of Bis-homopropargylic Alcohols **1** into Isochromenes **2**

entry	substrate	product	t (h)	yield (%)[a]
1	 **1a**	 **2a**	6 (4)	86 (60)[b]
2	 **1b**	 **2b**	15 (2)	62 (57)[b]
3	 **1c**	 **2c**	5 (2)	63 (67)[b]
4	 **3**	 **4**	2 (36)	85[b] (90)[c]
5	 **1d**	Dec.		
6	 **1e**	 **2e**	6	60
7	 **1f**	 **2f**	7	65
8	 **1g**	 **2g**	7	55
9	 **5**	 **6**	6	60
10	 **7**	 **8**	24	80[b,d]

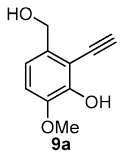
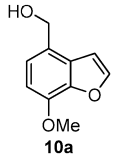
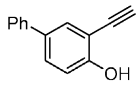
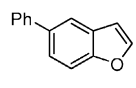
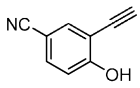
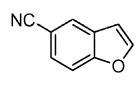
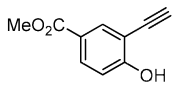
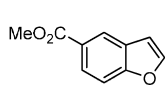
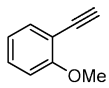
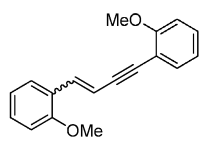
[a] Typical conditions: 10% $CpRuCl(PPh_3)_2$, n-$BuNH_2$, 90 °C. [b] 10% $CpRuCl(PPh_3)_2$, Py, 130 °C. [c] Without catalyst. [d] 90 °C. Dec = decomposition.

1b and **1c** gave good yields of the corresponding isochromenes **2b** and **2c** (entries 2 and 3). Interestingly, the alcohol functionality in **1** was mandatory for achieving 6-*endo* cyclizations by C−O bond formation since the 2-ethynylbenzoic acid **3** was smoothly converted by a 5-*exo* cyclization into 2-benzofuran-1-one **4** in an excellent yield (entry 4).[13]

On the other hand, benzylic alcohols must have terminal 2-alkynyl substituents in order to be cyclized since **1d** gave decomposition (entry 5), that seems to indicate that the cyclization is not produced by simple alkyne activation by the catalyst. Smooth 6-*endo* cyclizations occurred when secondary and even tertiary benzylic alcohols **1e**−**g** were cycloisomerized to isochromenes **2e**−**g** in quite good yields (entries 6−8). For the sake of comparison, when our new conditions were applied to aliphatic bis-homopropargylic alcohol **5**, smooth cycloisomerization took place to dihydropyran **6** in 60% yield,[14] whereas the double bis-homopropargylic alcohol **7**, with favorable Thorpe−Ingold effect,[15] gave spirodihydropyran **8** in a high 80% yield (entries 9 and 10).

Finally, the regioselectivity of the cyclization (6-*endo* vs 5-*endo*) was probed with substrate **9a**, which possesses benzylic and phenolic OH groups, obtaining exclusively the benzofuran **10a** (5-*endo*) in an excellent 82% yield,[16] showing the possibility of performing ruthenium-catalyzed cycloisomerizations of aromatic homopropargylic alcohols to benzofuran (Table 3, entry 1).[17] Thus, **9b** was smoothly

Table 3. Ru-Catalyzed Cycloisomerization of Homopropargylic Alcohols **9** into Benzofurans **10**

entry	substrate	product	*t* (h)	yield (%)
1	 **9a**	 **10a**	6	82[b]
2	 **9b**	 **10b**	2	84
3	 **9c**	 **10c**	1	54
4	 **9d**	 **10d**	2	59
5	 **11**	 **12** (E/Z: 9/1)	4	63[b]

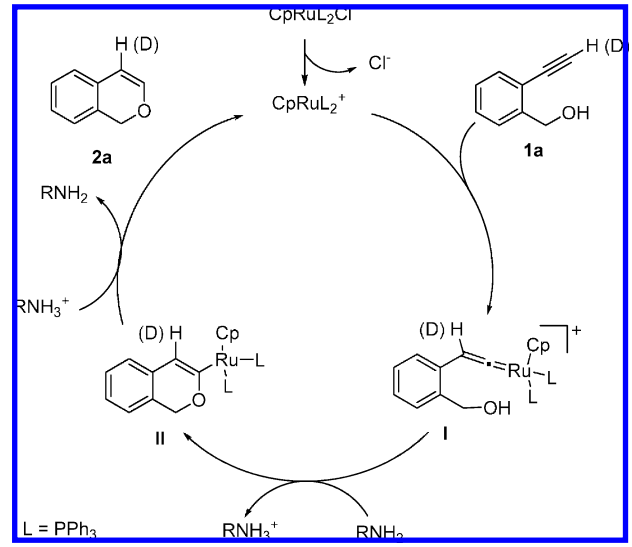
[a] 10% $CpRuCl(PPh_3)_2$, Py, 90 °C. [b] 130 °C.

converted in only 2 h to the benzofuran derivative **10b** in an excellent 84% yield (entry 2). Challenging functionalized benzofuranes **10c**,**d**, important cores in organic materials[18] and pharmaceuticals,[19] could be directly achieved in relatively good yields, in spite of nucleophilicity of phenols **9c**,**d** being reduced (entries 3 and 4).[20]

The presence of phenolic OH group was mandatory for C−O bond formation since 1-ethynyl-2-methoxybenzene **11** gave no cycloisomerized but dimeric linear enyne product **12** (entry 5).[21]

Having in mind all the precedents of C−O bond formation involving metal vinylidenes, these results may be satisfactorily explained according to the proposed mechanism shown in Scheme 2. After Cl^- dissociation from the starting Ru

Scheme 2. Proposed Catalytic Cycle for the Ru-Catalyzed Cycloisomerization



precatalyst and coordination to the alkyne **1a**, the key Ru vinylidene intermediate **I** could be formed.[22] This process could be suggested from isotopic labeling which shows

(10) For a general review of Ru-catalyzed reactions, see: Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *AngewChem., Int. Ed.* **2005**, *44*, 6630. For reviews of Ru-vinylidenes, see ref 2. For books, see: (a) Murahashi, S.-I., Ed. *Ruthenium in Organic Synthesis*; Wiley-VCH: Weinheim, 2004. (b) Bruneau, C., Dixneuf, P. H., Eds. *Topics in Organometallic Chemistry*; Springer: Berlin, 2004; Vol. 11.

(11) Solvent (DMF) and base ($NaHCO_3$) were used for cycloisomerization of bis-homopropargyl alcohols. See ref 5.

(12) Other Ru(II) catalysts and amines failed or gave lower yields. See the Supporting Information for details.

(13) The same result was obtained without catalyst by heating in pyridine: Kanazawa, C.; Terada, M. *Tetrahedron Lett.* **2007**, *48*, 933.

(14) Yield comparable to the one obtained using other Ru catalytic conditions (64%) and using Rh catalysts (61%). See refs 5 and 6 for more details.

(15) (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080. (b) Ingold, C. K. *J. Chem. Soc.* **1921**, *119*, 305. (c) Ingold, C. K.; Sako, S.; Thorpe, J. F. *J. Chem. Soc.* **1922**, *121*, 1117. (d) Hammond, G. In *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; Wiley: New York, 1956; pp 462−470. (e) Kanetis, J.; Kirby, A. J.; Koedjikov, A. H.; Pojarlieff, I. G. *Org. Biomol. Chem.* **2004**, *2*, 1098.

(16) The 5-*endo* is probably preferred on the basis of the driving force of forming a new aromatic furan ring when the phenolic OH reacts.

(17) To the best of our knowledge, only Ru-catalyzed oxidative cyclization of homopropargylic alcohols to γ-butyrolactones has been described. See refs 4 and 5.

(18) Friedman, M. R.; Toyne, K. J.; Goodby, J. W.; Hird, M. *J. Mater. Chem.* **2001**, *11*, 2759.

(19) Saitoh, M.; Kumitomo, J.; Kimura, E.; Hayase, Y.; Kobayashi, H.; Uchiyama, N.; Kawamoto, T.; Tanaka, T.; Mol, C. D.; Dougan, D. R.; Textor, G. S.; Snell, G. P.; Itoh, F. *Biorg. Med. Chem.* **2009**, *17*, 2017.

deuterium incorporation at the vinylic position of the final isochromene **2a**.[23] Nucleophilic attack by the pendant alcohol to the vinylidene with concurrent removal of a proton by the amine then provides the alkenyl Ru species **II**, which after protonolysis by the ammonium salt formed could provide the final isochromene **2a** with regeneration of the active catalyst.

In summary, Ru-catalyzed cycloisomerizations of aromatic homo- and bis-homopropargylic alcohols to benzofurans and isochromenes have been developed. These processes proved to be chemo- and regioselective (5- and 6-*endo* cyclizations) from key Ru vinylidene intermediates. The presence of an amine/ammonium base-acid pair is crucial for the catalytic cycle. The synthesis of benzofurans and isochromenes from the cycloisomerization of aromatic homo- and bis-homopropargylic alcohols by C−O bond formation significantly increases the scope of metal vinylidene intermediates in catalytic processes.[24]

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Supporting Information Available: Typical experimental procedure and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) On the other hand, the aliphatic homopropargylic alcohol 1,1-diphenylbut-3-yn-1-ol could be cycloisomerized to 2,2-diphenyl-2,3-dihydrofuran in 30% yield. See the Supporting Information for details.

(21) This type of alkyne dimerization has been observed before; see: Bassetti, M.; Pasquini, C.; Raneri, A.; Rosato, D. *J. Org. Chem.* **2007**, *72*, 4558.

(22) (a) Touchard, D. Haquette, P. Pirio, N. Toupet, L. Dixneuf, P. H. *Organometallics* **1993**, *12*, 3132. (b) Bustelo, E. Carbo, J. J. Lledós, A. Mereiter, K. Puerta, M. C. Valerga, P. *J. Am. Chem. Soc.* **2003**, *125*, 3311. (c) Wakatsuki, Y. *J. Organomet. Chem.* **2004**, *689*, 4092. See also ref 10.

(23) The deuteration experiment was performed with a 3:7 mixture of deuterated alkyne (shown in Scheme 2) and deuterated alcohol (not shown). See the Supporting Information for details.

(24) Initial results with aromatic alkynyl amines and amides are promising (C−N bond formation) and will be the subject of future reports.