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Iridium-Catalyzed Coupling Reaction of Primary Alcohols with 1-Aryl-1-propynes Leading to Secondary Homoallylic Alcohols

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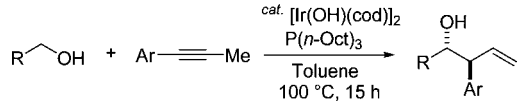
ABSTRACT



We report iridium-catalyzed coupling of 2-alkynes such as 1-aryl-1-propynes with primary alcohols leading to secondary homoallylic alcohols as products. This reaction involves an iridium-catalyzed novel catalytic transformation of 2-alkynes and primary alcohols through the formation of hydrido(π-allyl)iridium as a possible key intermediate.

Recently, iridium-catalyzed hydrogen autotransfer processes involving the use of alcohols as alkylating agents have been the topic of intensive investigation.[1] We succeeded in developing the iridium-catalyzed direct α-alkylation of ketones and active methylene compounds like cyanoacetate with alcohols and diols as well as β-alkylation of primary alcohols (Guerbet reaction) using alcohols as alkylated agents.[2] On the other hand, the transition metal-catalyzed addition of alcohols to alkynes is an important methodology leading to a wide variety of oxygen-containing compounds which are mainly referred to as the hydroalkoxylation reaction.[3] In addition, several iridium-catalyzed reactions of terminal alkynes with alcohols are also reported.[4]

Quite recently, Krische and co-workers reported an ruthenium or iridium-catalyzed transformation of alcohols with diene, allyl acetate, and allene to afford homoallylic alcohols as products.[5] In addition, the same group also reported the ruthenium-catalyzed direct C−H vinylation reaction of alcohols and alkynes to afford *allylic alcohols* as products.[6]

In this Letter, we wish to report iridium-catalyzed coupling of 2-alkynes such as 1-aryl-1-propynes with primary alcohols leading to secondary homoallylic alcohols as products.[7] This work is a novel iridium-catalyzed transformation of alcohols

(1) (a) *Iridium Complexes in Organic Synthesis*; Oro, L. A., Claver, C., Eds.; Wiley: Weinheim, Germany, 2009. (b) Guillena, G.; Rámon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2. (c) Ishii, Y.; Sakaguchi, S. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 909. (d) Takeuchi, R.; Kezuka, S. *Synthesis* **2006**, 3349. (e) Fujita, K.; Yamaguchi, R. *Synlett* **2005**, 560, and references cited therein.

(2) (a) Taguchi, K.; Nakagawa, H.; Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2004**, *126*, 72. (b) Maeda, K.; Obora, Y.; Sakaguchi, S.; Ishii, Y. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 689. (c) Morita, M.; Obora, Y.; Ishii, Y. *Chem. Commun.* **2007**, 2850. (d) Matsu-ura, T.; Sakaguchi, S.; Obora, Y.; Ishii, Y. *J. Org. Chem.* **2006**, *71*, 8306.

(3) For reviews see: Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev,* **2004**, *104*, 3079.

(4) (a) Hirabayashi, T.; Okimoto, Y.; Saito, A.; Morita, M.; Sakaguchi, S.; Ishii, Y. *Tetrahedron* **2006**, *62*, 2231. (b) Konkol, M.; Schmidt, H.; Steinborn, D. *J. Mol. Catal. A: Chem.* **2007**, *269*, 119.

(5) (a) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 34. (b) Patman, R. L.; Williams, V. M.; Bower, J. F.; Krische, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 5220. (c) Kim, I.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6340. (d) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14120. (e) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2514. (f) Kim, I. S.; Ngai, M.-Y.; Kriche, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891.

(6) Patman, R. L.; Chaulagain, M. R.; Williams, V. M.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2066.

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and alkynes to afford *homoallylic alcohols* as products through the formation of hydrido(π-allyl)iridium as a possible key intermediate, which indicated different reaction pathway from that used in Krische's work using alkynes.[6]

The reaction of 1-butanol (**1a**) with 1-phenyl-1-propyne (**2a**) was chosen as a model reaction and was carried out under various conditions (Table 1). For instance, **1a** (1 mmol) was allowed to react with **2a** (2 mmol) in the presence of $[Ir(OH)(cod)]_2$ (0.05 mmol) combined with tri(*n*-octyl)phosphine (0.30 mmol) in toluene (1 mL) at 100 °C for 15 h and gave 3-phenyl-1-hepten-4-ol (**3a**) in quantitative yield (95% isolated yield) (entry 1). The reaction is highly stereoselective to afford an *anti* isomer exclusively. In this reaction, the highest catalytic activity was attained by adding tri(*n*-octyl)phosphine as a ligand (entry 1). The addition of a lesser amount of tri(*n*-octyl)phosphine (10 mol %, Ir/P = 1:1) resulted in a considerably decreasing yield of **3a** (entry 2). Other added aryl and alkyl phosphine ligands indicated low catalytic activity, and no **3a** was obtained in the absence of the phosphine ligand (entries 3−9).

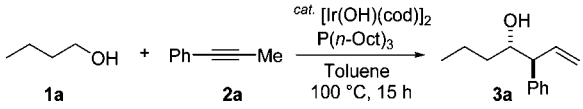
The yield of **3a** was still high (80%) even though the catalyst amount was reduced to half (2.5 mol %) (entry 10). Furthermore, the highest yield of **3a** was obtained with the ratio of **1a**:**2a** = 1:2, and the use of an equimolar amount of **1a** and **2a** under these reaction conditions resulted in a decrease of **3a** (65%) (entry 1 vs. entry 11). In this reaction, the formation of allylbenzene byproduct (3−20% based on **1a** used) was unavoidable (vide infra, Scheme 1).

As for the iridium complex, $[IrCl(cod)]_2$ also realized high catalytic activity and gave **3a** in high yield (entry 13). However, other selected iridium complexes such as $[Ir(cod)_2]^+BF_4^-$, $[IrCl(coe)_2]_2$, and $[Cp^*IrCl_2]_2$ showed low or no catalytic activities (entries 14−16). Needless to say, no **3a** was formed in the absence of an Ir complex (entry 17).

In the present reaction, various solvents can be employed. Under the reaction conditions identified in Table 1, entry 1 produces yields of **3a** in various solvents as follows: octane (99%), DMSO (95%), dioxane (90%), THF (81%), DMF (84%), 1,4-dichlorobutane (69%), and benzonitrile (20%).

Under optimized conditions, reactions of various primary alcohols (**1**) with 1-aryl-1-propynes (**2**) were carried out to afford the corresponding homoallylic alcohols in good to excellent yields (Table 2). Ethanol (**1b**), isobutyl alcohol (**1c**), 1-hexanol (**1d**), 1-octanol (**1e**), crotyl alcohol (**1f**), and β-methallyl alcohol (**1g**) were allowed to react with **2a** affording the corresponding homoallylic alcohols (**3b**−**g**) in high to excellent yields (entries 1−6). In addition, various 1-aryl-1-propynes (**2b**−**e**) can also be employed in this reaction and gave the corresponding homoallylic alcohols (**3h**−**k**) in high yields (entries 7−10). Unfortunately, 1-alkyl-1-propynes such as 2-butyne and 2-octyne were sluggish substrates to give only low yields of the desired homoallylic alcohols (<10% yield). The methyl substituent on the alkynes plays a crucial role in achieving the reaction. Thus, no coupling product was obtained from 4-octyne and phenylethylacetylene.

Table 1. Ir-Catalyzed Reaction of 1-Butanol (**1a**) with 1-Phenyl-1-propyne (**2a**) under Various Conditions[a]

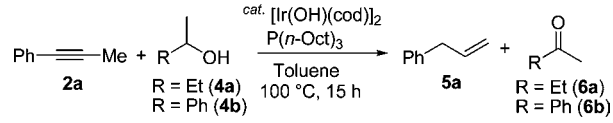


1a 2a 3a

entry	Ir-catalyst (mol %)	ligand (mol %)	yield of **3a**/%[b]
1	$[Ir(OH)(cod)]_2$ (5)	P(*n*-Oct)$_3$ (30)	quant (95)
2	$[Ir(OH)(cod)]_2$ (5)	P(*n*-Oct)$_3$ (10)	9
3	$[Ir(OH)(cod)]_2$ (5)	P(*n*-Bu)$_3$ (30)	80
4	$[Ir(OH)(cod)]_2$ (5)	P(*i*-Pr)$_3$ (30)	trace
5	$[Ir(OH)(cod)]_2$ (5)	PCy$_3$ (30)	trace
6	$[Ir(OH)(cod)]_2$ (5)	P(OMe)$_3$ (30)	4
7	$[Ir(OH)(cod)]_2$ (5)	P(OPh)$_3$ (30)	4
8	$[Ir(OH)(cod)]_2$ (5)	dppe (15)	11
9	$[Ir(OH)(cod)]_2$ (5)	none	n.d.[c]
10[d]	$[Ir(OH)(cod)]_2$ (2.5)	P(*n*-Oct)$_3$ (15)	80
11[e]	$[Ir(OH)(cod)]_2$ (5)	P(*n*-Oct)$_3$ (30)	65
12[f]	$[Ir(OH)(cod)]_2$ (5)	P(*n*-Oct)$_3$ (30)	35
13	$[IrCl(cod)]_2$ (5)	P(*n*-Oct)$_3$ (30)	90
14	$[Ir(cod)_2]^+BF_4^-$ (10)	P(*n*-Oct)$_3$ (30)	55
15	$[IrCl(coe)_2]_2$ (5)	P(*n*-Oct)$_3$ (30)	34
16	$[Cp^*IrCl_2]_2$ (5)	P(*n*-Oct)$_3$ (30)	n.d.[c]
17	none	P(*n*-Oct)$_3$ (30)	n.d.[c]

[a] Conditions: **1a** (1 mmol) was allowed to react with **2a** (2 mmol) in the presence of Ir catalyst (2.5−10 mol %) combined with phosphine ligand in toluene (1 mL) at 100 °C for 15 h. [b] GC yields based on **1a** used. The number in parentheses shows the isolated yield. In this reaction, allylbenzene (3−20% based on **2a**) was obtained as byproduct. [c] Not detected by GC. [d] $[Ir(OH)(cod)]_2$ (2.5 mol %) and P(*n*-Oct)$_3$ (15 mol %) were used as catalyst. [e] The reaction was performed with **1a** (1 mmol) and **2a** (1 mmol). [f] Reaction was performed at 60 °C.

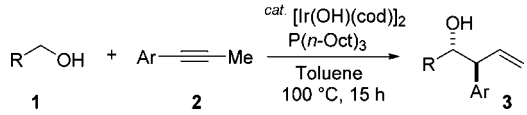
Scheme 1. Ir-Catalyzed Reaction of Secondary Alcohols (**4**) with 1-Phenyl-1-propyne (**2a**)

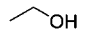
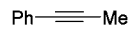
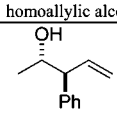
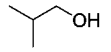
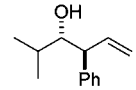
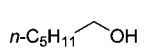
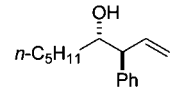
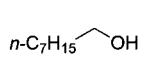
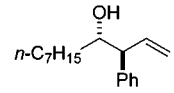
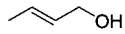
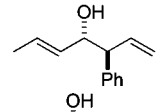
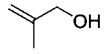
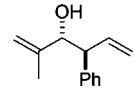
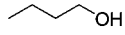
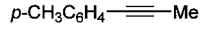
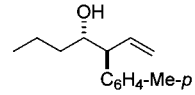
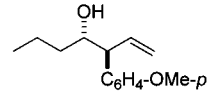
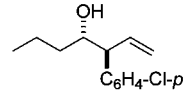
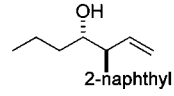


To obtain further insight into the reaction pathway, we carried out the reaction of *secondary alcohols* such as 1-phenyl-1-ethanol (**4a**) and 2-butanol (**4b**) with **2a** under these reaction conditions (Scheme 1). As a result, allylbenzene (**5a**) derived from **2a** was formed in quantitative yield with concomitant formation of acetophenone (**6a** from **4a**) or 2-butanone (**6b** from **4b**) in quantitative yields based on alcohols used. Similarly, the reaction of isopropyl alcohol (**4c**) with **2a** under these reaction conditions gave **5a** in quantitative yield (based on **4c** used). These results suggest

(7) Communicated in part in the following: (a) Hatanaka, S.; Obora, Y.; Ishii, Y., *Abstract of Papers of the 88th Annual Meeting of Chemical Society of Japan, Tokyo, Japan, 2008*; Chemical Society of Japan: Tokyo, Japan, 2008, 4H3−40. (b) Hatanaka, S.; Obora, Y.; Ishii, Y. *55th Symposium on Organometallic Chemistry, Osaka, Japan, 2008*; The Kinki Chemical Society: Osaka, Japan, 2008, P2B-27.

Table 2. Ir-Catalyzed Reaction of Alcohols (**1**) with Alkynes (**2**) Leading to Homoallylic Alcohols (**3**)[a]



entry	alcohol (**1**)		alkyne (**2**)		homoallylic alcohols (**3**)		yield/%[b]
1		(**1b**)		(**2a**)		(**3b**)	89 (85)
2		(**1c**)	**2a**			(**3c**)	94 (90)
3		(**1d**)	**2a**			(**3d**)	93 (90)
4		(**1e**)	**2a**			(**3e**)	89 (85)
5		(**1f**)	**2a**			(**3f**)	71 (65)
6		(**1g**)	**2a**			(**3g**)	65 (60)
7		(**1a**)		(**2b**)		(**3h**)	91 (88)
8	**1a**			(**2c**)		(**3i**)	99 (92)
9	**1a**			(**2d**)		(**3j**)	81 (80)
10	**1a**			(**2e**)		(**3k**)	97 (91)

[a] Conditions: **1** (1 mmol) was allowed to react with **2** (2 mmol) in the presence of $[Ir(OH)(cod)]_2$ (0.05 mmol) and $P(n\text{-Oct})_3$ (0.3 mmol) in toluene (1 mL) at 100 °C for 15 h. [b] GC yields. The numbers in parentheses show isolated yields.

that these alcohols behave as a hydrogen source and transferred to the Ir complex to form Ir-hydride species,[8] which was followed by the formation of π-allyl iridium species[9] as a key intermediate.

Quite recently, a stoichiometric transformation of 2-propynes with an osmium-dihydride complex was reported and led to a hydrido(π-allyl)osmium complex.[10] This study demonstrated the first example of the *catalytic* transformation of 1-aryl-1-propynes with primary alcohols as products through the formation of hydrido (π-allyl)iridium as a possible intermediate.

A stoichiometric reaction of **1a**, **2a**, and $[Ir(OH)(cod)]_2$/$P(n\text{-Oct})_3$ was carried out in an NMR tube in toluene-d_8. ^{1}H NMR spectra of the reaction mixture showed several peaks at around -23 ppm which can be assigned as proton signals of Ir-hydride.[8] However, due to instability of the complex, we could not determine the full structure of the expected π-allyl iridium intermediate at this point.

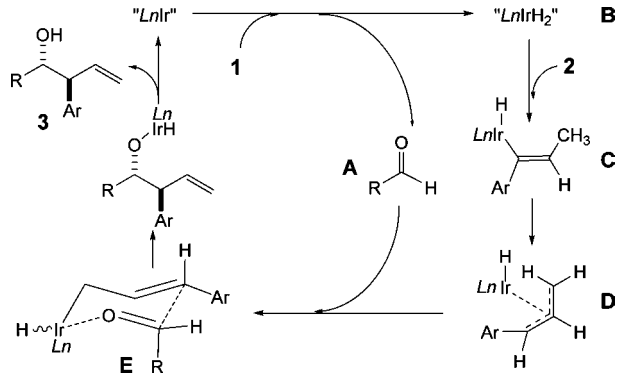
Accordingly, a detailed reaction mechanism of this reaction is not confirmed at this stage, but the reaction mechanism would be explained by the following sequential pathway (Scheme 2). First, the iridium catalyst serves as the hydrogen acceptor from **1** giving aldehydes (**A**) and an iridium-dihydride species (**B**).[2,8] Then alkynes (**2**) was inserted by Ir−H bond of **B** to form the hydrido(alkenyl)iridium species (**C**). The **C** was subjected to hydrogenation by Ir-H, followed

(8) Papers for iridium hydride: (a) Burk, M. J.; Crabtree, R. H.; McGrath, D. V. *Chem. Commun.* **1985**, 1829. (b) Gupta, M.; Hagen, C.; Kaska, W. C.; Cramer, R. E.; Jensen, C. M. *J. Am. Chem. Soc.* **1997**, *119*, 840. (c) Liu, F.; Goldman, A. S. *Chem. Commun.* **1999**, 655.

(9) Papers for π-allyl iridium: (a) Green, M.; Taylor, S. H. *Dalton Trans.* **1975**, 1143. (b) Schwartz, J.; Hart, D. W.; McGiffert, B. *J. Am. Chem. Soc.* **1974**, *96*, 5613. (c) Green, M.; Taylor, S. H. *Chem. Commun.* **1974**, 361.

(10) Esteruelas, M. A.; Hernandez, Y. A.; López, A. M.; Oliván, M.; Oñate, E. *Organometallics* **2007**, *26*, 2193.

Scheme 2. A Plausible Reaction Mechanism



by abstraction of hydrogen from the methyl group of **2** resulting in the formation of hydrido(π-allyl)iridium species (**D**) as an intermediate,[10] which further reacts with aldehydes (**A**) to afford homoallylic alcohols (**3**) as products through the formation of a six-membered transition state (**E**).

In conclusion, we reported the Ir-catalyzed coupling reaction of 1-aryl-1-propynes with primary alcohols to afford secondary homoallylic alcohols through the formation of hydrido(π-allyl)iridium as a possible intermediate. Further study of the characterization of the active intermediate species is currently under investigation.

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Supporting Information Available: Experimental procedure and compound characterization data (^{1}H NMR, ^{13}C NMR, IR, and MS) of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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