Communication

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Jiyu Kim, Sung-Woo Park, Mu-Hyun Baik, and Sukbok Chang

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Complete Switch of Selectivity in the C–H Alkenylation and Hydroarylation Catalyzed by Iridium: The Role of Directing Groups

Jiyu Kim,[†,‡] Sung-Woo Park,*[,‡,†] Mu-Hyun Baik,[‡,†] and Sukbok Chang*[,‡,†]

[†]Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 305-701, Korea

[‡]Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon 305-701, Korea

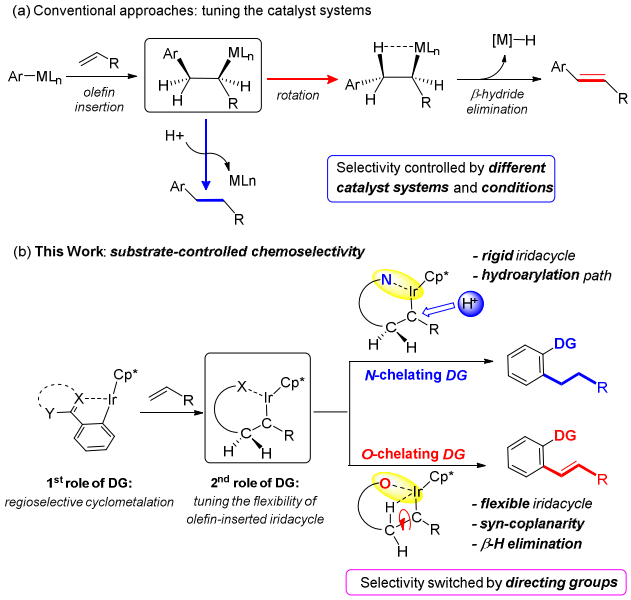
Supporting Information Placeholder

ABSTRACT: A complete switch in the Cp*Ir(III)-catalyzed paths between C–H olefination and hydroarylation was found to be crucially dependent on the type of directing groups. This dichotomy in product distribution was correlated to the efficiency in attaining *syn*-coplanarity of olefin-inserted 7-membered iridacycles. Theoretical studies support our hypothesis that the degree of flexibility of this key intermediate modulates the β-H elimination, which ultimately affords the observed chemoselectivity.

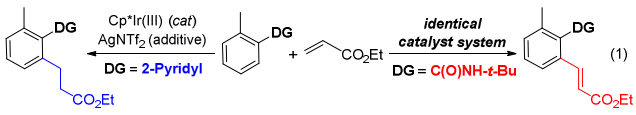
Metal-catalyzed carbon-carbon bond formation has played a pivotal role in synthetic chemistry.[1] For instance, olefination of aryl halides (Mizoroki–Heck reaction) has become one of the most efficient routes to vinylarenes.[2] More recently, direct C–H alkenylation of arenes was actively investigated as a straightforward approach to the same products (Scheme 1a).[3] In this process, a metal alkyl intermediate generated *in situ* upon the migratory insertion of a metal aryl species into alkenes, undergoes β-hydride elimination to give olefinated products.[1c,4] However, the change of catalyst and/or reaction conditions can alter the reaction pathway significantly; for instance, giving rise to alkylated compounds upon protonolysis.[5] Several catalytic systems are known for the hydroarylation of olefins (Murai-type reaction) to give alkylarene products selectively.[6]

Chelating groups play a central role in the metal-catalyzed direct C–H functionalization. For example, they give access to metallacyclic intermediates that are thought to be the reactive intermediates.[7] While directing groups often affect reaction efficiency, in addition to determining regioselectivity, the coordination ability of these pendants often affects the catalytic performance.[8] Sanford et al. described the perturbation of the kinetics of catalysis by structurally and/or electronically modifying the directing groups.[9] Their ability to dramatically *change the chemoselective pathway by the same catalyst system* has not been described to the best of our knowledge.[10] We herein present a novel example where an identical catalyst system switches the product distribution between C–H olefination and hydroarylation depending on the type of directing groups (Scheme 1b). Computational studies were also conducted to support our working hypothesis that the structural flexibility of the key iridacycle intermediate is central to attaining a *syn*-coplanar conformation, which in turn determines the efficiency of the β-hydride elimination.

Scheme 1. Arene C–H Alkenylation and Alkylation



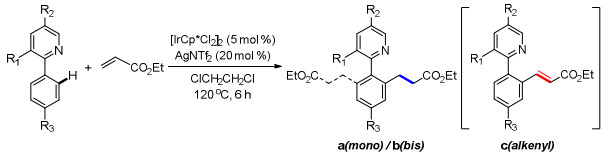
A distinct dichotomy in product distribution was initially observed in the Cp*Ir(III)-catalyzed reaction of ethyl acrylate with arene substrates bearing two different types of directing groups (eq 1): whereas a hydroarylated product was formed almost exclusively in good yield with the pyridyl chelation, an olefinated compound was obtained with high selectivity when an amide directing group was present (see the Supporting Information for details). This result clearly indicated that the directing groups can act as switches that enable either C–H olefination or hydroarylation by the same catalyst system. Significantly, this outcome was distinctive for the Cp*Ir(III) catalyst only in regard to the reaction efficiency and product selectivity. Similar systems, such as $[Ru(p\text{-cymene})Cl_2]_2$ or $[Cp^*RhCl_2]_2$ that are known catalysts for the highly facile C–H functionalization do not show the same behavior, however.[11] Instead, they provided either a mixture of two products with moderate selectivity or showed poor activity. A Cp*-modified catalyst, such as $[IrCl_2(\eta^5\text{-}C_5Me_4H)]_2$, displayed lower activity than $[Cp^*IrCl_2]_2$ (see the Supporting Information for details).



Generality of this dramatic effect of directing groups on the reaction path was examined next. First, a range of 2-phenylpyridine derivatives was found to undergo hydroarylation with high selectivity (Table 1). In this reaction, double hydroarylation took place to different extents, but the formation of olefinated compounds was almost negligible, especially with substrates bearing electron-neutral or donating substituents. However, when a nitro group was placed at the 2-pyridyl moiety, the selectivity was slightly decreased (entries 7–8), but still favoring the hydroarylation. No branched hydroarylated isomers were observed under the conditions tested.

A totally different outcome of selectivity was observed in the reaction of benzamides with ethyl acrylate (2 equiv) using the same Cp*Ir catalyst system (Table 2). In this case, olefinated products were formed almost exclusively (>98:2), and this excellent selectivity was maintained irrespective of the electronic variation in benzamide substrates.[12] Analysis of the crude reaction mixture revealed that 1 equiv of ethyl propionate was formed simultaneously.

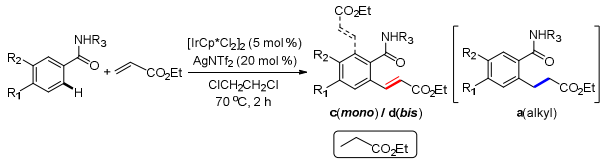
Table 1. C–H Hydroarylation with 2-Pyridyl Group[a]



Entry	R	Products (%)[b]		(a+b / c)[c]
1	R_1=H, R_2=H, R_3=H	**1a**: 47	**1b**: 20	>99:1
2	R_1=Me, R_2=H, R_3=H	**2a**: 58	**2b**: <1	>99:1
3	R_1=H, R_2=H, R_3=OMe	**3a**: 16	**3b**: 48	>99:1
4	R_1=H, R_2=H, R_3=Cl	**4a**: 45	**4b**: 10	>99:1
5	R_1=H, R_2=H, R_3=CF_3	**5a**: 29	**5b**: 7	>99:1
6	R_1=H, R_2=H, R_3=CHO	**6a**: 48	**6b**: 30	99:1
7	R_1=NO_2, R_2=H, R_3=H	**7a**: 33	**7b**: <1	91:9
8	R_1=H, R_2=NO_2, R_3=H	**8a**: 32	**8b**: <1	97:3

[a]Substrate (0.2 mmol) and ethyl arylate (1.2 equiv) in 1,2-dichloroethane. [b]Isolated yield. [c] Ratio of ***alkyl*(*mono*+*bis*):*alkenyl*** *products*, determined by ^{1}H-NMR of the crude reaction mixture.

Table 2. C–H Alkenylation with Amide Group[a]

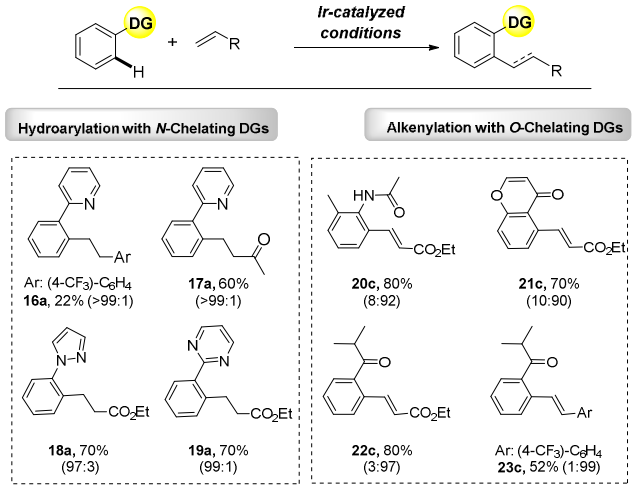


Entry	R	Products (%)[b]		(c+d / a)[c]
1	R_1=H, R_2=H, R_3=*t*-Bu	**9c**: 80	**9d**: 8	>99:1
2	R_1=H, R_2=Me, R_3=*t*-Bu	**10c**: 80	**10d**: 5	>99:1
3	R_1=OMe, R_2=H, R_3=*t*-Bu	**11c**: 57	**11d**: <1	>99:1
4	R_1=CF_3, R_2=H, R_3=*t*-Bu	**12c**: 25	**12d**: <1	>99:1
5	R_1=CH_2OH, R_2=H, R_3=*t*-Bu	**13c**: 77	**13d**: <1	>99:1
6	R_1=H, R_2=H, R_3=Me	**14c**: 94	**14d**: <1	>99:1
7	R_1=H, R_2=H, R_3=Adamantyl	**15c**: 65	**15d**: <1	98:2

[a]Substrate (0.2 mmol) and ethyl arylate (2 equiv) in 1,2-dichloroethane. [b]Isolated yield. [c] Ratio of ***alkenyl(mono*+*bis*):*alkyl*** *products*, determined by the ^{1}H-NMR of the crude reaction mixture.

We then wondered whether other directing groups and different olefins could also reproduce this notable selectivity switch. The Ir-catalyzed hydroarylation was highly favored over olefination in reaction of 2-phenylpyridine with a styrene derivative and methyl vinyl ketone, albeit in low to moderate yields (**16a** and **17a**, respectively). Pyrazole and pyrimidine were also found to be effective chelators leading to hydroarylated products with high selectivity (**18a** and **19a**, respectively). On the other hand, a high level of selectivity to deliver olefinated products was observed with substrates bearing oxygen chelators such as anilide (**20c**). Notably, this selectivity pattern was maintained with substrates bearing ketone chelators.[1b,1c,13] For instance, chromone (**21c**: X-ray structure shown in SI) and isobutyrophenone (**22c**) were selectively olefinated. In addition, an olefination path was predominant in reaction of a ketone substrate with a styrene derivative (**23c**). The observed high selectivity from both cyclic and acyclic ketone substrates (**21c** vs **22c**) implies that the cyclic nature of directing group is not required for the selectivity.

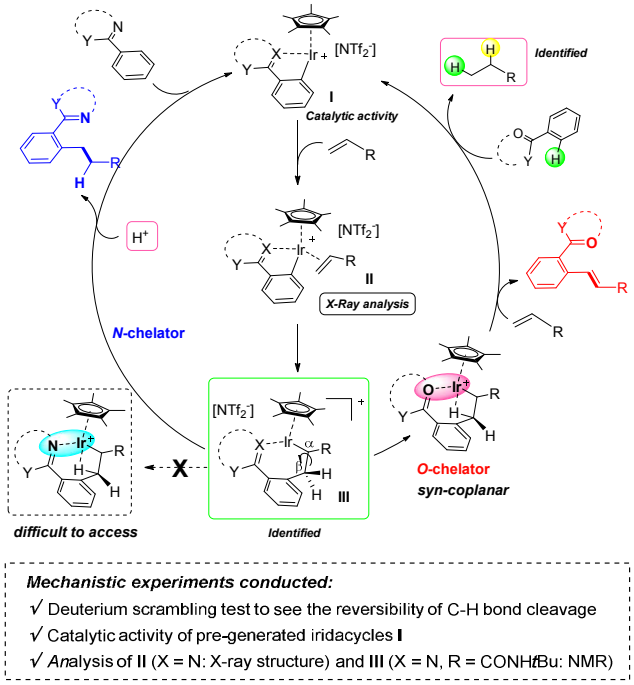
Scheme 2. Selectivity on Various Directing Groups[a,b]



[a] See the Supporting Information for detailed reaction conditions: isolated yields. [b]Ratio of hydroarylated/olefinated products in the crude reaction mixture determined by ^{1}H-NMR analysis.

The most plausible mechanism that gives access to the C–H hydroarylation and olefination pathways depending on the directing group is depicted in Scheme 3. Both reactions share identical steps at the beginning: C–H bond cleavage gives **I**, followed by olefin coordination (**II**) and migratory insertion to an alkene leading to the 7-membered iridacycle **III**.[4] The initial C–H bond cleavage step appeared irreversible in H/D exchange studies, both in hydroarylation of 2-phenylpyridine and alkenylation of *N*-*t*-butylbenzamide (see SI). Iridacycles **I** obtained from each type of substrates catalyzed the corresponding hydroarylation (X = N) and olefination (X = O) reaction. The olefin-coordinated iridacycle **II** (X = N, R = Ph) was isolated and its structure was characterized by X-ray crystallography (see SI). Significant deuterium incorporation (31%) was seen exclusively at the α-position relative to carbonyl of alkylated product when deuterated 2-phenylpyridine was reacted with ethyl acrylate. In the olefination of benzamides with 2 equiv of ethyl acrylate, 1 equiv of alkene worked as a sacrificial hydrogen acceptor[5e] as seen by the stoichiometric formation of ethyl propionate. In addition, an olefin-inserted 7-membered iridacycle **III** (X = N, R = CONH*t*-Bu) was characterized by NMR and HRMS analysis.

Scheme 3. Mechanistic Proposal

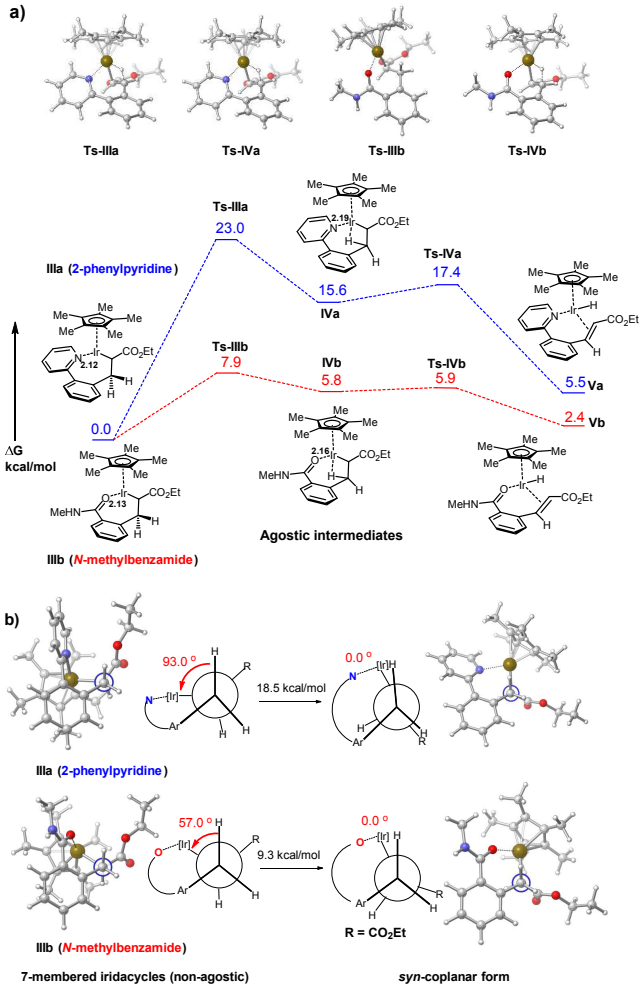


Density functional calculations supported our mechanistic proposal,[14] with computed reaction energy profile shown in Figure 1a: (*i*) The β-hydride elimination is slightly uphill by 5.5 and 2.4 kcal/mol from the iridacycles **III** for 2-phenylpyridine and *N*-methylbenzamide, respectively. (*ii*) The most difficult step is associated with the formation of a high energy intermediates **IVa** and **IVb**, each containing an agostic Ir–(β-CH) bond. (*iii*) β-Hydride elimination from the agostic intermediate is nearly barrierless.

On first sight, the transition state energy difference of 15.1 kcal/mol *vs.* the product energy difference of only 3.1 kcal/mol is puzzling, but these differences highlight the foundation of how the chemoselectivity is achieved: To allow β-hydride elimination, the iridacycle **III** must undergo significant structural change. And two features are key to discriminating the N- and O-donor ligands. First, the Ir(III) center presents a hard Lewis acidic binding site, which is a good match for the N-donor ligands that are hard Lewis bases. The resulting Ir(III)-N bonds are strong and robust leading to a relatively rigid iridacycle.[15] The O-donor ligands, however, are relatively soft Lewis bases and, as a result, the Ir(III)-O bonds are much more flexible. Second, the computed structures of the iridacycle reveal that there are significant structural differences, as illustrated in Figure 1b. The dihedral angle of Ir-C_α-C_β-H in the iridiacycle **IIIb** is 57.0° whereas it is 93.0° in **IIIa**. A *syn*-coplanar geometry, where this angle becomes 0°, is required to promote β-hydride elimination. Our calculations estimate that this flattening requires 9.3 and 18.5 kcal/mol, respectively. Thus, both the M-L bond characteristics and the iridacycle geometry allow **IIIb** to reach the key intermediate much more easily than **IIIa**.

In summary, the path of Cp*Ir(III)-catalyzed C–C bond formation was found to be controlled by directing groups on the chelating ligand. While *syn*-coplanarity of key 7-membered iridacycle intermediates can be attained readily with carbonyl directing groups eventually leading to olefinated products, strong nitrogen chelators favor the hydroarylation process. Theoretical studies strongly support our hypothesis on this mechanistic dichotomy and provide an intuitively comprehensible explanation for the chemoselectivity. The present study is a novel example that illuminates aspects of reaction control by directing groups to determine not only regioselectivity but also chemoselectivity in C–H functionalizations.

Figure 1. a) Energy profile of β-H elimination from **III** of 2-phenylpyridine and *N*-methylbenzamide. b) Relaxed PES scanning along the rotating torsional angle Ir-C_α-C_β-H from **III** to the artificial *syn*-coplanarity.



ASSOCIATED CONTENT

Supporting Information

Procedures and additional data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Authors

swpark908@kaist.ac.kr; sbchang@kaist.ac.kr

Notes

The authors declare no competing financial interest.

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(12) *N,N*-Dimethylbenzamide was also reacted efficiently with ethyl acrylate under the same conditions to give olefinated products selectively in good yield (see supporting information for details).

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(15) DFT calculations carried out to validate the coordination ability for each directing group (see supporting information for details).

Table of Contents