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Diene-Ligated Iridium Catalyst for Allylation Reactions of Ketones and Imines

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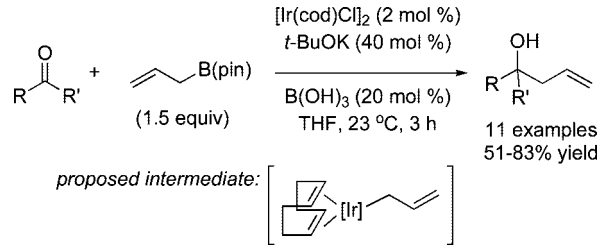
ABSTRACT



[Ir(cod)Cl]$_2$ is a highly reactive catalyst for allylation reactions of ketones using allylboronic ester. Mechanistic experiments are consistent with formation of a nucleophilic allyliridium(I) complex that is activated by the diene ligand toward attack of a ketone. Aryl and alkyl ketones react smoothly at room temperature. Aldimines also undergo allylation under these reaction conditions, requiring increased reaction times relative to the corresponding ketones.

Olefin ligands, incorporated into the substrate or added as exogenous ligands, can influence the rates of catalytic organometallic reactions.[1] The use of dienes and phosphino-olefins as ligands in asymmetric catalysis has recently developed as an important alternative to the use of phosphines, particularly in reactions catalyzed by rhodium and iridium complexes.[2] Diene ligands have been employed in several transformations,[1] including allylic substitution reactions that proceed through electrophilic allyliridium(III) intermediates.[2b] In this communication, we report that cyclooctadiene-ligated allyliridium(I) complexes are catalytic *nucleophiles* that react with ketones at room temperature.

Development of catalytic methods for ketone allylation is challenging, due in part to the decreased reactivity of these compounds relative to their aldehyde counterparts. Furthermore, few catalytic enantioselective methods for this transformation exist.[3,4] We examined allylation of ketones as part of our program in the development of new transition-metal-catalyzed allylation reactions. In preliminary studies, we determined that while N-heterocyclic carbene-ligated allylpalladium complexes catalyze allylation reactions of aldehydes, imines, α,β-unsaturated *N*-acylpyrroles, and alkylidene malononitriles, analogous reactions of ketones were sluggish.[5]

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(2) (a) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508–11509. (b) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628–1629. (c) For a review, see: Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3364–3366.

(3) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763–2793.

(4) Examples of catalytic enantioselective allylation of ketones. Allylborane: (a) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910–8911. (b) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660–12661. Allylsilane: (c) Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 14556–14557. Allyltin: (d) Casolari, S.; D'Addario, D.; Tagliavini, E. *Org. Lett.* **1999**, *1*, 1061–1063. (e) Kim, J. G.; Waltz, K. M.; Kwiatkowski, D.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 12580–12585. Chiral reagents: (f) Burns, N. Z.; Hackman, B. M.; Ng, P. Y.; Powelson, I. A.; Leighton, J. L. *Angew. Chem.* **2006**, *45*, 3811–3813. (g) Canales, E.; Prasad, G.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 11572–11573.

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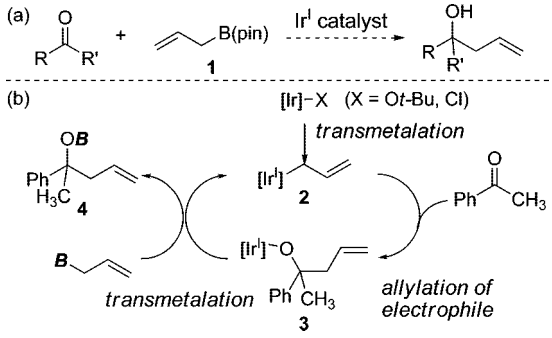
To identify improved catalysts for ketone allylation, we examined other d^8 transition metal complexes, including iridium complexes.[6] We hypothesized that allyliridium(I) complexes would be sufficiently nucleophilic to react with ketones, in part due to the low oxidation state of the metal. We designed an iridium-catalyzed reaction of ketones with allylboronic ester (Scheme 1). The transformation would

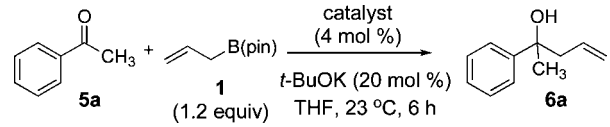
Scheme 1. Iridium-Catalyzed Allylation Reaction



initiate by a transmetalation reaction to generate a nucleophilic allyliridium(I) complex (**2**). This complex would react with the ketone to provide an iridium alkoxide complex (**3**). A subsequent transmetalation reaction would regenerate the catalyst and liberate the product (**4**). We have validated this hypothesis and found that $[Ir(cod)Cl]_2$ is a highly reactive catalyst for ketone allylation using allylboronic esters at room temperature. In related studies, Krische has achieved allylation of aldehydes using allyl acetate at 100 °C using $[Ir(cod)Cl]_2$ in the presence of bidentate phosphine ligands.[7,8] Mechanistic studies determined that these reactions proceed via nucleophilic allyliridium(III) intermediates.

In mechanistic studies, we have determined that ligation of Ir^I by *either* a diene or a bidentate phosphine provides a catalyst for ketone allylation (Table 1). $[Ir(cod)Cl]_2$ catalyzes allylation of acetophenone in three hours at room temperature, using 1.2 equiv of allylboronic ester. Iridium phosphine complexes, prepared from $[Ir(coe)_2Cl]_2$ and a bidentate phosphine, such as **7**, also catalyze the transformation, albeit with slower rates of reaction (entries 3, 5, and 6). Ligation by both cyclooctadiene and a phosphine slows the reaction (entry 4). Chiral phosphines screened yielded the homoallylic

Table 1. Allylboration of Acetophenone Catalyzed by Iridium Complexes[a]



entry	catalyst	conversion (%)[b]
2	$[Ir(cod)Cl]_2$	100
3	$[Ir(coe)_2Cl]_2$	<5
3[c]	$[Ir(coe)_2Cl]_2$ + $Cy_2PCH_2CH_2PCy_2$ (**7**)	27
4[c]	$[Ir(cod)Cl]_2$ + phosphine **7**	44
5[c]	$[Ir(coe)_2Cl]_2$ + (*R*)-BINAP	31
6[c]	$[Ir(coe)_2Cl]_2$ + (*R*,*R*)-Me-DUPHOS	44
7[c]	$[Ir(coe)_2Cl]_2$ + norbornadiene	15
8[c]	$[Ir(coe)_2Cl]_2$ + cod	100

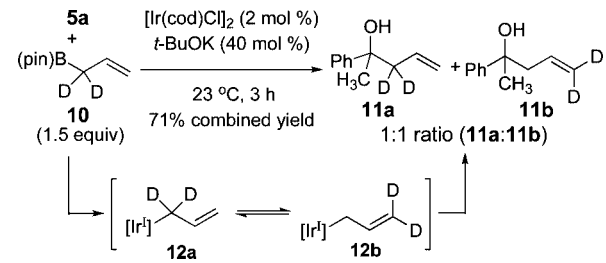
[a] See Supporting Information for full experimental details. [b] Conversion to **6a** was measured by ^1H NMR spectroscopy using an internal standard, 1,4-bistrifluoromethylbenzene. [c] 5 mol % of the indicated ligand was employed.

alcohol with no preference for either enantiomer (entries 5 and 6). Iridium complexes that are not ligated by a diene or phosphine, such as $[Ir(coe)_2Cl]_2$, do not catalyze the reaction (entry 2).

With a highly reactive catalyst identified, we examined allylation of a series of ketones (Table 2). A combination of KO*t*-Bu and boric acid as additives provided the highest yield of tertiary homoallylic alcohols.[9] A variety of aromatic and heteroaromatic ketones react under these reaction conditions. Substrates with either electron-withdrawing or electron-donating substituents reacted within 3 h. Halide substituents including bromide were tolerated, and no products resulting from oxidative addition into the C−X bond were observed.[10] Aliphatic ketones also reacted, although with a slight decrease in yield. Reactions of aldimines were slower than reactions of ketones and required increased reaction times. Nonetheless, *p*-methoxyphenyl (PMP) protected imines (**8**) reacted to afford homoallylic amines (**9**) in good yields.

Mechanistic experiments were consistent with our working hypothesis shown in Scheme 1. Allylation of acetophenone with deuterated boronic ester **10** provided a mixture of products, **11a** and **11b** (Scheme 2). This result is consistent

Scheme 2. Deuterium Scrambling Experiments are Consistent with Intermediacy of Nucleophilic Allyliridium(I) Complexes



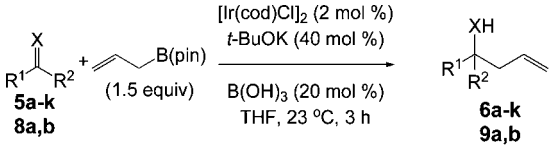
(5) (a) Barczak, N. T.; Grote, R. E.; Jarvo, E. R. *Organometallics* **2007**, *26*, 4863–4865. (b) Grote, R. E.; Jarvo, E. R. *Org. Lett.* **2009**, *11*, 485–488. (c) Shaghafi, M. B.; Kohn, B. L.; Jarvo, E. R. *Org. Lett.* **2008**, *10*, 4743–4746. (d) Waetzig, J. D.; Swift, E. C.; Jarvo, E. R. *Tetrahedron* **2008** *64*, in press.

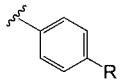
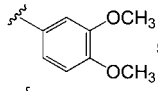
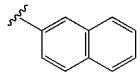
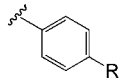
(6) (a) Takeuchi, R.; Kashio, M. *J. Am. Chem. Soc.* **1998**, *120*, 8647–8655. (b) Markovic, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 11680–11681.

(7) (a) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**,ASAP. (b) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6340–6341. See also: Masuyama, Y.; Chiyo, T.; Kurusu, Y. *Synlett* **2005**, 2251–2253.

(8) Iridium-catalyzed allylation of aldehydes using allenes and dienes: (a) Skucas, E.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 12678–12679. (b) Bower, J. F.; Skucas, E.; Patman, R. L.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 15134–15135. (c) Bower, J. F.; Patman, R. L.; Krische, M. J. *Org. Lett.* **2008**, *10*, 1033–1035.

Table 2. Scope of Allylation Reaction



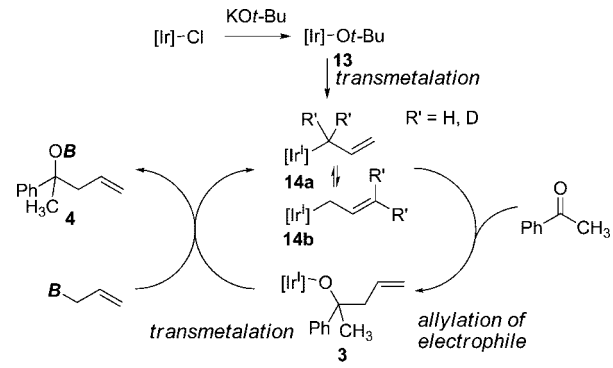
entry	X	R^1	R^2	substrate	product	yield (%)[a]
1	O	CH_3		**5a**, R = H	**6a**	78
2	O	CH_3		**5b**, R = F	**6b**	83
3	O	CH_3		**5c**, R = Cl	**6c**	82
4	O	CH_3		**5d**, R = Br	**6d**	83
5	O	CH_3		**5e**, R = OCH_3	**6e**	70
6	O	CH_3		**5f**	**6f**	65
7	O	CH_3		**5g**	**6g**	73
8	O	CH_3		**5h**	**6h**	51
9	O	CH_3		**5i**	**6i**	77
10[b]	O	CH_3	*c*-Hex	**5j**	**6j**	57
11	O	Et	Ph	**5k**	**6k**	73
12[c]	NPMP	H		**8a**, R = H	**9a**	68
13[c]	NPMP	H		**8b**, R = Br	**9b**	69

[a] Isolated yield after column chromatography. See Supporting Information for full experimental details. [b] Reaction performed with 2 equiv of allylboronic acid pinacol ester for 24 h. [c] Reaction performed with 20 mol % KO*t*-Bu and no $B(OH)_3$ for 12 h.

with transmetalation to form a *nucleophilic* allyliridium(I) complex that rapidly isomerized to scramble the deuterium label (**12a** and **12b**).[11] Both allyliridium(I) isomers reacted with acetophenone, generating the observed mixture of products. Alternative mechanisms, wherein the iridium catalyst functions as a Lewis acid, would be regiospecific and generate only product **11b**.[12] Reactions performed using the deuterated substrate **10** under the optimized conditions with $B(OH)_3$ also resulted in a 1:1 mixture of **11a** and **11b**. The recovered allylboronic ester did not isomerize during the course of the reactions with and without $B(OH)_3$.

We have refined our working hypothesis for the mechanism for the reaction (Scheme 3) based on our mechanistic

Scheme 3. Plausible Mechanism for Iridium-Catalyzed Allylation Reaction



experiments. $[Ir(cod)Cl]_2$ is a precatalyst and reacts with alkoxide in solution to afford an iridium(I) alkoxide **13**. Control experiments with $[Ir(cod)OMe]_2$ confirm that iridium(I) alkoxide complexes are viable reaction intermediates. Under standard reaction conditions for allylation of acetophenone (Table 2, entry 1), use of $[Ir(cod)OMe]_2$ as a catalyst afforded 77% yield. Subsequent transmetalation affords allyliridium(I) complexes **14a** and **14b**.[13] The allyliridium(I) complex, activated by the diene ligand, reacts with the electrophile to afford a new iridium alkoxide (**3**). The characteristics of diene ligand that activate the complex are under investigation. Transmetalation of iridium alkoxide **3** regenerates the catalyst, completing the catalytic cycle.

We have demonstrated that diene-ligated iridium(I) complexes catalyze allylation reactions of ketones and imines. A variety of ketones, including aromatic, heteroaromatic, and aliphatic ketones, afford tertiary homoallylic alcohols in good yields. Mechanistic experiments are consistent with formation of a nucleophilic allyliridium complex as a key catalytic intermediate. Future studies will include the development of enantioselective catalysts for this transformation.

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Supporting Information Available: Experimental details and spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802598C

(9) See Supporting Information for details. KO*t*-Bu and $B(OH)_3$ may facilitate the transmetalation event. Studies to elucidate the role of additives are ongoing. (a) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687–7691. (b) Zhao, P.; Incarbito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 1876–1877.

(10) Three-centered oxidative addition into aryl halide bonds by Ir(I): Mureinik, R. J.; Weitzberg, M.; Blum, J. *Inorg. Chem.* **1979**, *18*, 915–918.

(11) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4978–4983.

(12) (a) See ref 3. (b) Rauniya, V.; Zhai, H.; Hall, D. *J. Am. Chem. Soc.* **2008**, *130*, 8481–8490.

(13) Ir alkoxide complexes: (a) Rees, W. M.; Churchill, M. R.; Fettinger, J. C.; Atwood, J. D. *Organometallics* **1985**, *4*, 2179–2185. (b) Zhao, J.; Hesslink, H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 7220–7227.