Iridium-Catalyzed Branch-Selective Hydroarylation of Vinyl Ethers via C−H Bond Activation

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S *Supporting Information*

ABSTRACT: Iridium-catalyzed hydroarylation of vinyl ethers via a directed C−H bond activation of aromatic compounds gave high yields of the corresponding addition products with high branch selectivity.

Transition-metal-catalyzed functionalization of aromatic rings via C−H activation has realized the step-economy synthesis of useful compounds in organic chemistry.[1] In particular, ortho-selective functionalization has been achieved by use of directing groups.[2] In 1986, Lewis and Smith reported the first catalytic ortho-ethylation of phenol with ethylene catalyzed by a Ru complex containing an ortho-metalated triphenyl phosphite linkage.[2a] Murai and co-workers reported the first general and efficient ortho-alkylation of aromatic ketones under Ru catalysis in 1993,[2b] and in the past few decades, many catalytic hydroarylation reactions of alkenes with the aromatic C−H bond have been developed. Most of the reports on transition-metal-catalyzed hydroarylation reactions via C−H activation have described the addition to alkenes with linear selectivity.[2b,3] On the other hand, several examples of the reaction of vinyl arenes under Co[4] and Ni catalysis[5] show the branch selectivity due to a stability of η^3-benzyl metal species.[6] Ru-catalyzed hydroarylation of styrene with N-methylaniline has also been reported to proceed with branch selectivity.[7] Recently, regiocontrolled hydroarylation reactions of alkenes catalyzed by Co or Ir catalysts were reported by Yoshikai,[8] Shibata,[9] and Bower.[10] Few reports, however, involve the branch-selective hydroarylation of non-styrene-type alkenes.[10] Development of the directed branch-selective alkene hydroarylation reaction is valuable toward the construction of enantioenriched benzylic stereocenters in an atom-economical manner. In this respect, the use of readily available vinyl ethers[11] in the branch-selective hydroarylation will provide one of the useful methodologies for the synthesis of chiral benzylic ethers.[12]

Recently, we reported the iridium-catalyzed annulation of aromatic imines with 1,3-dienes or alkynes via a directed C−H bond activation,[13] where a cationic iridium complex coordinated with 1,5-cyclooctadiene as a ligand undergoes the ortho-C−H activation to form an aryl hydridoiridium(III) species as a key intermediate.[13c] Here we report that the similar catalytic system is effective at catalyzing a branch-selective hydroarylation of vinyl ethers with aromatic compounds containing nitrogen directing groups. Preliminary results of the asymmetric variant of the reaction by use of a chiral diene ligand[14] are also described.

Kakiuchi and co-workers reported the Ru-catalyzed cross-coupling reaction via C−H bond activation of 2-phenylpyridine

derivatives with vinyl ethers leading to vinyl arenes.[15] On the other hand, the use of vinyl ethers in the hydroarylation has been limited to the intramolecular reaction under Rh catalysis. Successful intramolecular hydroarylation of aromatic imines having a vinyl ether moiety was reported by Bergman, Ellman and co-workers[16] Rh-catalyzed intermolecular hydroarylation of ethyl vinyl ether with benzophenone was reported by Brookhart and co-workers, where a linear selective reaction proceeded in low yield (10% yield).[17] In this context, we found that an Ir complex can catalyze intermolecular hydroarylation of vinyl ethers with high branch selectivity. Thus, treatment of 2-phenylpyridine (**1a**) with 1.5 equiv of n-butyl vinyl ether (**2a**) in the presence of $[IrCl(cod)]_2$ (5 mol % Ir, cod = 1,5-cyclooctadiene) and $NaBAr^F_4$ $[Ar^F = 3,5\text{-}(CF_3)_2C_6H_3]$ (10 mol %) in toluene at 80 °C for 12 h gave a 98% yield of branch-selective hydroarylation product **3aa** as well as a small amount of dialkylation product **4aa**, where the formation of other regioisomers was not detected (Table 1, entry 1). Catalytic reaction without $NaBAr^F_4$ gave no addition product (entry 2), and the use of $[IrCl(coe)_2]_2$ or $[RhCl(cod)]_2$ instead of $[IrCl(cod)]_2$ resulted in no formation of the addition product (entries 3 and 4). The reaction at 60 °C also proceeded well, giving a 99% yield of the addition product **3aa** (entry 5).

Table 1. Ir-Catalyzed Hydroarylation of 2a with 1a[a]
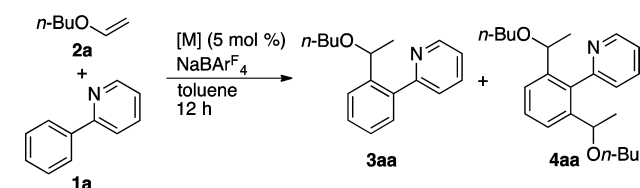
entry	[M]	temp (°C)	yield (%)[b]	
			3aa	**4aa**
1	$[IrCl(cod)]_2$	80	98	1
2[c]	$[IrCl(cod)]_2$	80	0	0
3	$[IrCl(coe)_2]_2$	80	0	0
4	$[RhCl(cod)]_2$	80	0	0
5	$[IrCl(cod)]_2$	60	99[d]	1
6[e]	$[IrCl(cod)]_2$	60	91	4

[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), [M] (5 mol % of M), and $NaBAr^F_4$ (10 mol %) in toluene (0.40 mL) for 12 h. [b]Determined by ^{1}H NMR. [c]Performed without $NaBAr^F_4$. [d]Isolated yield. [e]Performed with 3 equiv of **2a** for 24 h.

Reaction of **1a** with 3 equiv of **2a** for a prolonged reaction time (24 h) gave the monoalkylation product **3aa** in 91% yield accompanied by the dialkylation product **4aa** in 4% yield (entry 6).[18] The result indicates that the second alkylation is much slower than the first one, probably because the bulky ortho-functional group of the monoalkylation product **3aa** inhibits the 2-pyridyl group from taking the coplanar conformation with the benzene ring to undergo C–H activation.

The results obtained for the Ir-catalyzed branch-selective hydroarylation of several vinyl ethers with **1a** are summarized in Table 2. A variety of alkyl vinyl ethers **2a–e** and aryl vinyl ethers

Table 2. Ir-Catalyzed Hydroarylation of Vinyl Ethers 2 with 1a[a]

entry	vinyl ether 2	product	isolated yield (%)
1	2a	3aa: R = n-Bu	99
2	2b	3ab: R = i-Bu	96[b]
3	2c	3ac: R = Et	90
4	2d	3ad: R = benzyl	91[b]
5	2e	3ae: R = PMB ((4-MeOC6H4)CH2)	96[b]
6	2f	3af: Ar = Ph	91
7	2g	3ag: Ar = 4-MeC6H4	98
8	2h	3ah: Ar = 4-MeOC6H4	93[b]
9[c]	2i	3ai: Ar = 4-FC6H4	90 (94/6)[d]
10[c]	2j	3aj: Ar = 4-ClC6H4	93
11	2k	3ak: Ar = 3-MeC6H4	91 (98/2)[d]
12	2l	3al: Ar = 2-MeC6H4	98
13[c,e,f]	2m Me3SiO	3am	88
14[c]	2n	3an: n = 1	95
15[c,e]	2o	3ao: n = 2	68
16[c,g]	2p EtO	3ap	19

[a]Reaction conditions: **1a** (0.20 mmol), **2a** (0.30 mmol), [IrCl(cod)]2 (5 mol % Ir), and NaBArF4 (10 mol %) in toluene (0.80 mL) at 60 °C for 12 h. [b]Formation of 3–5% of double alkylation products **4** was observed. [c]At 80 °C. [d]Isolated as a mixture of inseparable **3** and **4**. The value in parentheses represents a ratio of **3**/**4**. [e]Performed with 3 equiv of vinyl ether **2** for 48 h. [f]After treatment with K2CO3 in MeOH. [g]Performed with 5 equiv of **2p** for 48 h.

2f–l gave high yields of the corresponding hydroarylation products **3aa–3al** (entries 1–12). Reaction of trimethylsilyl vinyl ether **2m** also took place at 80 °C for 48 h using 3 equiv of the vinyl ether to give alcohol **3am** after a treatment of the crude reaction mixture with K2CO3 in MeOH (entry 13). Cyclic vinyl ethers **2n** and **2o** also underwent the hydroarylation with **1a** to give the corresponding products **3an** and **3ao** in 95 and 68% yield, respectively (entries 14 and 15). On the other hand, reaction of an acyclic alkenyl ether, ethyl 1-propenyl ether (**2p**, E/Z = 1:2), gave only a low yield (19%) of the addition product **3ap** even under harsh conditions (5 equiv of **2p** at 80 °C for 48 h,

entry 16), and methyl 2-propenyl ether (**2q**), 1-octene (**2r**), and styrene (**2s**) did not undergo the hydroarylation.

Table 3 summarizes the results obtained for the reaction of several 2-phenylpyridine derivatives **1** with **2a**. Reactions of 2-

Table 3. Ir-Catalyzed Hydroarylation of 2a with Pyridine Derivatives 1[a]

entry	1	temp. (°C)	product	isolated yield (%)
1	1b: R1 = Me	60	3ba	97
2[b]	1c: R1 = MeO	40	3ca	93
3[b]	1d: R1 = F	40	3da	92[c]
4	1e	80	3ea	89
5[d]	1f	80	3fa	72
6	1g	60	3ga	96
7[e]	1h	80	3ha	90

[a]Reaction conditions: **1** (0.20 mmol), **2a** (0.30 mmol), [IrCl(cod)]2 (5 mol % Ir), and NaBArF4 (10 mol %) in toluene (0.80 mL) for 12 h. [b]For 20 h. [c]Formation of 3% of double alkylation product **4da** was observed. [d]Performed with 3 equiv of **2a** for 48 h. [e]In dioxane.

phenylpyridines substituted at the 4-position with electron-donating groups, Me (**1b**) and MeO (**1c**), and an electron-withdrawing group F (**1d**) are all good substrates to give high yields of the addition products **3ba–3da** (entries 1–3). In the reaction of meta-substituted **1e**, a less sterically hindered C–H bond was selectively activated to give **3ea** in 89% yield (entry 4). 2-(2-Thienyl)pyridine (**1f**) also underwent the addition reaction with **2a** to give **3fa** (entry 5). The alkylation of 6-methyl-2-phenylpyridine (**1g**) and 7,8-benzoquinoline (**1h**) also proceeded with branch selectivity, giving **3ga** and **3ha** in 96 and 90% yield, respectively (entries 6 and 7).

The present catalytic system was also applicable to the reaction of aromatic compounds having other directing groups than the 2-pyridyl groups (Table 4). Benzothiazole **1i** and oxazoline **1j** also worked well as the directing group to give **3ia** and **3ja** in 80 and 94% yield, respectively (entries 1 and 2). The reaction of ketoxime **1k** gave a moderate yield of the addition product **3ka** (entry 3). In the reaction of ketimine **1l**, the ortho-alkylated ketone **3la** was obtained in 84% yield after an acidic workup of the crude reaction mixture with aqueous HCl (entry 4).

Because 1,5-cyclooctadiene works as a chelating ligand of the Ir complex through the present reaction, the use of chiral diene ligands provides a promising catalytic system for the asymmetric reaction via C–H bond activation.[3f,4a,10,19] The Ir complex coordinated with a chiral diene ligand based on a tetrafluoro-benzobarrelene framework,[20] [IrCl((S,S)-Fc-tfb*)]2, displayed a high catalytic activity in the hydroarylation reaction. Thus, the reaction of **1a** with 1.5 equiv of vinyl ether **2c** and **2f** gave high

Table 4. Ir-Catalyzed Hydroarylation of 2a with 1[a]

entry	1		product	isolated yield (%)
1	1i		3ia	80
2[b]	1j		3ja	94
3	1k		3ka	61
4[c,d]	1l		3la	84

[a]Reaction conditions: **1** (0.20 mmol), **2a** (0.60 mmol), [IrCl(cod)]$_2$ (5 mol % Ir), and NaBAr$^F_4$ (10 mol %) in toluene (0.80 mL) at 80 °C for 48 h. [b]Performed with 1.5 equiv of **2a** for 20 h. [c]Performed with 1.2 equiv of **1l** and **2a** (1 equiv). [d]Acidic workup with aq HCl.

yields of addition products **3ac** and **3af** with 77 and 76% ee, respectively (Scheme 1).[21]

Scheme 1. Asymmetric Hydroarylation of Vinyl Ethers
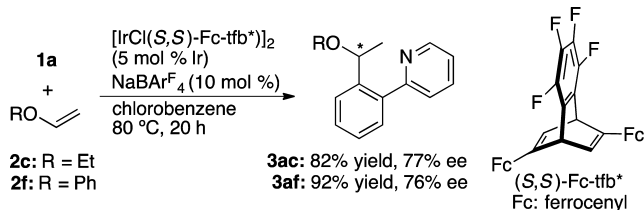
Results of deuterium-labeling experiments[3m,10] provided us with mechanistic insights into the catalytic cycle (Scheme S1). Treatment of deuterated phenylpyridine **1a-d_5** (C$_6$D$_5$-2-Py) with 1.5 equiv of ethyl vinyl ether **2c** gave **3ac-d**, where deuterium atoms on the phenyl group of **1a-d_5** are transferred into the methyl and methine groups (Scheme S1a). The ortho position of the addition product was partially incorporated with hydrogen. The recovered **1a-d_5** had a significant amount of hydrogen at the ortho positions. These results indicate that the C–H activation and insertion steps are reversible, and the reductive elimination step determines the regioselectivity. On the other hand, in the reaction of **1a-d_5** with 1.5 equiv of 4-methoxystyrene (**2t**), no hydroarylation occurred, but the deuterium contents at the ortho positions of recovered **1a-d_5** decreased and the deuterium incorporation into the methylene terminus and the α-position of **2t** was observed (Scheme S1b). This result indicates that C–H activation and insertion steps are reversible.

On the basis of the results of the deuterium-labeling experiments, we postulate a catalytic cycle of the present hydroarylation shown in Scheme 2. The ortho-C–H activation of **1a** assisted by coordination of the pyridine nitrogen to Ir forms aryl hydridoiridium(III) species **B**.[3k] A branch-selective alkene insertion of vinyl ether **2** to the Ir–H bond forms **C**, and successive irreversible reductive elimination gives addition product **3** and regenerates catalyst **A**.[22] On the other hand, a linear selective insertion to the Ir–H bond proceeds to form **C′**,

Scheme 2. Proposed Catalytic Cycle
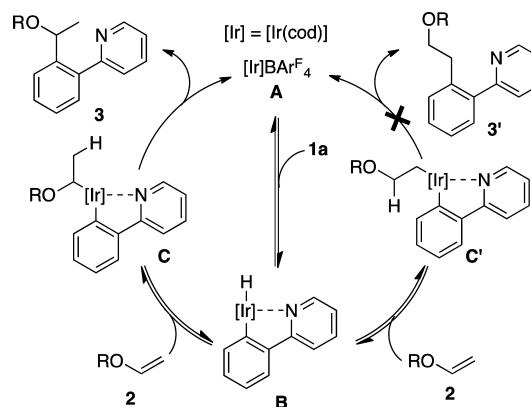
but **C′** does not undergo reductive elimination and returns to **B** via β-hydrogen elimination.[23]

In summary, we have developed the Ir-catalyzed branch-selective hydroarylation of vinyl ethers with aromatic compounds containing nitrogen directing groups via C–H activation. The asymmetric variant with good enantioselectivity has also been realized by use of the Ir/chiral diene catalyst. Deuterium-labeling experiments indicated that the branch selectivity originated in the reductive elimination step.

■ ASSOCIATED CONTENT

S **Supporting Information**
Experimental procedures and compound characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b03099.

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Notes
The authors declare no competing financial interest.

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(18) Dialkylation product **4aa** was formed as a mixture of diastereomers (55:45).

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(21) In the presence of $[IrCl((S,S)\text{-Fc-tfb*})]_2$, the hydroarylation reaction of styrene did not proceed at all, and in the reaction of **1a** with 1-octene, formation of the linear adduct in 2% yield was observed.

(22) Reductive elimination leading to the branch adduct would be facilitated by steric and electronic effects. Reductive elimination of the bulky secondary alkyliridium(III) is faster than the primary one because the steric congestion is relieved by the reductive elimination. On the other hand, during reductive elimination of the α-alkoxyethyliridium(III) species, some degree of coordination of α-oxygen in the developing product may be present in the transition state, resulting in energy of the transition state lower than that in the case of the β-alkoxyethyliridium(III), although the details are not yet clear. For studies on the reductive elimination of alkyl arylpalladium complexes, see: Culkin, D. A.; Hartwig, J. F. *Organometallics* **2004**, *23*, 3398.

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