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Synthesis of Fused Oxabicyclic Systems by Metal-Catalyzed Intramolecular Addition of 1,3-Cycloalkyldiones to Alkynes

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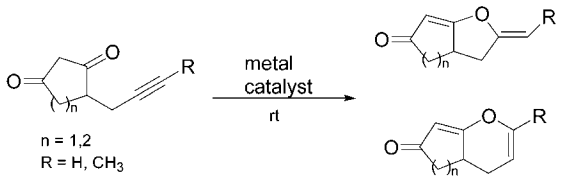
ABSTRACT



Readily available 4-propargyl-1,3-cyclohexanediones and cyclopentanediones can be chemo- and regioselectively cycloisomerized to synthetically appealing fused oxabicyclic systems by simply stirring at room temperature with catalytic amounts of an appropriate metal complex.

The feasibility of activating alkynes by coordination to electrophilic transition metal complexes has led to the development of a variety of catalytic cycloisomerization reactions involving carbon−carbon or carbon−heteroatom bond formation.[1] In the case of heterocyclizations, alcohols, amines, and carbocyclic acids have been widely employed as nucleophiles (essentially in palladium-catalyzed processes);[2] however, carbonyl groups have only been used in the synthesis of furanes.[3] Herein we show that readily available β-oxocyclohexa- and β-oxocyclopentanones can cyclize chemo- and regioselectively with pendant α'-propargyl substituents to give fused dihydropyran or dihydrofuran systems. The cycloisomerization reaction takes place under very mild conditions upon treatment with a variety of electrophilic transition metal catalysts.

Our research in this area started with experiments to determine whether the enol **1**[4] would cyclize to the bridged bicarbocycle **2** upon reaction with $W(CO)_5$·L. Hypothetically, this tungsten complex might induce the formation of **2** via a metal vinylidene intermediate that would undergo nucleophilic attack at the α-position.[5] However, room-temperature reaction of the enol **1** with 20 mol % $W(CO)_5$·THF in THF did not give **2** but gave only the oxabicycle **3**, which was isolated in a 55% yield. The same oxabicycle can also be formed by treatment of **1** with 10 mol % $Pd(OAc)_2$ in THF (40 °C, 1h, 50% yield).

The novelty of these results coupled to the potential synthetic interest of the resulting highly functionalized

(1) For reviews, see: (a) Méndez, M.; Echavarren, A. M. *Eur. J. Org. Chem.* **2002**, 15. (b) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (c) McDonald, F. E. *Chem. Eur. J.* **1999**, *5*, 3103.

(2) (a) Utimoto, K. *Pure Appl. Chem.* **1983**, *55*, 1845. (b) Wang, Z.; Lu X. *J. Org. Chem.* **1996**, *61*, 2254. (c) Wakabayashi, T.; Ishii, Y.; Ishikawa, K.; Hidai, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2123. (d) Wolf, L. B.; Tjen, K. C. M.; ten Brink, H. T.; Blaauw, R. H.; Hiemstra, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2002**, *344*, 70 and references therein.

(3) (a) Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5816. (b) Cacchi, S.; Fabrizi, G.; Moro, L. *J. Org. Chem.* **1997**, *62*, 5327. (c) Miki, K.; Nishino, F.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 5260. For an application to the preparation of bridged oxabicycles, see: (d) Iwasawa, N.; Shido, M.; Husama, H. *J. Am. Chem. Soc.* **2001**, *123*, 5814.

(4) This compound was synthesized from 1,2-cyclohexanedione; see Supporting Information and: Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L. *Chem. Eur. J.* **2002**, *8*, 2923.

(5) (a) Maeyama, K.; Iwasawa, N. *J. Am. Chem. Soc.* **1998**, *120*, 1928. (b) Iwasawa, N.; Maeyama, K.; Kusama, H. *Org. Lett.* **2001**, *3*, 3871. (c) McDonald, F. E.; Olson, T. C. *Tetrahedron Lett.* **1997**, *38*, 7691.

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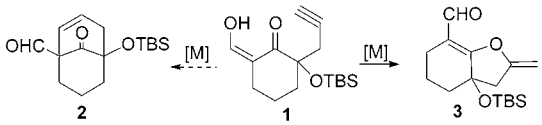
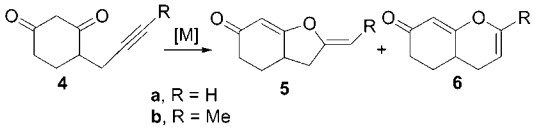
Scheme 1



oxabicyclic products, prompted us to examine these cyclizations further using related but synthetically straightforward substrates such as the cyclohexanediones **4**. These precursors can be obtained in two simple steps and good yield from commercially available 1,3-cyclohexanedione.[6]

Treatment of a THF solution of cyclohexanedione **4a** with 5 mol % $Pd(OAc)_2$, at room temperature, gave the expected 5-*exo*-dig oxacyclization product **5a** in 85% yield. As indicated in Table 1, the reaction also takes place with a smaller amount of catalyst, although it takes longer (entry 2). Using either previously generated $W(CO)_5$·THF or irradiating a THF solution of **4a** in the presence of catalytic amounts of $W(CO)_6$ afforded the same bicycle, likewise in good yield. Carrying out this latter experiment in the presence of Et_3N (4 equiv), conditions previously used in the cyclization of alkynols,[7] also gave exclusively the *exo* product. The transformation is also catalyzed by $PtCl_2$ and even by $CpRuCl(PPh_3)_2$, although with the latter it takes several days for completion at room temperature. It should be remarked that the cyclization is promoted by neither acids such as HCl, TFA, or TsOH nor bases (*t*BuOK in DMSO), even under stoichiometric conditions.

Table 1. Metal-Catalyzed Oxacyclization of **4**[a]



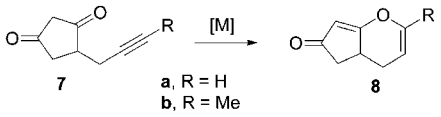
entry	**4**	catalyst (mol %)	products (ratio)[b]	yield[c]	time
1	**4a**	$Pd(OAc)_2$ (5)	**5a**	85%	2 min
2	**4a**	$Pd(OAc)_2$ (2)	**5a**	78%	3 h
3	**4a**	$W(CO)_5$·THF (10)	**5a**	85%	0.5 h
4	**4a**	$W(CO)_5$·THF (10)[d]	**5a**	90%	0.5 h
5	**4a**	$PtCl_2$ (10)	**5a**	79%	15 min
6	**4a**	$CpRuCl(PPh_3)_2$ (10)	**5a**	80%	7 days
7	**4a**	$PdCl_2(CH_3CN)_2$(10)	**5a**	71%	2 days
8	**4b**	$Pd(OAc)_2$ (5)	**5b/6b** (8:1)	75%	8 h
9	**4b**	$PtCl_2$ (5)	**5b/6b** (1:14)	91%	9 h
10	**4b**	$W(CO)_5$·THF (10)	**5b/6b** (1:11)	83%	5 days

[a] All reactions were carried out at room temperature, under an argon atmosphere, by adding the catalyst to a solution of the substrate in THF (0.1 M, or 1 M in the case of entry 4) and were stopped after apparent consumption of the starting material. [b] Calculated by ^1H NMR after workup. [c] Isolated yield. [d] Prepared in situ by irradiating a THF suspension of $W(CO)_6$ and the substrate for 3−4 h with a high-pressure Hg lamp.

Substituted alkynes also cyclized, but in this case, we also observed the formation of products arising from a 6-*endo*-dig cyclization mode. Hence, treatment of 4-but-2-ynylcyclohexane-1,3-dione (**4b**) with catalytic amounts of $Pd(OAc)_2$ at room temperature produced the dihydrofuran derivative **5b** together with a small amount of the enolether **6b**. Remarkably, this *endo* product predominates when $PtCl_2$ or $W(CO)_5$·THF is used as a catalyst. The reaction with $PtCl_2$ was completed in a few hours at room temperature, whereas 4 days were required with the tungsten catalyst. Thus, these results show that by choosing the appropriate catalyst, it is possible to control the formation of either the *endo* or the *exo* regiosomer, when R = Me. As far as we know, no such regiochemical difference between Pd(II) and Pt(II) catalysts has been reported hitherto in other cyclizations.

We were next curious about the performance of the cyclopentanedione homologues, as a similar oxacyclization would produce interesting fused cyclopenta[*b*]pyran or cyclopenta[*b*]furan skeletons.[8] The poor solubility of cyclopentadione **7a** in THF required the use of dioxane as a cosolvent. Treatment of **7a**[6] with 10 mol % $PtCl_2$ in 2:1 THF/dioxane at room temperature produced exclusively the *endo*-dig oxacyclization product **8a** in 76% isolated yield. Use of dioxane or acetone as the only solvent gave poorer results, so THF seems to be necessary for the reaction to proceed well. The reaction also works with substituted alkynes such as **7b**, again yielding exclusively the 6-*endo* product. As shown in Table 2, with the cyclopentanedione precursors, $Pd(OAc)_2$ led to a regiochemical outcome similar to using $PtCl_2$ and $W(CO)_5$·THF.

Table 2. Metal-Catalyzed Oxacyclization of **7**[a]



entry	**7**	catalyst (mol %)	product	yield	time
1	**7a**	$PtCl_2$ (10)	**8a**	76%	3 days
2	**7a**	$W(CO)_5$·THF (20)	**8a**	74%	5 days
3	**7a**	$Pd(OAc)_2$ (10)	**8a**	65%	3 days
4	**7b**	$PtCl_2$ (10)	**8b**	85%	1 day
5	**7b**	$W(CO)_5$·THF (20)	**8b**	67%	5 days
6	**7b**	$Pd(OAc)_2$ (10)	**8b**	78%	3 days

[a] All reactions were carried out at room temperature under an argon atmosphere by adding the catalyst to a 0.1 M solution of the substrate in 2:1 THF−dioxane, except for that of entry 5, which was carried out in THF, and were stopped after apparent consumption of the starting material.

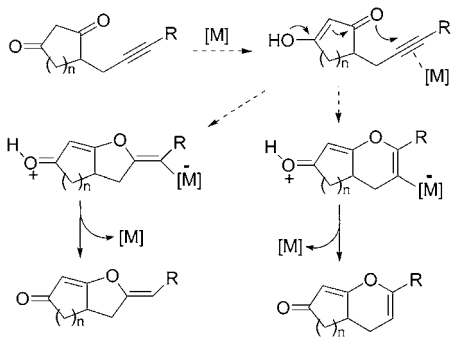
(6) See Supporting Information and: Stork, G.; Danheiser, R. *J. Org. Chem.* **1973**, *38*, 1775.

(7) Tungsten-catalyzed isomerization of several 4-alkyn-1-ols proceeds in a *endo*-selective fashion: McDonald, F. E.; Reddy, K. S.; Díaz, Y. *J. Am. Chem. Soc*. **2000**, *122*, 4304.

(8) These are important frameworks for the synthesis of prostaglandin derivatives. See for instance: (a) Newton, R. F.; Wadsworth, A. H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 823. (b) Skuballa, V. *Tetrahedron Lett.* **1980**, *21*, 3261. (c) Herndon, J. W.; Matasi, J. T. *Tetrahedron Lett.* **1992**, *33*, 5725.

The above oxacycloisomerizations most probably proceed under kinetic control by coordination of the transition metal to the alkyne to form a (η^2-alkyne)metal complex that can then undergo anti attack of the carbonyl oxygen (Scheme 2). Protonolysis of the resulting vinyl−metal species would lead to the products.

Scheme 2



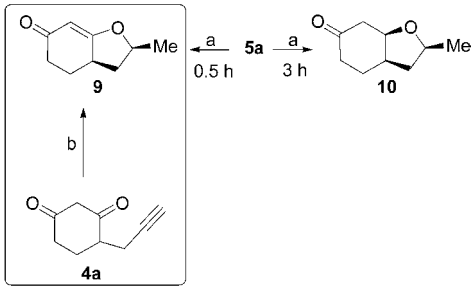
The formation of the *exo* cyclized products of **1** and **4a** in the reaction with $W(CO)_5$·THF contrasts with the results obtained in the cyclization of 4-alkyn-1-ols[7] and rules out a pathway involving a metal−vinylidene intermediate. This might also explain the absence of carbocyclization products, although the formation of the oxacycle would presumably be kinetically preferred anyway.[9]

The dependence of regioselectivity on the catalysts in the cyclization of **4b** must be related to some subtle interplay of electronic and steric factors in the alkyne−metal complex together with the relative intrinsic strain that develops in the formation of the *exo*- or *endo*-bicycles. In the case of the cyclopentadiones, this strain seems to override the intrinsic regiochemical preferences for nucleophilic attack to the alkyne−metal complex.

Because of their high functionalization, the bicyclic products obtained in the above cyclizations should be amenable to divergent manipulation to obtain a variety of fused oxabicyclic systems. As an example, it was possible to hydrogenate **5a** chemoselectively to obtain just one diastereoisomer of the tetrahydrobenzofuranone derivative **9** (95% yield).[10] On the other hand, allowing the hydrogenation to proceed for a longer period of time affords the cis-fused bicycle **10** (71%), which is equipped with three stereocenters.

Most interestingly, it is possible to carry out both the cyclization and hydrogenation in a single step; thus, **4a** can be directly converted into **9** by treatment with $Pd(OAc)_2$ (4 mol %) and Pd/C in THF at room temperature under a H_2 atmosphere (balloon pressure, 30 min, 65% yield).[11]

Scheme 3[a]



[a] Conditions: (a) H_2, Pd/C, EtOAc. (b) $Pd(OAc)_2$ (5%), Pd/C, THF, H_2, 1 h, 20 °C.

In summary, we have developed a simple, straightforward route to 7-oxabicyclo[4.3.0]nonane, 2-oxabicyclo[4.4.0]-decane and 2-oxabicyclo[3.3.0]octane derivatives consisting of a novel metal-catalyzed ketone−alkyne cycloisomerization. The cyclization reaction requires just room-temperature stirring of the substrate with catalytic amounts of an appropriate metal complex and provides products with considerable synthetic potential. Work to elucidate the mechanistic basis of the *endo*/*exo* regioselectivity and to further exploit the synthetic potential of the bicyclic products is underway.

Acknowledgment. This work was supported by the E.R.D.F and the Spanish Ministry of Science and Technology (SAF2001-3120). M.G. and J.R.R. thank the Galician Government and the Spanish Ministry of Education and Culture for their respective predoctoral fellowships.

Supporting Information Available: Experimental procedures, including the preparation of **1**, **4**, and **7**, and spectroscopic data for selected compounds, particularly for those requiring stereo- and regiochemical identification. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) This conclusion is inferred from a qualitative MM2 analysis of the strain energy of the oxabicyclic and bridged carbobicyclic products.

(10) This type of bicyclic framework forms the basic skeletons of a variety of natural products such as bisabolane-type sesquiterpenoids. See for instance: (a) Takao, K.; Tsujita, T.; Hara, M.; Tadano, K. *J. Org. Chem.* **2002**, *67*, 6693. (b) Weyerstahl, P.; Meisel, T. *Liebigs. Ann. Chem.* **1994**, 415.

(11) For other applications of metal-catalyzed alkene-forming reactions coupled with hydrogenation, see: Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312.