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Highly efficient catalytic routes to spiroketal motifs

Selvasothi Selvaratnam [a], Joanne H. H. Ho [b], Paul B. Huleatt [a], Barbara A. Messerle [b,*], Christina L. L. Chai [a,*]

[a] Institute of Chemical and Engineering Sciences, Agency for Science, Technology and Research (A*STAR), 1 Pesek Road, Jurong Island, Singapore 627833, Singapore
[b] School of Chemistry, University of New South Wales, Kensington, NSW 2052, Australia

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ABSTRACT

The versatile and efficient synthesis of a variety of spiroketal motifs via the double intramolecular hydroalkoxylation of aliphatic and aromatic alkyne diols was achieved using simple and readily accessible Ir(I) and Rh(I) cyclooctadiene complexes as catalysts.

The spiroketal functionality is an important structural motif that is often found in biologically active natural products including insect pheromones,[1,2] polyether antibiotics,[3] and spongistatins/altohyrtins.[4] In light of this, there is much interest in the development of synthetic methodologies that will enable rapid and efficient access to spiroketal skeletons under the mildest possible reaction conditions. The latter is important in view of the complexity of the functionalities that may be present on the spiroketal moiety. Not surprisingly, a number of synthetic routes to spiroketals have been reported. Most of these routes utilize dihydroxyketones or equivalents as intermediates.[5,6]

The limitations of these methods are that often multi-step syntheses are involved and they require purification of mixtures that can be rather complex.

Surprisingly, examples of single-step transition metal-catalyzed approaches to spiroketals are rather limited. Pd(II), Pt(II), and Au(I) complexes have been utilized to catalyze the hydroalkoxylation of internal alkynols.[7–9] $[Ir(\mu\text{-}Cl)(COD)]_2$ (COD = 1,5-cyclooctadiene) and Rh(I) complexes of the type $[Rh(PR_3)_3Cl]$ and $[Rh(\mu\text{-}Cl)(COD)]_2$ have also been reported to promote the tandem hydroalkoxylation of terminal propargylic alcohols.[10,11] In the case of the rhodium complexes, the addition of excess phosphine ligand (up to 55%) is necessary to suppress side reactions. Recently, Messerle et al.[12] demonstrated that Ir(I) and Rh(I) complexes bearing *N*-donor ligands ($[Ir(PyP)(CO)_2]BPh_4$ {PyP = 1-[(2-diphenylphosphino)ethyl]pyrazole} and $[Rh(bim)(CO)_2]BPh_4$ {bim = bis(*N*-methylimidazol-2-yl)methane}) can efficiently catalyze the double hydroalkoxylation of both terminal and internal alkyne diols.

As part of our ongoing program to develop efficient synthetic routes to *O*,*O*-acetals, we report here a rapid and versatile route to the construction of spiroketal skeletons via the double intramolecular hydroalkoxylation of alkyl and aryl internal alkyne diols, using the very simple Ir(I) and Rh(I) cyclooctadiene catalysts **1**–**3**. These catalysts can be easily prepared in one step from the corresponding commercially available dimeric metal complexes.[13]

Our initial studies were performed with the alkyne diol **4**, which was easily prepared via the ring opening of methyloxirane with the lithio derivative of 1-(2-tetrahydropyranyloxy)-4-pentyne. Removal of the THP protecting group afforded the desired diol **4**.[14] Treatment of the alkyne diol **4** with 1 mol % of $[Ir(COD)_2]BARF$ (**1**) at room temperature in 1,1,2,2-tetrachloroethane-d_2, $(CDCl_2)_2$ gave the corresponding spiroketal **11** with quantitative conversion in 0.5 h (Table 1, entry 1).[15,16] Decreasing the catalytic loading to 0.5 mol % gave the desired product with similar high conversion in 1.5 h. The spiroketal **11** was obtained as a mixture of two diastereomers in the ratio of 1.7:1. In contrast, Utimoto reported that the Pd(II)-catalyzed cyclization of substrate **4** yielded the corresponding spiroketal in a 1:1 diastereomeric ratio.[7a] The Rh(I) catalyst **2** proved to be less efficient than its Ir(I) analogue **1** in promoting the double hydroalkoxylation reaction of alkyne diol **4**. Complete conversion was only achieved in 2.5 h at 90 °C with a catalyst loading of 5 mol %.

* Corresponding authors. Tel.: +61 2 9385 4653; fax: +61 2 9385 6141 (B.A.M.), tel.: +65 6796 3902; fax: +65 6316 6184 (C.L.L.C).
E-mail addresses: b.messerle@unsw.edu.au (B.A. Messerle), Christina_Chai@ices.a-star.edu.sg (C.L.L. Chai).

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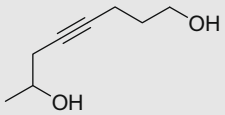
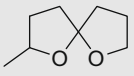
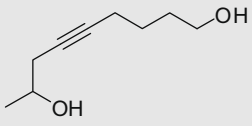
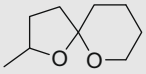
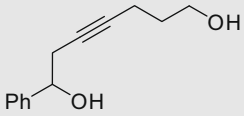
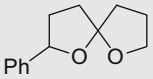
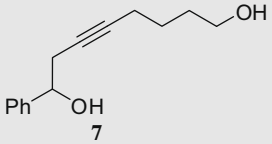
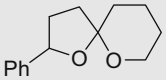
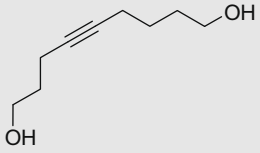
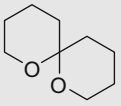
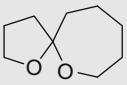
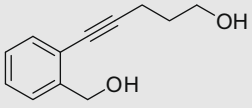
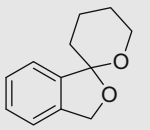
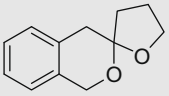
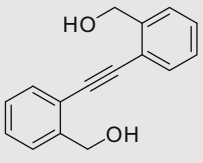
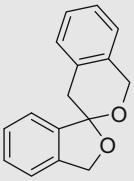
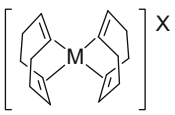
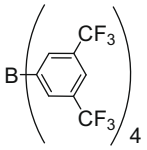
Table 1
[Ir(COD)$_2$]BARF (**1**), [Rh(COD)$_2$]BARF (**2**), and [Rh(COD)$_2$]PF$_6$ (**3**) catalyzed synthesis of spiroketals from alkyne diols[a]

Entry	Substrate	Product(s)	Catalyst (mol %)	Temperature (°C)	>98% Conversion (h)
1	 **4**	 **11**	**1**, 0.5 **1**, 1.0 **2**, 1.0 **2**, 5.0	25 25 90 90	1.5 0.5 20.0 2.5
2	 **5**	 **12**[b]	**1**, 0.5 **2**, 5.0 **3**, 5.0	90 90 90	2.0 20.0 4.5
3	 **6**	 **13**	**1**, 1.0 **2**, 5.0 **3**, 5.0	90 90 90	1.5 24.0 2.5
4	 **7**	 **14**	**1**, 1.0 **2**, 5.0 **3**, 5.0	25 90 90	0.5 24.0[c] 5.5
5	 **8**	 **15**  **16**	**1**, 5.0 **2**, 5.0 **3**, 5.0	90 90 90	16.0 **15**:**16** = 3.1:1 N/A[d] 42.0 **15**:**16** = 3.4:1
6	 **9**	 **17**  **18**	**1**, 5.0 **2**, 5.0 **3**, 5.0	90 90 90	2.0 **17**:**18** = 1:1.3 36.0 **17**:**18** = 1:2.3 3.5 **17**:**18** = 1:2.5
7	 **10**	 **19**	**1**, 5.0 **2**, 5.0 **3**, 5.0	90 90 90	3.5 24.0 4.5

[a] Reactions were performed in 1,1,2,2-tetrachloroethane-d_2 on an NMR scale. The identities of the products were confirmed by GC–MS, ^{1}H, and ^{13}C NMR spectroscopy. All new compounds have been characterized, while the physical and spectroscopic data of known compounds were compared with those reported in the literature.[17]
[b] Pheromone component of the common wasp *Paravespula vulgaris*.
[c] Time at 60% conversion. Reaction proceeded to completion in 8 days.
[d] The reaction did not go to completion after 48 h and was aborted.



BARF = 

1: M = Ir, X = BARF
2: M =Rh, X = BARF
3: M =Rh, X = PF_6

Encouraged by these results, the transformation of a range of alkyl and aryl internal alkyne diols was examined (Table 1). The data in Table 1 demonstrate the versatility of the spirocyclization reaction as [4.4], [4.5], [5.5], and [4.6] spiroketal motifs can be synthesized from appropriate precursors. In all cases, the iridium catalyst **1** was superior in promoting the double hydroalkoxylation of the alkyne diols as compared to its rhodium analogue **2**.

It was noted that the efficiency of the Rh(I) complex **2** in catalyzing the spirocyclization reaction decreased with increasing chain length and/or bulkiness of the substituent present on the alkyne (substrates **5–7**). For complete consumption of the starting alkyne diols, reaction times of up to 24 h were frequently required. However, when the counterion of the Rh complex was replaced with the more coordinating counterion PF_6^-, complete conversions to products were obtained in much shorter reaction times (catalyst **2** vs **3**). The increased efficiency of the PF_6^- counterion could be attributed to the stabilization of the reactive intermediates by the PF_6^- anion or the enhanced stability of PF_6^- relative to the $BARF^-$ counterion.

The cyclization of the unsubstituted alkyne diol, 4-nonyne-1,9-diol (**8**) resulted in the formation of two regioisomers. With the Ir(I) catalyst (**1**), [5.5] and [4.6] spiroketals, **15** and **16**, were formed in the ratio 3.1:1 within 16 h. The reaction was much slower with the Rh(I) catalyst **3**. This reaction went to completion in 42 h, and the products **15** and **16** were formed in a 3.4:1 ratio. By comparison, in previous reports of the spiroketalization of **8** using $PdCl_2$ as a catalyst, the [4.6] spiroketal **16** was obtained selectively.[7a] de Brabander et al.[8] in turn found that the $PdCl_2$-catalyzed cyclization of **8** resulted in a 1:2.5 mixture of spiroketals **15** and **16**. It is noteworthy that these observations suggest that Pd(II) catalysts favor the formation of the [4.6] spiroketal while the use of Ir(I) and Rh(I) catalysts **1** and **3**, under our conditions, favors the [5.5] spiroketal.

The transition metal-catalyzed cyclization of 5-(2-(hydroxymethyl)phenyl)pent-4-yn-1-ol (**9**) led to the formation of the two possible regioisomeric spiroketals **17** and **18**. With the Ir catalyst **1** under our reaction conditions, almost equal amounts of **17** and **18** were formed. This is in contrast to the observations of Crabtree et al.[18] where the use of an Ir(III) hydride catalyst favored the formation of spiroketal **18** over **17** in a ratio of 11:1. In our studies, treatment of diol **9** with the Rh catalysts (**2** or **3**) gave a mixture of spiroketals **17** and **18** in a 1:2.3 or 1:2.5 ratio. In comparison, the treatment of substrate **9** with Ir(I) and Rh(I) catalysts bearing *N*-donor ligands was recently reported to give the spiroketals **17** and **18** in 1:1 and 1.7:1 ratios, respectively.[12]

The substrate scope was also extended to diaryl alkyne diols. Cyclization of the aromatic substrate **10** to spiroketal **19** proceeded smoothly with all three catalysts **1–3**. It should be noted that the reaction times for the conversion of substrates **9** and **10** with the Ir catalyst **1** are very much shorter than the corresponding reactions with the Ir catalyst bearing *N*-donor ligands. The presence of *N*-donor ligands on the Ir retards the hydroxyalkoxylation reaction.

In summary, we have demonstrated that easily prepared Ir(I) and Rh(I) complexes efficiently promote the double cyclization reaction of a range of aliphatic and aromatic alkyne diols. The ease of preparation of these substrates combined with the simplicity of the metal complexes provides a straightforward and valuable route to the preparation of biologically active spiroketals. In addition, in some of the examples above, excellent conversion to the spiroketals is achieved with short reaction times and low catalyst loadings. Work is currently underway in our laboratories to develop chiral metal catalysts for the enantioselective synthesis of spiroketals.

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15. *A typical procedure is as follows*: All the metal-catalyzed reactions were performed on small scale in NMR tubes fitted with a concentric Teflon Young top with $(CDCl_2)_2$ as solvent. All additions and weighings were carried out in a glove box. In a typical experiment, the substrate (20–30 mg) was weighed into an NMR tube and diluted with about 0.2 mL of solvent. The catalyst (1–12 μmol, 0.5–5 mol %) was then weighed into a sample bottle and dissolved in the same solvent (0.4 mL). It was then transferred to the NMR tube using a syringe. The catalytic reaction was performed at elevated temperature (90 °C) by heating in an oil bath. The conversion of starting material to product was determined by integration of selected ^{1}H NMR signals of the product relative to selected ^{1}H NMR signals of the substrate. The diastereomeric ratio of the products was determined by ^{1}H NMR spectroscopy, and GC analysis, in comparison with data reported in the literature.
16. *General procedure for the isolation of product from the NMR-scale reaction in $(CDCl_2)_2$*: Upon completion of the reaction, as determined by ^{1}H NMR spectroscopy, the content of the tube was poured into a small beaker, the NMR tube rinsed with diethyl ether and the mixture was diluted with *n*-pentane. The resulting solution was passed through a short pad of silica. The solvent was removed in vacuo and the product characterized by ^{1}H NMR, ^{13}C NMR spectroscopy and GC–MS (HP-5 column) analysis. New compounds have been characterized.
17. *Spectral data for selected compounds*: (a) **1:** reddish-brown solid, ^{1}H NMR (400 MHz, CD_2Cl_2) δ 2.35 (m, 16H, CH_2 of COD), 5.02 (br s, 8H, CH of COD), 7.48 (br s, 4H of BARF), 7.64 (m, 8H of BARF); ^{19}F NMR (CD_2Cl_2) δ −63.5 (s); Anal. Calcd for $C_{48}H_{36}IrBF_{24}{\cdot}0.5CH_2Cl_2$: C, 44.31; H, 2.82. Found: C, 44.69; H, 2.75. (b) *Compound* **6:** colorless oil, ^{1}H (400 MHz, $CDCl_3$) δ 1.66 (m, 2H, CH_2), 2.23 (m, 2H, CH_2), 2.53 (m, 2H, CH_2), 3.65 (t, J = 6 Hz, 2H, OCH_2), 4.76 (dt, J = 6.2 Hz, 1.6 Hz, 1H, CH), 7.30 (m, 5H, Ar-H); ^{13}C (100 MHz, $CDCl_3$) δ 15.5 (CH_2), 29.9 (CH_2), 31.3 (CH_2), 61.9 (OCH_2), 72.6 (CH), 76.7 (≡C), 82.5 (C≡), 125.7 (Ar-CH), 127.8 (Ar-CH), 128.4 (Ar-CH), 142.8 (quart. C). HRMS (ESI): *m/z* calcd for $C_{13}H_{16}O_2Na$ $(M+Na)^+$ 227.10425, found 227.10512. (c) *Compound* **7**: colorless oil, ^{1}H (400 MHz, $CDCl_3$) δ 1.57 (m, 4H, $CH_2 \times 2$), 2.17 (m, 2H, CH_2), 2.55 (m, 2H, CH_2), 3.60 (t, J = 6.2 Hz, 2H, OCH_2), 4.70 (dt, J = 5.2 Hz, 2.4 Hz, 1H, CH), 7.28 (m, 5H, Ar-H); ^{13}C (100 MHz, $CDCl_3$) δ 18.5 (CH_2), 25.1 (CH_2), 29.9 (CH_2), 31.8 (CH_2), 62.4 (OCH_2), 72.6 (CH), 76.5 (≡C–), 83.1 (–C≡), 125.8 (Ar-CH), 127.8 (Ar-CH), 128.4 (Ar-CH), 142.8 (quart. C). HRMS (ESI): *m/z* calcd for $C_{14}H_{18}O_2Na$ $(M+Na)^+$ 241.11990, found 241.12101. (d) Compounds **9**–**10** and **17**–**19**: spectral data have been reported in Refs. 12a and b.
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