

Hydroxoiridium - Catalyzed sp^3 C–H Alkylation of Indoline Derivatives with Terminal Alkenes

Ikumi Nakamura, Daisuke Yamauchi, Takahiro Nishimura

Citation	Asian Journal of Organic Chemistry, 7(7); 1347-1350
Issue Date	2018-07
Type	Journal Article
Textversion	author
Supporting Information	Supporting Information is available at https://doi.org/10.1002/ajoc.201800189 .
Rights	This is the peer reviewed version of the following article: Asian Journal of Organic Chemistry, Vol.7 Issu.7, pp.1347-1350., which has been published in final form at https://doi.org/10.1002/ajoc.201800189 . This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.
DOI	10.1002/ajoc.201800189

Self-Archiving by Author(s)
Placed on: Osaka City University

Hydroxoiridium-Catalyzed sp^3 C–H Alkylation of Indoline Derivatives with Terminal Alkenes

Ikumi Nakamura,^[a] Daisuke Yamauchi,^[b] and Takahiro Nishimura*^[a]

[a] I. Nakamura, Prof. Dr. T. Nishimura (0000-0002-7032-8613)
Department of Chemistry, Graduate School of Science
Osaka City University, Sumiyoshi-ku, Osaka 558-8585 (Japan)
E-mail: tnishi@sci.osaka-cu.ac.jp

[b] D. Yamauchi
Department of Chemistry, Graduate School of Science
Kyoto University, Sakyo, Kyoto 606-8502 (Japan)

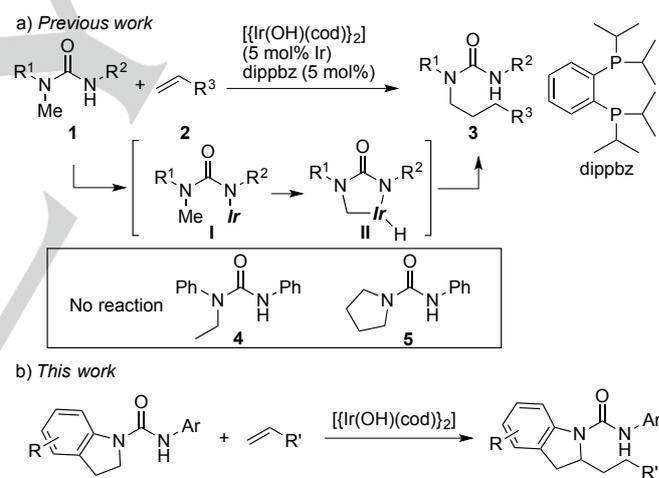
Supporting information for this article is given via a link at the end of the document.

Abstract: Direct alkylation of a secondary sp^3 C–H bond of indoline derivatives having a urea moiety with terminal alkenes proceeded in the presence of a hydroxoiridium/1,5-cyclooctadiene catalyst, which would generate an amidoiridium intermediate by the reaction with an urea N–H moiety of the indolines, giving the linear addition products in high yields.

Direct C–H alkylation reaction with unsaturated bonds is one of the most useful and attractive methods realizing highly atom-efficient C–C bond formations in synthetic organic chemistry.^[1] The sp^3 C–H bond adjacent to nitrogen is reactive towards transition metal catalysis, and the selective alkylation has been developed by using a variety of early and late transition metal catalysts.^[2–7] In particular, directed C–H activation has played an important role in such transformations using late transition metals. For example, Ru-catalyzed alkylations of the sp^3 C–H bond of 2-(*N*-alkylamino)pyridines with alkenes were reported by Jun^[5a] and Murali,^[5b] independently. Shibata and co-workers reported enantioselective sp^3 C–H bond activation of *N*-2-(alkylamino)pyridines catalyzed by cationic iridium/chiral bisphosphine complexes.^[6b,c,e] Very recently, Tran and Yu reported Ir-catalyzed C–H alkylation of cyclic amines substituted with a thiocarbonyl group.^[6f] In this context, we recently reported direct C–H alkylation of an aminomethyl group of ureas **1** with terminal alkenes catalyzed by a hydroxoiridium/phosphine complex (Scheme 1a).^[8] The reaction proceeded via amidoiridium species **I** to give the linear addition products **3**. Unfortunately, however, the catalytic system can not be applied to the alkylation of a secondary C–H bond of the aminoalkyl group included in compound **4** or **5**. The deuterium-labeling experiments proved that the C–H activation does not occur. During our efforts to develop the direct C–H alkylation,^[6g,8] we found that indoline derivatives having a urea moiety are good substrates for the secondary sp^3 C–H alkylation (Scheme 1b). Here we report that the direct alkylation of secondary C–H bonds of indoline derivatives with terminal alkenes is catalyzed by a hydroxoiridium complex coordinated with 1,5-cyclooctadiene.

Treatment of *N*-phenylindoline-1-carboxamide (**1a**) with 4-methoxystyrene (**2a**) in the presence of $[\{\text{Ir}(\text{OH})(\text{cod})\}_2]$ (5 mol% of Ir, cod = 1,5-cyclooctadiene) in toluene at 60 °C for 20 h gave the hydroalkylation product **3aa** in 99% yield (Table 1, entry 1). The sp^3 C–H alkylation occurred at the 2-position of the indoline ring with the high linear selectivity (over 98%), and an sp^2 C–H bond at the 7-position was inert. The reaction in 1,4-dioxane

proceeded as well (entry 2), but THF, DMF, and 1,2-dichloroethane were less effective as solvents (entries 3–5). Although a chloroiridium complex $[\{\text{IrCl}(\text{cod})\}_2]$ had no catalytic activity (entry 6), the combined use of $[\{\text{IrCl}(\text{cod})\}_2]$ and bases such as K_2CO_3 and K_3PO_4 promoted the present reaction (entries 7 and 8). The presence of binap (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) as a ligand completely inhibited the reaction (entry 9). The hydroxorhodium complex displayed no catalytic activity (entry 10).



Scheme 1. Ir-catalyzed sp^3 C–H alkylation of ureas.

Table 1. Reaction optimization of Ir-catalyzed C–H alkylation of indoline.^[a]

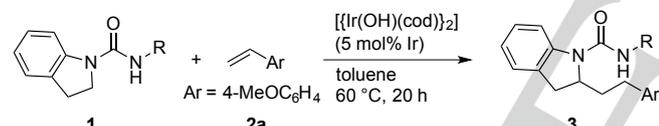
Entry	Catalyst	Solvent	Yield [%] ^[b]
1	$[\{\text{Ir}(\text{OH})(\text{cod})\}_2]$	Toluene	99
2	$[\{\text{Ir}(\text{OH})(\text{cod})\}_2]$	1,4-Dioxane	89
3	$[\{\text{Ir}(\text{OH})(\text{cod})\}_2]$	THF	58
4	$[\{\text{Ir}(\text{OH})(\text{cod})\}_2]$	1,2-Dichloroethane	12
5	$[\{\text{Ir}(\text{OH})(\text{cod})\}_2]$	DMF	12

6	[[IrCl(cod)] ₂]	Toluene	0
7 ^[c]	[[IrCl(cod)] ₂]	Toluene	69
8 ^[d]	[[IrCl(cod)] ₂]	Toluene	37
9 ^[e]	[[Ir(OH)(cod)] ₂]	Toluene	0
10	[[Rh(OH)(cod)] ₂]	Toluene	0

[a] Reaction conditions: **1** (0.10 mmol), **2a** (0.15 mmol), and [[Ir(OH)(cod)]₂] (5 mol% of Ir) in solvent (0.10 mL) at 60 °C for 20 h. [b] Determined by ¹H NMR. [c] With K₂CO₃ (10 mol%). [d] With K₃PO₄ (10 mol%). [e] With 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (binap, 6 mol%).

The reactivity of the indoline derivatives was found to be greatly influenced by the substituents R on the urea nitrogen (Table 2). The high reactivity comparable to **1a** (entry 1) was observed for *N*-(4-(trifluoromethyl)phenyl)indoline-1-carboxamide (**1b**) giving **3ba** quantitatively (entry 2). In contrast, an electron-donating MeO group on the phenyl of **1c** decreased its reactivity (entry 3). Indoline **1d** having a 3,4,5-trifluorophenyl group had low solubility resulting in a low yield of the alkylation product **3da** (entry 4).^[9] Neither indoline **1e** having *ortho*-(trifluoromethyl)phenyl nor **1f** substituted with 3,5-bis(trifluoromethyl)phenyl reacted with **2a** probably due to their steric bulkiness (entries 5 and 6). Although the alkylation of indoline **1g** having a benzyl group did not proceed at all (entry 7), **1h** substituted with an electron-withdrawing 2,2,2-trifluoroethyl group showed a moderate reactivity giving **3ha** in 28% yield (entry 8).

Table 2. Effect of substituents of ureas.^[a]



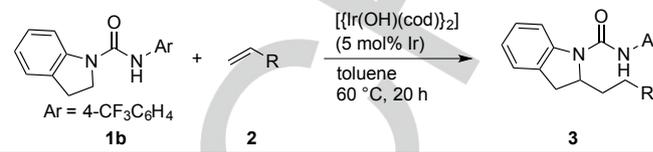
Entry	R	3	Yield [%] ^[b]
1	Ph (1a)	3aa	99 (98:2)
2	4-CF ₃ C ₆ H ₄ (1b)	3ba	99 (98:2)
3	4-MeOC ₆ H ₄ (1c)	3ca	39 (95:5)
4	3,4,5-F ₃ C ₆ H ₂ (1d)	3da	28 (95:5)
5	2-CF ₃ C ₆ H ₄ (1e)	3ea	0
6	3,5-(CF ₃) ₂ C ₆ H ₃ (1f)	3fa	0
7	PhCH ₂ (1g)	3ga	0
8	CF ₃ CH ₂ (1h)	3ha	28 (>99:1)

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), and [[Ir(OH)(cod)]₂] (5 mol% of Ir) in toluene (0.10 mL) at 60 °C for 20 h. [b] Isolated yield.

Table 3 summarizes the results obtained for the hydroalkylation of several terminal alkenes **2** with *N*-(4-(trifluoromethyl)phenyl)indoline-1-carboxamide (**1b**). Styrene (**2b**) and its derivatives **2c–f** are good substrates to give the corresponding alkylation products **3bb–bf** in high yields (entries 1–5). Allylbenzene (**2g**) and 1-hexene (**2h**) also reacted with **1b** to give **3bg** and **3bh**, respectively, in good yields (entries 6 and 7). The reactions of vinyl ethers **2i–k** gave also linear addition

products **3bi–bk** in good yields (entries 8–10), in contrast to the branch-selectivity observed in the reactions of sp² C–H alkylation with vinyl ethers.^[10] Electron-deficient alkenes such as methyl vinyl ketone and diethyl vinylphosphonate, and internal alkenes, (*E*)-2-octene and cyclooctene, were not applicable to the present reaction.

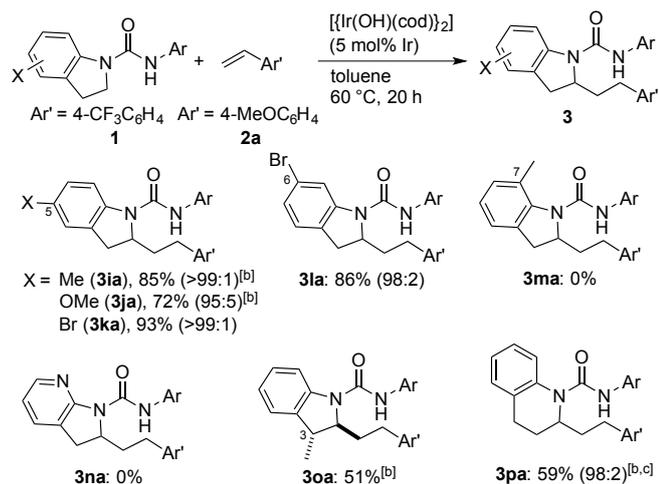
Table 3. Scope of alkenes.^[a]



Entry	R	3	Yield [%] ^[b]
1	Ph (2b)	3bb	89 (98:2)
2	4-MeC ₆ H ₄ (2c)	3bc	91 (98:2)
3	4-ClC ₆ H ₄ (2d)	3bd	92 (98:2)
4	3-ClC ₆ H ₄ (2e)	3be	92 (98:2)
5	2-ClC ₆ H ₄ (2f)	3bf	91 (98:2)
6	PhCH ₂ (2g)	3bg	77 (>99:1)
7	<i>n</i> -Bu (2h)	3bh	85 (>99:1)
8	<i>O-n</i> -Bu (2i)	3bi	82 (95:5)
9	<i>O-t</i> -Bu (2j)	3bj	64 (>99:1)
10	OPh (2k)	3bk	91 (98:2)

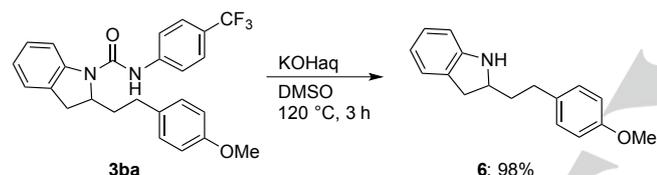
[a] Reaction conditions: **1b** (0.20 mmol), **2** (0.60 mmol), and [[Ir(OH)(cod)]₂] (5 mol% of Ir) in toluene (0.20 mL) at 60 °C for 20 h. [b] Isolated yield.

As shown in Scheme 2, several substituted indoline **1** reacted with *para*-methoxystyrene (**2a**) to give the alkylation products. Functional groups (X) at the 5 and 6 positions of the aromatic rings of the indolines **1i–l** were tolerated in the reaction, giving high yields of adducts **3ia–la**.^[11] In contrast, indoline **1m** substituted with a 7-methyl group or 7-azaindoline **1n** displayed no reactivity. A high diastereoselectivity was observed for the reaction of indoline **1o** having a methyl group at the 3 position, giving *trans*-**3oa** in 51% yield. Tetrahydroquinoline **1p** also reacted with **2a** to give **3pa** in 59% yield in the presence of 10 mol% of Ir.



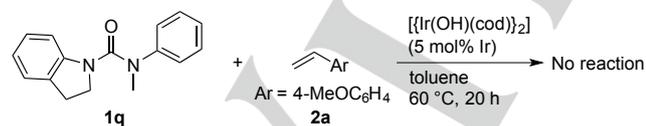
Scheme 2. Ir-catalyzed sp^3 C–H alkylation of indolines.^[a] [a] Reaction conditions: **1** (0.20 mmol), **2a** (0.60 mmol), and $[\text{Ir}(\text{OH})(\text{cod})_2]$ (5 mol% of Ir) in toluene (0.20 mL) at 60 °C for 20 h. [b] In xylene (0.2 mL). [c] 10 mol% of Ir was used.

A urea moiety of **3ba** obtained here was readily removed by basic hydrolysis, giving free indoline **6** in high yield (Scheme 3).



Scheme 3. Transformation into a free indoline derivative.

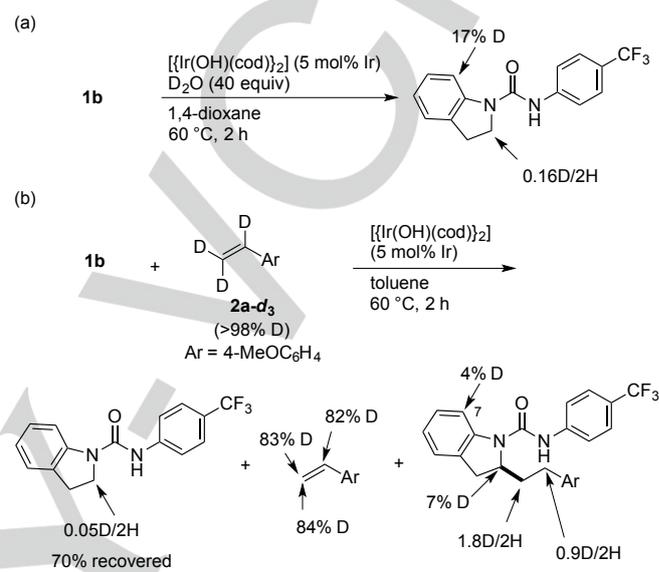
Mechanistic insight into the catalytic cycle was provided by the experiments shown in Schemes 4 and 5. Tetrasubstituted urea **1q** was inert under the present reaction conditions (Scheme 4). As described before, the reaction was efficiently catalyzed by the hydroxoiridium complex, and bases were essential for promoting the reaction by using the chloroiridium (Table 1). These results indicate that the formation of the amidoiridium species is essential for the efficient C–H activation.



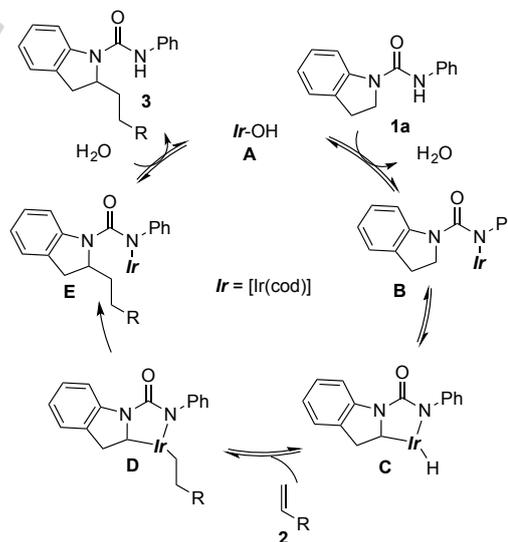
Scheme 4. Reaction of tetrasubstituted urea.

The results of deuterium-labeling experiments was shown in Scheme 5. Treatment of **1b** with D_2O (40 equiv) in the presence of $[\text{Ir}(\text{OH})(\text{cod})_2]$ in 1,4-dioxane at 60 °C for 2 h gave deuterated **1b** containing deuterium at the 2 position of a methylene group (0.16D/2H) as well as at the 7-position (17% D, Scheme 5a).^[12] ^2H NMR spectroscopic analysis also supported the H/D exchange. As shown in Scheme 5b, indoline **1b** recovered after the reaction with deuterated alkene **2a-d₃** in

toluene at 60 °C for 2 h displayed partial H/D exchange at the 2 position (0.05D/2H). A partial H/D exchange of recovered alkene **2a-d₃** was also observed. These results indicate that the C–H activation and the alkene insertion are reversible. The deuterium incorporation at the 7 position of product **3ba** was separately confirmed by the reaction of **3ba** with **2a-d₃**: a 11% deuterium incorporation was observed in the reaction of **3ba** with **2a-d₃** (1.5 equiv) in the presence of the Ir catalyst at 60 °C for 2 h.



Scheme 5. Deuterium-labeling experiments.



Scheme 6. Proposed catalytic cycle.

Based on the deuterium-labeling experiments, the catalytic cycle proposed for the present C–H alkylation of indoline **1a** with alkene **2** is illustrated in Scheme 6. The reaction of indoline **1a** with the hydroxoiridium **A** forms amidoiridium **B**. Oxidative addition of the methylene C–H bond to Ir forms alkyl(hydrido)iridium(III) species **C**.^[14] Linear-selective alkene

insertion into the Ir–H bond forms **D**, and irreversible reductive elimination gives amidoiridium **E**. Hydrolysis of **E** leading to **3** regenerates species **A**.

In summary, we have developed direct alkylation of a secondary sp³ C–H bond of indoline derivatives with terminal alkenes. The reaction was efficiently catalyzed by a hydroxoiridium/1,5-cyclooctadiene complex. The methylene group adjacent to the nitrogen atom of the indolines was selectively alkylated with the terminal alkenes, giving the linear addition products in an atom-economical manner.

Experimental Section

Indoline **1** (0.20 mmol), alkene **2** (for solid compounds, 0.60 mmol), and [IrCl(cod)]₂ (3.2 mg, 0.0050 mmol, 5 mol% of Ir) were placed in a Schlenk tube under N₂. Toluene (0.20 mL) and alkene **2** (for liquid compounds, 0.60 mmol) were added successively. The Schlenk tube was capped with a glass stopper and heated at 60 °C for 20 h with stirring. The solvent was removed on a rotary evaporator, and the residue was subjected to preparative TLC on silica gel eluted with EtOAc/hexane (1:4) to give **3**.

Acknowledgements ((optional))

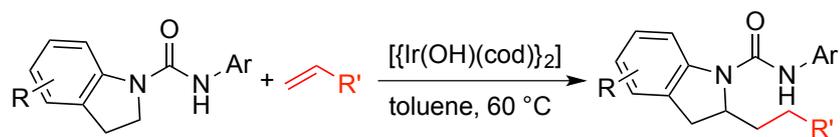
This work was supported by JSPS KAKENHI Grant No. 15H03810.

Keywords: iridium • indoline • alkenes • C–H activation • synthetic methods

References:

- [1] For selected reviews, see: a) F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, *35*, 826; b) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731; c) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077; d) K. Godula, D. Sames, *Science* **2006**, *312*, 67; e) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; *Angew. Chem.* **2009**, *121*, 5196; f) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; g) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; h) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315; i) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726; *Angew. Chem.* **2013**, *125*, 11942; j) Q.-Z. Zheng, N. Jiao, *Tetrahedron Lett.* **2014**, *55*, 1121; k) N. Yoshikai, *Bull. Chem. Soc. Jpn.* **2014**, *87*, 843; l) L. Yang, H. Huang, *Chem. Rev.* **2015**, *115*, 3468; m) Z. Dong, Z. Ren, S. J. Thompson, Y. Xu, G. Dong, *Chem. Rev.* **2017**, *117*, 9333.
- [2] For selected reviews of sp³ C–H functionalization, see: a) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417; b) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654; c) O. Baudoin, *Chem. Soc. Rev.* **2011**, *40*, 4902; d) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74; *Angew. Chem.* **2014**, *126*, 76; e) X. Yang, G. Shan, L. Wang, Y. Rao, *Tetrahedron Lett.* **2016**, *57*, 819.
- [3] For selected reviews of sp³ C–H functionalization adjacent to a nitrogen atom, see: a) P. Beak, W. J. Zajdel, D. B. Reitz, *Chem. Rev.* **1984**, *84*, 471; b) K. R. Campos, *Chem. Soc. Rev.* **2007**, *36*, 1069; c) E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel, B. U. W. Maes, *Chem. Eur. J.* **2012**, *18*, 10092.
- [4] For selected reviews of early transition metal-catalyzed hydro-aminoalkylation of alkenes, see: a) P. W. Roesky, *Angew. Chem. Int. Ed.* **2009**, *48*, 4892; *Angew. Chem.* **2009**, *121*, 4988; b) E. Chong, P. Garcia, L. L. Schafer, *Synthesis* **2014**, *46*, 2884; c) S. A. Ryken, L. L. Schafer, *Acc. Chem. Res.* **2015**, *48*, 2576. For selected recent examples, see: d) J. Dörfler, B. Bytyqi, S. Hüller, N. M. Mann, C. Brahms, M. Schmidtman, S. Doye, *Adv. Synth. Catal.* **2015**, *357*, 2265; e) J. Dörfler, T. Preuß, C. Brahms, D. Scheuer, S. Doye, *Dalton Trans.* **2015**, *44*, 12149; f) A. E. Nako, J. Oyamada, M. Nishiura, Z. Hou, *Chem. Sci.* **2016**, *7*, 6429.
- [5] For examples of ruthenium-catalyzed sp³ C–H alkylation, see: a) C.-H. Jun, D.-C. Hwang, S.-J. Na, *Chem. Commun.* **1998**, 1405; b) N. Chatani, T. Asaumi, S. Yorimitsu, T. Ikeda, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **2001**, *123*, 10935; c) S. D. Bergman, T. E. Storr, H. Prokopcová, K. Aelvoet, G. Diels, L. Meerpoel, B. U. W. Maes, *Chem. Eur. J.* **2012**, *18*, 10393; d) M. Schinkel, L. Wang, K. Bielefeld, L. Ackermann, *Org. Lett.* **2014**, *16*, 1876; e) A. A. Kulago, B. F. Van Steijvoort, E. A. Mitchell, L. Meerpoel, B. U. W. Maes, *Adv. Synth. Catal.* **2014**, *356*, 1610.
- [6] For examples of iridium-catalyzed sp³ C–H alkylation, see: a) B. DeBoef, S. J. Pastine, D. Sames, *J. Am. Chem. Soc.* **2004**, *126*, 6556; b) S. Pan, K. Endo, T. Shibata, *Org. Lett.* **2011**, *13*, 4692; c) S. Pan, Y. Matsuo, K. Endo, T. Shibata, *Tetrahedron* **2012**, *68*, 9009; d) G. Lahm, T. Opatz, *Org. Lett.* **2014**, *16*, 4201; e) Y. Tahara, M. Michino, M. Ito, K. S. Kanyiva, T. Shibata, *Chem. Commun.* **2015**, *51*, 16660; f) A. T. Tran, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 10530; *Angew. Chem.* **2017**, *129*, 10666; g) M. Nagai, M. Nagamoto, T. Nishimura, H. Yorimitsu, *Chem. Lett.* **2017**, *46*, 1176.
- [7] For selected examples of sp³ C–H alkylation, adjacent to nitrogen atom, with unsaturated C–C bonds, see: Rh; a) Y. Ishii, N. Chatani, F. Kakiuchi, S. Murai, *Organometallics* **1997**, *16*, 3615; Ir; b) S. Sakaguchi, T. Kudo, Y. Ishii, *Angew. Chem. Int. Ed.* **2001**, *40*, 2534; *Angew. Chem.* **2001**, *113*, 2602; c) K. Tsuchikama, M. Kasagawa, K. Endo, T. Shibata, *Org. Lett.* **2009**, *11*, 1821; d) T. Shibata, H. Hirashima, M. Kasagawa, K. Tsuchikama, K. Endo, *Synlett* **2011**, 2171.
- [8] D. Yamauchi, T. Nishimura, H. Yorimitsu, *Angew. Chem. Int. Ed.* **2017**, *56*, 7200; *Angew. Chem.* **2017**, *129*, 7306.
- [9] A full conversion of **1d** into **3da** (87% yield) was observed in the reaction in 1,4-dioxane.
- [10] a) Y. Ebe, T. Nishimura, *J. Am. Chem. Soc.* **2015**, *137*, 5899; b) M. Hatano, Y. Ebe, T. Nishimura, H. Yorimitsu, *J. Am. Chem. Soc.* **2016**, *138*, 4010; c) D. Yamauchi, T. Nishimura, H. Yorimitsu, *Chem. Commun.* **2017**, *53*, 2760.
- [11] The reaction in toluene slightly gave low yields of the corresponding products.
- [12] Treatment of **2b** with D₂O in toluene showed a trace of deuterium incorporation.
- [13] M. Hatano, T. Nishimura, H. Yorimitsu, *Org. Lett.* **2016**, *18*, 3674.
- [14] Recent DFT calculations of Ir-catalyzed branch-selective hydroarylation of terminal alkenes suggest the pathway including the insertion of the alkene into an Ir–carbon bond. sa) G. Huang, P. Liu, *ACS Catal.* **2016**, *6*, 809; b) M. Zhang, G. Huang, *Dalton Trans.* **2016**, *45*, 3552.

Entry for the Table of Contents



A hydroxoiridium complex catalyzed direct alkylation of a secondary sp^3 C–H bond of indoline derivatives with terminal alkenes. The reaction proceeded via an amidoiridium intermediate by the reaction with an urea N–H moiety of the indolines and the hydroxoiridium. The methylene group adjacent to the nitrogen atom of the indolines was selectively alkylated with the terminal alkenes, giving the linear addition products.