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Synthesis of spiroketals by iridium-catalyzed double hydroalkoxylation*

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Abstract: A highly efficient approach to the synthesis of spiroketals involves the double cyclization of alkynyl diols using transition-metal catalysts. The iridium complex $[Ir(PyP)(CO)_2]BPh_4$ where PyP = 1-[2-(diphenylphosphino)ethyl]pyrazole is an effective catalyst for promoting the formation of spiroketals via this double hydroalkoxylation reaction. The complex promotes the formation of a series of spiroketal products from alkynyl diol starting materials such as 3-ethynylpentane-1,5-diol and 2-(4-hydroxybut-1-ynyl)benzyl alcohol. Stereoselective cyclization occurs for 3-ethynylpentane-1,5-diol, 3-ethynylhexane-1,6-diol. The cycloadditions occur in all but one case with quantitative conversion in under 24 h at 120 °C.

Keywords: catalysis; alkyne diols; transition metals; spiroketals; hydroalkoxylation.

INTRODUCTION

The transition-metal-catalyzed addition of OH to alkynes and alkenes has received considerable attention as an atom-economical method for the construction of the C–O bond [1]. The catalyzed intramolecular hydroalkoxylation using alkenol, alkynol, and enyne as well as dienyne precursors is an effective approach to the synthesis of important five- and six-membered oxygen-containing heterocycles [1]. The most widely used catalysts for hydroalkoxylation include complexes of molybdenum, tungsten [1,2], ruthenium [3,4], and, in particular, palladium [1,5–7]. Isolated examples of platinum [8,9], gold [10,11], iridium [12–14], and rhodium [15] based catalysts for promoting hydroalkoxylation are known.

Spiroketals are fused oxygen heterocycles found in biologically active compounds [16] such as HIV protease inhibitors [17]. A number of approaches have been developed for spiroketal synthesis, but these often rely on multiple reaction steps and hence are not optimally efficient [16–18]. In an efficient, one-step transition-metal-catalyzed approach to constructing spiroketals, $PdCl_2(PhCN)_2$ and $PdCl_2$, have been used to catalyze the hydroalkoxylation of alkyne diol substrates [5], and very recently simple gold halides have been used for the analogous synthesis of cyclic ketals [11]. The intermolecular addition of two OH groups of alcohols to a single alkyne moiety has also been successfully catalyzed using $[Ir(\mu\text{-}Cl)(COD)]_2$ (COD= 1,5-cyclooctadiene) [14] and gold complexes with phosphine ligands [10]. Ruthenium-catalyzed alkene metathesis has been used for the synthesis of spiroketals, however, the difficulty of preparing the substrates for metathesis is a significant drawback [19]. Transition metals with ligand systems which have the potential for development as chiral catalysts would provide the

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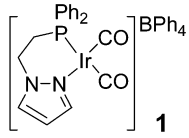
possibility of developing enantioselective routes to important cyclic ketals. We report here the Ir(I) complex (**1**) [20] catalyzed formation of spiroketals and bicyclic ketals via the intramolecular double hydroalkoxylation of alkynyl diols.



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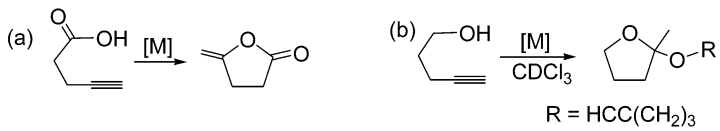
RESULTS AND DISCUSSION

Hydroalkoxylation with cationic rhodium and iridium complexes

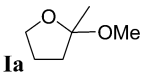
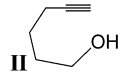
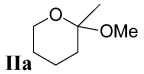
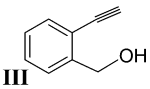
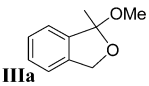
We have previously reported that the cationic rhodium complex, $[Rh(bim)(CO)_2]BPh_4$ (**2**) [bim = bis(*N*-methylimidazol-2-yl)methane] is an effective catalyst for hydroalkoxylation (Scheme 1) [21] and that the iridium complex $[Ir(PyP)(CO)_2]BPh_4$ (**1**) where PyP = 1-[(2-diphenylphosphino)ethyl]pyrazole is efficient in catalyzing the addition of thiophenol to a number of alkynes [20]. The iridium complex (**1**) was found to be a significantly more effective catalyst than the rhodium complex (**2**) in promoting the intramolecular cyclization of 4-pentynoic acid and 4-pentynol (Scheme 1). Complex **1** promoted quantitative conversions of 4-pentynoic acid to dihydro-5-methylenefuran-2(3*H*)-one in less than 3 h at room temperature with 1 mol % (**1**) in $CDCl_3$ (Scheme 1a) and of 4-pentyn-1-ol to tetrahydro-2-methyl-2-(pent-4-ynyloxy)furan in 30 h at 60 °C with 2 mol % (**1**) in $CDCl_3$ (Scheme 1b).



Scheme 1

The cyclization of a series of alkynol substrates catalyzed by the iridium complex **1** was carried out in $CDCl_3$, in the presence of a 5–6-fold excess quantity of methanol (Table 1). All three alkynols, **I**, **II**, and **III**, cleanly cyclized in *exo* mode to form cyclic ketals (**Ia**, **IIa**, **IIIa**) with incorporation of one molecule of methanol. The alternative cyclic ketal product resulting from incorporation of the alkynol starting material, e.g., Scheme 1b, R = $(CH_2)_3CCH$, was not formed in any of these reactions, probably due to the methanol being present in excess. A similar observation has been reported recently with $[Ir(\mu\text{-Cl})(COD)]_2$ catalyzed hydroalkoxylation of alkynols in methanol as the solvent [14]. The reaction slowed as the ring size increased (entries 1 and 2), or as the strain associated with the cyclic product increased (entries 1 and 3). Although the iridium catalyst (**1**) is able to facilitate the cyclization of 5-hexyn-1-ol, no equivalent reaction was observed with the rhodium complex (**2**) (in acetone-d_6) [21].

Table 1 Iridium(I) (**1**)[a] catalyzed cyclization of alkynols in the presence of an excess of MeOH[b] [22].

Entry	Alkynol	Product	Time (h)	% Conv.[c] (yield[d])
1	 **I**	 **Ia**	22	100 (72)
2	 **II**	 **IIa**	46	90 (76)
3	 **III**	 **IIIa**	65	96 (90)

[a]NMR scale; 2 mol % catalyst loading, at 60 °C in $CDCl_3$ (0.7–0.8 mL), [substrate] = 0.4–0.5 M.
[b]5–6-fold excess of MeOH.
[c]Determined by ^{1}H NMR.
[d]Isolated yields, average of two runs.

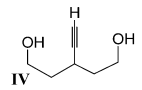
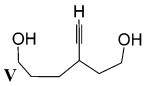
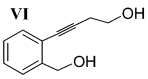
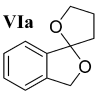
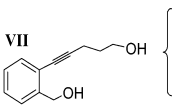
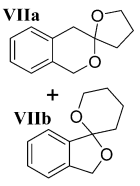
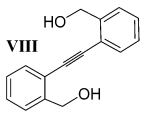
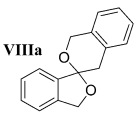
Iridium complex for catalyzed spiroketal synthesis

The methoxy-substituted ketal products (**Ia**, **IIa**, and **IIIa**) were thought to form as a result of the addition of methanol to an intermediate metal-bound vinyl species [21]. Using suitable diol substrates, it was reckoned that this reaction could take place intramolecularly to afford spiroketals. A number of alkyne diols, **IV**, **V**, **VI**, **VII**, and **VIII** (Table 2), were synthesized from readily available starting materials in one or two steps [22]. In the presence of complex **1** in $CDCl_3$ at 60 °C (Table 2), the intramolecular cyclization to the spiroketal products proceeded cleanly with high conversions from starting materials. No products resulting from the intermolecular reactions were detected by ^{1}H NMR. The cyclization of substrates with terminal acetylenes (**IV** and **V**, Table 2) proceeded at significantly higher rates than the reaction of nonterminal acetylene substrates. The cyclization of **VIII** to **VIIIa** is particularly slow due to the low solubility of **VIII** in $CDCl_3$.

The cyclization of these alkyne diols was also carried out in $(CDCl_2)_2$ at higher temperature (120 °C), and significantly faster reaction rates were observed (Table 2). Negligible quantities of side products were formed even at 120 °C, as observed by ^{1}H NMR of the crude reaction mixture. The rates of cyclization of nonterminal acetylene substrates remained significantly slower in comparison to terminal acetylene substrates.

On cyclization of **IV** and **V** to **IVa** and **Va**, respectively, only the *cis*-isomers were formed where the –H and $–CH_3$ substituents of the two fused carbon positions are *cis* to each other, as determined by ^{1}H NOESY NMR. This can be rationalized by the steric constraints imposed on formation of the 5,5- and 5,6-fused bicyclic systems present in the spiroketal products [23]. On cyclization of **VII**, the two possible products were formed in equal quantities at high temperature, indicating that the rates of formation of the pair of five- and six-membered heterocycles are equivalent, even though the isolated six-membered heterocycle is formed significantly more slowly (Table 1).

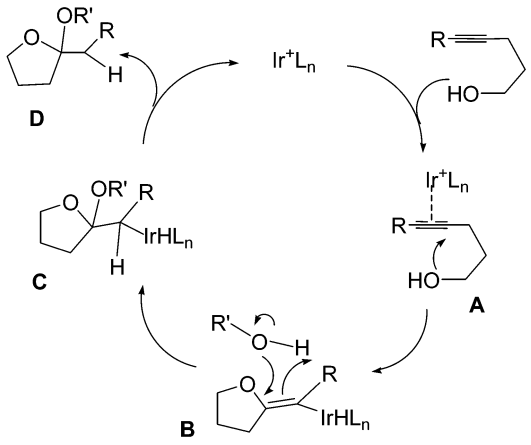
Table 2 Iridium(I) (**1**) catalyzed synthesis of spiroketals from alkyne diols[a] [22].

Alkyne diols	Product(s)	Time (h) % Conv.[b] (yield[c])	
		60 °C $CDCl_3$	120 °C $(CDCl_2)_2$
 **IV**	 **IVa**	32 >98 (83)	4 >98
 **V**	 **Va**	34 >98 (87)	7 >98
 **VI**	 **VIa**	168 86[d] (62)	22[e] >98
 **VII**	 **VIIa** + **VIIb**	81[e] 79[d] (74) **VIIa:VIIb =** 44:56	22[e] >98 **VIIa:VIIb =** 50:50
 **VIII**	 **VIIIa**	504[e] 80 (47)	174[e] >98

[a]NMR scale, 3 mol % of **1**, substrate = 43–50 mg, $CDCl_3$ or $(CDCl_2)_2$ = 0.7–0.8 mL.
[b]Determined by ^{1}H NMR.
[c]Isolated yields, average of 2 runs.
[d]Proceeded to completion after 2 weeks.
[e]5 mol % of **1**.

Mechanism

While the mechanism of the reactions is still under investigation, a working mechanism is proposed (Scheme 2). The first step of the reaction cycle is thought to be the activation of the carbon–carbon triple bond by coordination to the iridium center [24], allowing intramolecular C–O addition of the first alcohol via migratory insertion to form a metal-bound vinyl intermediate (**B**) [21]. The formation of the second ring as a spiroketal system is then most likely to follow by intramolecular attack of the second hydroxyl group at the β carbon of metal-bound **B**. The relatively slow cyclization of the nonterminal acetylene substrates (Table 2) is most likely due to steric hindrance of the substituents on the acetylene, which would slow the initial acetylene activation by iridium. Trost et al. [15] observed rhodium-catalyzed *endo*-cycloisomerization of terminal alkyne alcohols, and proposed that this proceeded via Rh-vinylidene intermediates. The reactions presented here (Table 2) proceeded smoothly with cyclization of alkynol substrates having both terminal and nonterminal acetylenes and formation of only the *exo*-addition products, which suggests the formation of the five-membered *exo*-cyclic metal-bound intermediate (**B**).



Scheme 2 Proposed mechanism.

CONCLUSIONS

In conclusion, we have developed a highly efficient, atom-economical method for the synthesis of spiroketals by the iridium-mediated double cyclization of readily available alkyne diols. Work is currently in progress in our laboratory to develop chiral iridium catalysts related to **1** for the enantioselective synthesis of spiroketals.

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REFERENCES AND NOTES

1. F. Alonso, I. P. Beletskaya, M. Yus. *Chem. Rev.* **104**, 3079 (2004).
2. F. E. McDonald. *Chem. Eur. J.* **5**, 3103 (1999).
3. B. M. Trost and Y. H. Rhee. *J. Am. Chem. Soc.* **124**, 2528 (2002).
4. B. Seiller, C. Bruneau, P. H. Dixneuf. *J. Chem. Soc., Chem. Commun.* 493 (1994).
5. K. Utimoto. *Pure Appl. Chem.* **55**, 1845 (1983).
6. B. Gabriele, G. Salerno, A. Fazio, R. Pittelli. *Tetrahedron* **59**, 6251 (2003).
7. I. Kadota, L. M. Lutete, A. Shibuya, Y. Yamamoto. *Tetrahedron Lett.* **42**, 6207 (2001).
8. J. W. Hartman and L. Sperry. *Tetrahedron Lett.* **45**, 3787 (2004).
9. H. Qian, X. Q. Han, R. A. Widenhoefer. *J. Am. Chem. Soc.* **126**, 9536 (2004).
10. J. H. Teles, S. Brode, M. Chabanas. *Angew. Chem., Int. Ed.* **37**, 1415 (1998).
11. S. Antoniotti, E. Genin, V. Michelet, J.-P. Genêt, *J. Am. Chem. Soc.* **127**, 9976 (2005).
12. H. Nakagawa, Y. Okimoto, S. Sakaguchi, Y. Ishii. *Tetrahedron Lett.* **44**, 103 (2003).
13. D. M. T. Chan, T. B. Marder, D. Milstein, N. J. Taylor. *J. Am. Chem. Soc.* **109**, 6385 (1987).
14. E. Genin, S. Antoniotti, V. Michelet, J.-P. Genêt. *Angew. Chem., Int Ed.* **44**, 2 (2005).
15. B. M. Trost and Y. H. Rhee. *J. Am. Chem. Soc.* **125**, 7482 (2003).
16. V. P. Vaillancourt, N. E. Pratt, F. Perron, K. F. Albizati. In *The Total Synthesis of Natural Products*, Vol. 8, J. ApSimon (Ed.), p. 533, Wiley-Interscience, New York (1992).

17. A. K. Ghosh, S. Leshchenko, M. Noetzel. *J. Org. Chem.* **69**, 7822 (2004).
18. B. D. Schwartz, P. Y. Hayes, W. Kitching, J. J. De Voss. *J. Org. Chem.* **70**, 3054 (2005).
19. A. Deiters and S. Martin. *Chem. Rev.* **104**, 2199 (2004).
20. S. Burling, L. D. Field, B. A. Messerle, K. Q. Vuong, P. Turner. *Dalton Trans.* 4181 (2003).
21. S. Elgafi, L. D. Field, B. A. Messerle. *J. Organomet. Chem.* **607**, 97 (2000).
22. P. Deslongchamps. *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press, Oxford (1983).
23. A preliminary low-temperature NMR experiment (^{1}H NOESY) has demonstrated the coordination of 1-pentyne to the iridium center in (**1**).
24. Full experimental details will be published in another publication.