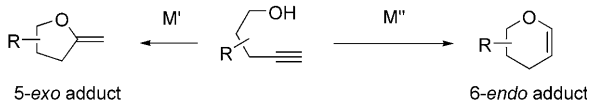
Catalytic Tandem Reactions

DOI: 10.1002/ange.200501150

An Ir^I-Catalyzed *exo*-Selective Tandem Cycloisomerization/Hydroalkoxylation of Bis-Homopropargylic Alcohols at Room Temperature**

Emilie Genin, Sylvain Antoniotti, Véronique Michelet, and Jean-Pierre Genêt**

Over the past few years, significant research has been directed toward the development of new methodologies that provide synthetic efficiency and atom economy.[1] Among them, tandem reactions, which allow the formation of several new bonds in a single step from readily available materials, are of particular interest.[2] Moreover, the potential of transition-metal-catalyzed heterocyclization reactions of unsaturated substrates has been regularly demonstrated, as they give a direct method for the synthesis of highly valuable nitrogen- and oxygen-containing heterocycles.[3] Palladium catalysis, in particular, has been the driving force behind many advances in the synthesis of heterocyclic derivatives.[4] However, cyclizations mainly occur at high temperature or in the presence of a base, copper co-catalysts, or other oxidants, and this has stimulated the search for alternative transition-metal catalysts.[3,4] In the course of our ongoing program concerning catalytic tandem reactions with functionalized enynes,[5] we became interested in the cyclization of bis-homopropargylic alcohols, which have shown challenging behaviors either in their *endo*- or *exo*-selective cyclizations in the presence of palladium, molybdenum, tungsten, ruthenium, and rhodium catalysts (Scheme 1).[1,3,4,6] We therefore turned our attention to iridium complexes, which have recently been reported to exhibit promising catalytic properties,[7,8] and we wish to report herein the first Ir^I-catalyzed *exo*-selective tandem cycloisomerization/hydroalkoxylation that proceeds exclusively and efficiently at room temperature and that involves inter- and intramolecular C–O bond formation.



Scheme 1. Metal-catalyzed cyclization of bis-homopropargylic alcohols. M′ = Pd; M″ = Mo, W, Ru, Rh, Pd.

Our initial experiments were performed with bis-homopropargylic alcohol **1a** as a model substrate, which is easily prepared by malonic addition to the corresponding halide and reduction of the resultant diester. Even though Ir^I catalysts have recently been shown to promote 1,6-enyne carbon–carbon cycloisomerization,[7j] the $[\{Ir(cod)Cl\}_2]$ dimer catalyst led to a completely different reaction in methanol at room temperature. The cyclization occurred very smoothly in the presence of 2.5 mol% of $[\{Ir(cod)Cl\}_2]$ at room temperature in a very short time with the concomitant addition of methanol to give the functionalized furanyl ketal **2a** in 99% yield (Table 1, entry 1). The use of an Ir^I catalyst is crucial as no reaction occurred either without catalyst or with $IrCl_3$. Interestingly, whereas the reaction of such bis-homopropargylic substrates catalyzed by transition metals such as Rh, Ru, W, and Mo usually leads to 6-*endo* cyclization products,[6] the cyclization was found to be 5-*exo*-selective, as no six-membered cyclic derivative was detected. The tandem addition of methanol was particularly intriguing as it has only rarely been reported in the literature: scarce examples are limited to the use of Pd catalysts and need a co-catalyst or other additive to be effective.[4e,9] We therefore embarked on a general study of this reaction in the presence of an Ir^I catalyst (Table 1). With the aim of examining the influence of the side chain R^1, we prepared several bis-homopropargylic alcohols by malonic addition of the corresponding alkyl bromide, reduction of the resultant diester functions, and, for some substrates, monoprotection of the diols.[10] The reactions were conducted in MeOH at room temperature in the presence of 1–2.5 mol% of $[\{Ir(cod)Cl\}_2]$.

The butyl-substituted alkyne **1b** was transformed into the ketal **2b** in a high 99% yield (Table 1, entry 2). Surprisingly, the addition of the remaining alcohol was not observed in these cases, presumably because MeOH, which is a potential ligand for the Ir complex, is present in excess close to the substrate.[11] The reaction conditions are compatible with other substitution patterns on alcohols **1**, such as a propargyl group (entry 3). Alcohols **1d–f** underwent smooth and rapid cyclization and functionalization (entries 4–6) to give the corresponding acetals **2d–f** in excellent yields (90–99%). Lowering the catalyst loading was possible (entry 6) with a slight enhancement of the reaction time. These derivatives constitute important building blocks for an easy access to natural product[12] and can be easily transformed into C1-substituted furans by treatment with functionalized silanes in the presence of a Lewis acid.[13]

To illustrate the synthetic utility of this tandem reaction, we envisaged the use of other alcohols for the intermolecular addition step. Other nucleophiles such as ethanol and allylic alcohol could be successfully used under the same reaction conditions at room temperature in the presence of 1–2.5 mol% of the $[\{Ir(cod)Cl\}_2]$ catalyst (Table 2).

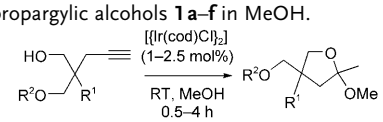
Such a process offers a control of the R^1 and R^3 groups in the final furanyl product simply by varying the halide used in the preliminary malonate alkylation and the nature of the alcohol used as the solvent. This mode of functionalization also allows the introduction of structural diversity that cannot

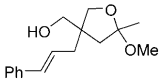
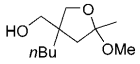
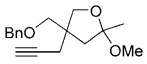
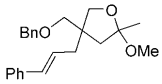
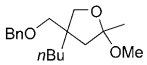
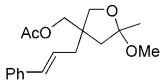
[*] E. Genin, Dr. S. Antoniotti, Dr. V. Michelet, Prof. J.-P. Genêt
Laboratoire de Synthèse Sélective Organique et Produits Naturels
E.N.S.C.P., UMR 7573
11 rue P. et M. Curie, 75231 Paris Cedex 05 (France)
Fax: (+33) 1-4407-1062
E-mail: veronique-michelet@enscp.fr
jean-pierre-genet@enscp.fr

[**] This work was supported by the Centre National de la Recherche Scientifique (CNRS). E.G. is grateful to the Ministère de l'Education et de la Recherche for financial support (2003–2006).

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 1: Cyclization/hydroalkoxylation of bis-homopropargylic alcohols **1a–f** in MeOH.



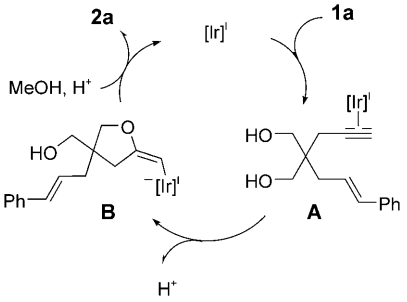
Entry		R^1	R^2	Product		*t* [h]	Yield [%][a]
1[b]	**1a**	(*E*)-cinnamyl	H		**2a**	0.5	99
2[b]	**1b**	*n*Bu	H		**2b**	0.5	99
3[b]	**1c**	propargyl	Bn[d]		**2c**	0.5	99
4[b]	**1d**	(*E*)-cinnamyl	Bn[d]		**2d**	0.5	91
5[b]	**1e**	*n*Bu	Bn[d]		**2e**	1.5	90
6[c]	**1f**	(*E*)-cinnamyl	Ac		**2f**	4	99

[a] Yield of isolated product; 1/1 mixture of diastereomers. [b] 2.5 mol% of catalyst. [c] 1 mol% of catalyst. [d] Bn = benzyl.

be achieved selectively by the functionalization of simple furanyl rings. Alcohols bearing either an unsaturated (entries 1, 2, and 4) or an alkyl (entry 3) side chain were cleanly, and in a very short time, cyclized with concomitant addition of EtOH to the ethoxy-substituted derivatives **3a**, **3c**, **3e**, and **3g** in good to excellent yields (78–99%). The cycloisomerization/hydroethoxylation was also effective with phenyl- (entry 5) and benzyl-substituted (entry 6) alcohols, as the substituted furans **3h**,**i** were obtained in 71% and 99% yields.

The addition of allyl alcohol was also very interesting as it could give an entry to further functionalization and other transition-metal-catalyzed reactions. Various substrates were efficiently converted into the corresponding allyloxy-substituted furans (entries 7–11). The reaction of diols **1a** and **1c**, which bear an (*E*)-cinnamyl and propargyl side chain, respectively, afforded the ketals **4a** and **4c** in high yields (entries 7 and 8). Benzyl-protected alcohols and allyl derivative **1g** (entries 9–11) could also be cyclized and functionalized to give furans **4e**, **4g**, and **4i** in 86–99% yield. These promising results prompted us to test the efficiency of our system for the formation of six-membered functionalized rings that are found as subunits of a number of cytotoxic natural products.[9d,12] Dimethyl 3-butynylmalonate[14] was alkylated in the presence of cinnamyl bromide to give the diester, which was subsequently reduced and monobenzylated to give the alcohol **1j**. Indeed, this cycloisomerization/hydroalkoxylation process is not limited to the synthesis of functionalized furans, as alcohol **1j** undergoes an equally facile and efficient Ir^I-catalyzed *exo*-selective tandem reaction to give, in 24 h, the functionalized pyrans **2j** and **3j** in high (99%) yield (Table 2, entries 12 and 13).

Next, we focused on the mechanism of the reaction. Two competitive mechanisms for this transformation may be envisioned, one based on a metal–vinylidene intermediate[6,8] and the other based on electrophilic alkyne activation.[3] Despite the fact that iridium catalysts can promote the formation of vinylidene intermediates from alkynes,[8] this mechanism was excluded owing to the *exo*-selective nature of the cyclization instead of the expected 6-*endo*-cyclization. A second mechanism based on the Lewis acidic character of the metal is much more probable (Scheme 2). The reaction may

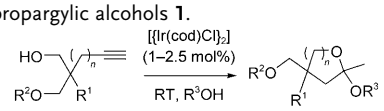


Scheme 2. Postulated mechanism for the formation of cyclic ketals from bis-homopropargylic alcohols.

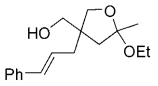
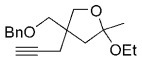
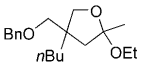
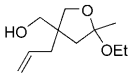
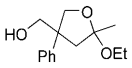
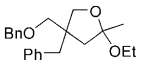
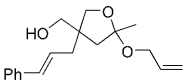
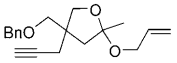
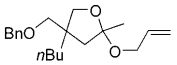
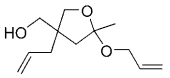
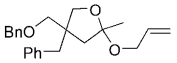
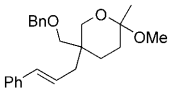
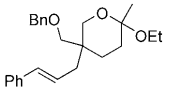
be initiated by the formation of the π-alkynyl complex **A** by the complexation of the unsaturated triple bond to the Ir^I catalyst. Subsequent addition of the alcohol, which was supposed to occur *anti* to the π-complex **A**,[3a] would lead to a σ-complex **B**, which is favored in polar protic solvents such as MeOH, via a transient zwitterionic intermediate.[15] Proton transfer may then be followed by the intermolecular addition of MeOH to give the cyclic ketal **2a**.[16,17] An alternate pathway involving an Ir^{III} hydride species, and therefore a reductive elimination, cannot be ruled out.

Labeling studies performed in the presence of 2.5 mol% of $[\{Ir(cod)Cl\}_2]$ either in CD_3OD for the cyclization of **1a** or in MeOH for the reaction of the deuterated alkyne $[D_1]$-**1a**

Table 2: Cyclization/hydroalkoxylation of bis-homopropargylic alcohols **1**.



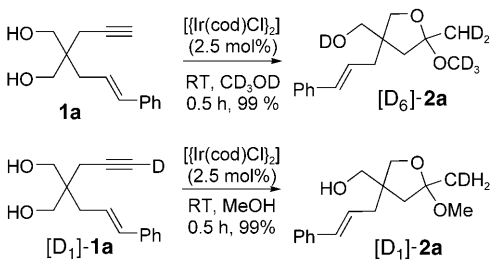
1a–j **2–4 a–j**

Entry		R^1	R^2	Product		t [h]	Yield [%][a]
1[b]	**1a**	(*E*)-cinnamyl	H		**3a**	0.5	99
2[b]	**1c**	propargyl	Bn		**3c**	2.5	99
3[b]	**1e**	*n*Bu	Bn		**3e**	0.5	99
4[c]	**1g**	allyl	H		**3g**	0.7	78
5[c]	**1h**	Ph	H		**3h**	0.7	71
6[c]	**1i**	Bn	Bn		**3i**	1.3	99
7[b]	**1a**	(*E*)-cinnamyl	H		**4a**	2.5	99
8[b]	**1c**	propargyl	Bn		**4c**	2.5	99
9[b]	**1e**	*n*Bu	Bn		**4e**	2.7	99
10[c]	**1g**	allyl	H		**4g**	2.5	86
11[c]	**1i**	Bn	Bn		**4i**	22	88
12[b]	**1j**	(*E*)-cinnamyl	Bn		**2j**	24	99
13[b]	**1j**	(*E*)-cinnamyl	Bn		**3j**	24	99

[a] Yield of isolated product; 1/1 mixture of diastereomers. [b] 2.5 mol% of catalyst. [c] 1 mol% of catalyst.

were in good agreement with the proposed mechanism, as the cycloisomerization/hydroalkoxylation reactions afforded the unique formation of the corresponding deuterated derivatives [D_6]-**2a** or [D_1]-**2a**, respectively (Scheme 3). No deuterium scrambling, which would result from insertion of iridium into a C–H(D) bond, was observed.

In summary, we have developed a general, efficient, and atom-economic method for the synthesis of cyclic ketals starting from easily accessible bis-homopropargylic alcohols. The [{Ir(cod)Cl}$_2$] dimer is used for the first time to promote a tandem cyclization/hydroalkoxylation reaction at room temperature in a very short time to give functionalized derivatives. The reaction conditions are compatible with various functional groups. Considering the ease of preparation of these substrates, this method provides a new route for constructing functionalized furanyl and pyranyl building blocks and is therefore a valuable tool for the synthesis of natural or biologically active products. The proposed reaction mechanism presumably involves a Lewis acid type activation, followed by an intramolecular cyclization, a protonolysis step, and the intermolecular addition of an alcohol molecule. The



Scheme 3. Labeling experiments for the cyclization reactions of **1a** and [D_1]-**1a**.

high catalytic activity of [{Ir(cod)Cl}$_2$], along with the very mild reaction conditions, would probably allow the use of weaker nucleophiles, both as inter- and intramolecular partners.

Experimental Section

Representative standard procedure: A mixture of bis-homopropargylic alcohol **1a** (70 mg, 0.3 mmol) and [{Ir(cod)Cl}$_2$] (5.1 mg, 2.5 mol%) in degassed methanol (0.6 mL) was stirred under argon at room temperature for 30 min. After completion of the reaction, the mixture was filtered through a short pad of celite (eluent: EtOAc) and the solvents were evaporated under reduced pressure to give 79 mg of ketal **2a**. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.43$ (s, 3H), 1.44 (s, 3H), 1.72 (d, $J = 13.3$ Hz, 1H), 1.84 (d, $J = 13.3$ Hz, 1H), 1.98 (d, $J = 13.3$ Hz, 1H), 2.00 (d, $J = 13.3$ Hz, 1H), 2.36–2.50 (m, 4H), 3.21 (s, 3H), 3.22 (s, 3H), 3.51–3.85 (m, 8H), 6.18 (dt, $J = 15.7$, 7.3 Hz, 2H), 6.47 (d, $J = 15.7$ Hz, 2H), 7.21–7.37 ppm (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.0$, 21.8, 38.8, 41.8, 47.0, 47.7, 48.3, 48.6, 48.5, 48.7, 67.9, 68.0, 73.7, 73.9, 108.3, 108.5, 126.0, 126.4, 126.9, 127.5, 127.6, 128.8, 132.9, 133.7, 137.6 ppm. CI MS (NH_3): m/z: 248 $[M-MeOH+NH_4]^+$, 231 $[M-MeOH+H]^+$. HRMS calculated for $C_{15}H_{19}O_2$ $[M-MeOH+H]^+$: 231.1385; found 231.1389.

Received: March 31, 2005
Published online: July 11, 2005

Keywords: atom economy · cyclization · homogeneous catalysis · iridium · tandem reaction

[1] For recent reviews on atom-economical processes, see: a) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695–705; b) P. N. Anastas, M. M. Kirchhoff, *Acc. Chem. Res.* **2002**, *35*, 686–694; c) B. M. Trost, D. F. Toste, A. B. Pinkerton, *Chem. Rev.* **2001**, *101*, 2067–2096; d) B. M. Trost, M. J. Krische, *Synlett* **1998**, 1–16; e) B. M. Trost, *Science* **1991**, *254*, 1471–1477.

[2] For reviews on tandem reactions, see: a) L. F. Tietze, F. Haunert, *Stimulating Concepts in Chemistry* (Eds: F. Vögtle, J. F. Stoddart, M. Shibasaki), Wiley-VCH, Weinheim, **2000**, pp. 39–64; b) G. Poli, G. Giambastiani, A. Heumann, *Tetrahedron* **2000**, *56*, 5959–5989; c) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; d) S. E. Denmark, A. Thorarensen, *Chem. Rev.* **1996**, *96*, 137–165; e) J. D. Winkler, *Chem. Rev.* **1996**, *96*, 167–176; f) M. Malacria, *Chem. Rev.* **1996**, *96*, 289–306.

[3] For representative examples, see: a) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079–3160; b) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127–2198; c) M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem.* **2004**, *116*, 3448–3479; *Angew. Chem. Int. Ed.* **2004**, *43*, 3368–3398.

[4] For representative examples, see: a) G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, *104*, 2285–2310; b) G. Balme, N. Monteiro, D. Bouyssi, *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E. I. Negishi), Wiley, New York, **2002**, pp. 2245–2265; c) T. Hosokawa, S.-I. Murahashi, *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E. I. Negishi), Wiley, New York, **2002**, pp. 2169–2192; d) J. Tsuji, *Palladium Reagents and Catalysis*, Wiley-VCH, New York, **1996**; e) T. Hosokawa, S.-I. Murahashi, *Acc. Chem. Res.* **1990**, *23*, 49–54; f) K. Utimoto, *Pure Appl. Chem.* **1983**, *55*, 1845–1852.

[5] a) L. Charruault, V. Michelet, R. Taras, S. Gladiali, J.-P. Genêt, *Chem. Commun.* **2004**, 850–851; b) C. Nevado, L. Charruault, V. Michelet, C. Nieto-Oberhuber, M. P. Muñoz, M. Méndez, M.-N. Rager, J.-P. Genêt, A. M. Echavarren, *Eur. J. Org. Chem.* **2003**, 706–713; c) L. Charruault, V. Michelet, J.-P. Genêt, *Tetrahedron Lett.* **2002**, *43*, 4757–4760; d) J.-C. Galland, M. Savignac, J.-P. Genêt, *Tetrahedron Lett.* **1997**, *38*, 8695–8698. For recent reviews, see: e) A. M. Echavarren, C. Nevado, *Chem. Soc. Rev.* **2004**, *33*, 431–436; f) M. Méndez, V. Mamane, A. Fürstner, *Chemtracts* **2003**, *16*, 397–425; g) G. C. Lloyd-Jones, *Org. Biomol. Chem.* **2003**, *1*, 215–236; h) C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.* **2002**, *102*, 813–834.

[6] For selected studies with W-based catalysts, see: a) E. Alcazar, J. M. Pletcher, F. E. McDonald, *Org. Lett.* **2004**, *6*, 3877–3880; b) F. E. McDonald, K. S. Reddy, *Angew. Chem.* **2001**, *113*, 3765–3767; *Angew. Chem. Int. Ed.* **2001**, *40*, 3653–3655; c) F. E. McDonald, *Chem. Eur. J.* **1999**, *5*, 3103–3106. For recent studies with Rh- and Ru-based catalysts, see: d) B. M. Trost, M. T. Rudd, *J. Am. Chem. Soc.* **2005**, *127*, 4763–4766; e) B. M. Trost, Y. H. Rhee, *Org. Lett.* **2004**, *6*, 4311–4313; f) B. M. Trost, M. T. Rudd, M. G. Costa, P. I. Lee, A. E. Pomerantz, *Org. Lett.* **2004**, *6*, 4235–4238; g) B. M. Trost, Y. H. Rhee, *J. Am. Chem. Soc.* **2003**, *125*, 7482–7483; h) B. M. Trost, Y. H. Rhee, *J. Am. Chem. Soc.* **2002**, *124*, 2528–2533.

[7] For selected Ir-catalyzed C–C bond-forming reactions, see: a) N. Kinoshita, K. H. Marx, K. Tanaka, K. Tsubaki, T. Kawabata, N. Yoshikai, E. Nakamura, K. Fuji, *J. Org. Chem.* **2004**, *69*, 7960–7964, and references cited therein; b) D. B. Grotjahn, J. M. Hoerter, J. L. Hubbard, *J. Am. Chem. Soc.* **2004**, *126*, 8866–8867; c) M. Janka, W. He, A. J. Frontier, R. Eisenberg, *J. Am. Chem. Soc.* **2004**, *126*, 6864–6865; d) G. Lipowsky, N. Miller, G. Helmchen, *Angew. Chem.* **2004**, *116*, 4695–4698; *Angew. Chem. Int. Ed.* **2004**, *43*, 4595–4597; e) R. Takeuchi, Y. Nakaya, *Org. Lett.* **2003**, *5*, 3659–3662; f) H. Takaya, K. Yoshida, K. Isozaki, H. Terai, S.-I. Murahashi, *Angew. Chem.* **2003**, *115*, 3424–3426; *Angew. Chem. Int. Ed.* **2003**, *42*, 3302–3304; g) T. Koike, X. Du, T. Sanada, Y. Danda, A. Mori, *Angew. Chem.* **2003**, *115*, 93–96; *Angew. Chem. Int. Ed.* **2003**, *42*, 89–92; h) T. Shibata, S. Kadowaki, M. Hirase, K. Takagi, *Synlett* **2003**, 573–575; i) S. Sakaguchi, T. Kubo, Y. Ishii, *Angew. Chem.* **2001**, *113*, 2602–2604; *Angew. Chem. Int. Ed.* **2001**, *40*, 2534–2536; j) N. Chatani, H. Inoue, T. Morimoto, T. Muto, S. Murai *J. Org. Chem.* **2001**, *66*, 4433–4436, and references cited therein; k) T. Shibata, K. Takagi, *J. Am. Chem. Soc.* **2000**, *122*, 9852–9853; l) R. Takeuchi, M. Kashio, *Angew. Chem.* **1997**, *109*, 268–270; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 263–265; m) C.-H. Jun, Z. Lu, R. H. Crabtree, *Tetrahedron Lett.* **1992**, *33*, 7119–7120; n) N. Chatani, S. Ikeda, K. Ohe, S. Murai, *J. Am. Chem. Soc.* **1992**, *114*, 9710–9711.

[8] For references on iridium–vinylidene intermediates, see: a) C. S. Chin, G. Won, D. Chong, M. Kim, H. Lee, *Acc. Chem. Res.* **2002**, *35*, 218–225; b) S.-I. Murahashi, H. Takaya, *Acc. Chem. Res.* **2000**, *33*, 225–233; c) T. Ohmura, S. Yorozuya, Y. Yamamoto, N. Miyaura, *Organometallics* **2000**, *19*, 365–367. For reviews on other metal–vinylidene intermediates, see: d) [1a]; e) C. Bruneau, P. H. Dixneuf, *Acc. Chem. Res.* **1999**, *32*, 311–323; f) M. I. Bruce, *Chem. Rev.* **1991**, *91*, 197–257.

[9] For a reaction with alkenes, see: a) T. Hosokawa, F. Nakajima, A. Iwasa, S.-I. Murahashi, *Chem. Lett.* **1990**, 1387–1390. For a reaction with alkynes, see: b) B. Gabriele, G. Salerno, M. Costa, *Synlett* **2004**, 2468–2483, and references cited therein; c) B. Gabriele, G. Salerno, F. De Pascali, M. Costa, G. P. Chiusoli, *J. Organomet. Chem.* **2000**, *593–594*, 409–415; d) J. A. Marshall, M. M. Yanik, *Tetrahedron Lett.* **2000**, *41*, 4717–4721.

[10] T. W. Greene, P. G. M. Wuts, in *Protective Groups in Organic Synthesis*, Wiley, New York, **1999**. The alcohols were synthesized under conventional monoprotection conditions (NaH, BnBr, nBu$_4$NI, THF for the monobenzylation reaction and Ac_2O, DMAP, pyridine, CH_2Cl_2 for the monoacetylation reaction).

[11] In other solvents, such as acetone, acetonitrile, or toluene, the reaction is quite sluggish and involves the intramolecular addition of both hydroxy groups to give the bicyclic ketal.

[12] a) C. Xu, E.-I. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E. I. Negishi), Wiley, New York, **2002**, pp. 2289 – 2305; b) M. C. Elliot, E. Williams, *J. Chem. Soc. Perkin Trans. 1* **2001**, 2303 – 2340; c) M. C. Elliot, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1291 – 1318; d) F. Q. Alali, X.-X. Liu, J. L. McLaughlin, *J. Nat. Prod.* **1999**, *62*, 504 – 540.
[13] M. D. Lewis, J. K. Cha, Y. Kishi, *J. Am. Chem. Soc.* **1982**, *104*, 4976 – 4977.
[14] For the preparation of **1j**, see: G. J. Laidig, L. S. Hegedus, *Synthesis* **1995**, 527 – 530.
[15] Isolation of the enol ether and detection of the σ-complex were unsuccessful. For Pt- and Pd-catalyzed hydroalkoxylation of alkenes, see: a) H. Qian, X. Han, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2004**, *126*, 9536 – 9537; b) J. E. Bäckvall, B. Akermark, S. O. Ljunggren, *J. Am. Chem. Soc.* **1979**, *101*, 2411 – 2415.
[16] No traces of the dimethoxy ketal were detected when the dibenzylate of diol **1a** was treated with $[\{Ir(cod)Cl\}_2]$/MeOH, which excludes an intermolecular addition of MeOH prior to the intramolecular process. For recent syntheses of dimethoxy ketals from alkynes in the presence of Pd, Pt, Cu, Au, or Zn see: a) D. Masui, Y. Ishii, M. Hidai, *Chem. Lett.* **1998**, 717 – 718; b) J. W. Hartman, L. Sperry, *Tetrahedron Lett.* **2004**, *45*, 3787 – 3788; c) S. H. Bertz, G. Dabbagh, P. Cotte, *J. Org. Chem.* **1982**, *47*, 2216 – 2217; d) Y. Fukuda, K. Utimoto, *J. Org. Chem.* **1991**, *56*, 3729 – 3731; e) J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem.* **1998**, *110*, 1475 – 1478; *Angew. Chem. Int. Ed.* **1998**, *37*, 1415 – 1418; f) K. Breuer, J. H. Teles, D. Demuth, H. Hibst, A. Schäfer, S. Brode, H. Domgörgen, *Angew. Chem.* **1999**, *111*, 1495 – 1502; *Angew. Chem. Int. Ed.* **1999**, *38*, 1401 – 1405.
[17] The addition of R^3OH may also be catalyzed by an $[Ir^I]$ complex.

