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Asymmetric Alkylation of *N*-Sulfonylbenzamides with Vinyl Ethers via C−H Bond Activation Catalyzed by Hydroxoiridium/Chiral Diene Complexes

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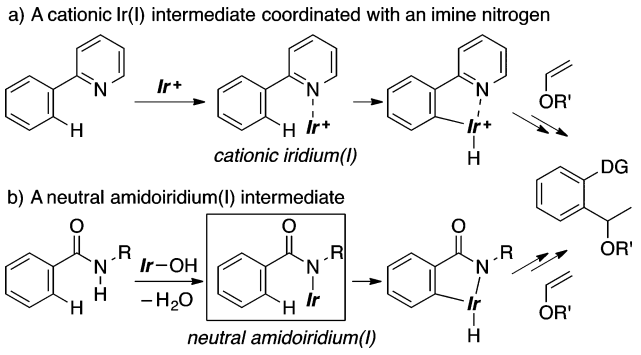
Supporting Information

ABSTRACT: Asymmetric alkylation of *N*-sulfonylbenzamides with vinyl ethers via a directed C−H bond activation gave high yields of the corresponding addition products with high branch- and enantioselectivity.

Direct functionalization of aromatic compounds via C−H bond activation of unactivated aromatic rings is emerging as one of the most desirable methodologies of the atom- and step-economical synthesis of useful compounds in organic chemistry.[1] A large number of catalytic systems using transition metal complexes have been developed for the direct carbon−carbon bond formation of aromatic compounds. The *ortho*-selective alkylation has been achieved by use of directing groups, and in most cases of the alkylation with alkenes, a linear selectivity has been successfully presented.[2] A branch-selective alkylation,[3] which enables an asymmetric construction of benzylic stereocenters, has also been recently developed in the reaction of vinyl arenes[4] and simple alkenes,[5] but the asymmetric variant of the reaction involving the C−H bond activation remains significantly underdeveloped.[6,7] In this respect, we recently reported a branch-selective alkylation of aromatic compounds with a variety of alkyl and aryl vinyl ethers,[8,9] where a cationic Ir complex catalyzes the reaction of aromatic compounds having nitrogen-based directing groups such as 2-pyridyl, 2-benzothiazolyl, 2-oxazolyl, and imino groups (Scheme 1a). We also presented preliminary promising results of the enantioselective alkylation of 2-phenylpyridine with vinyl ethers, although the enantioselectivity is modest (77% ee). In terms of synthetic utility, the use of simple and convertible directing groups is desirable, and thus we next focused on an aromatic amide that can form an amidoiridium(I) species as an active intermediate for the *ortho*-C−H activation (Scheme 1b). Here we report the asymmetric direct alkylation of *N*-sulfonyl aromatic amides[10] with vinyl ethers. The reaction was efficiently catalyzed by a hydroxoiridium complex without adding any bases or additives. The use of a chiral diene ligand enabled the enantioselective alkylation to give the corresponding products in high yields with high branch- and enantioselectivity.

Scheme 1. Ir-Catalyzed Branch-Selective Alkylation with Vinyl Ethers



We found that a hydroxoiridium complex can catalyze the alkylation of *N*-sulfonylbenzamides with vinyl ethers with high branch-selectivity. Thus, treatment of 3-methyl-*N*-(methanesulfonyl)benzamide (**1a**) with 1.5 equiv of butyl vinyl ether (**2a**) in the presence of $[Ir(OH)(cod)]_2$ (5 mol % Ir, cod =1,5-cyclooctadiene) in toluene at 80 °C for 20 h gave an 84% yield of branched adduct **3aa** as a sole addition product (Table 1, entry 1). The reaction was not catalyzed by a chloroiridium complex $[IrCl(cod)]_2$ (entry 2) and a cationic complex formed from $[IrCl(cod)]_2$ and $NaBAr^F_4$ [Ar^F = 3,5-$(CF_3)_2C_6H_3$] (entry 3), the latter of which displayed a high catalytic activity in the alkylation of 2-phenylpyridines.[8] These results indicate that an amidoiridium species formed from the hydroxoiridium complex with benzamide **1a** is a key intermediate as shown in Scheme 1b.[11,12] A hydroxorhodium complex $[Rh(OH)(cod)]_2$ showed no catalytic activity for the reaction (entry 4). The use of chiral diene ligands[13] enabled the asymmetric variant of the reaction. Chiral diene ligands based on a tetrafluorobenzobarrelene (tfb) framework have been recently developed in the Rh- and Ir-catalyzed asymmetric reactions.[14] Chiral tfb* ligands substituted with Me, benzyl (Bn), Ph, and ferrocenyl (Fc) all displayed high enantioselectivity (94−96% ee) in the reaction of **1a** with **2a** at 70 °C (entries 5−8), and Me-tfb* was selected as the ligand for further investigation (entry 5). The use of (*R*)-binap resulted in a low yield of the product with low enantioselectivity (42% ee, entry 9). An electron-deficient substituent on the amide nitrogen of **1** greatly influenced the reactivity; methanesulfonyl (**1a**, entry 5) displayed higher reactivity than *p*-toluenesulfonyl (**1b**, entry 10), and a primary amide **1c** did not undergo the alkylation at all (entry 11). In addition, 3,*N*-dimethyl-*N*-(methanesulfonyl)-benzamide (**1d**) did not show any reactivity under the present reaction conditions (entry 12).[15] These results indicate that the

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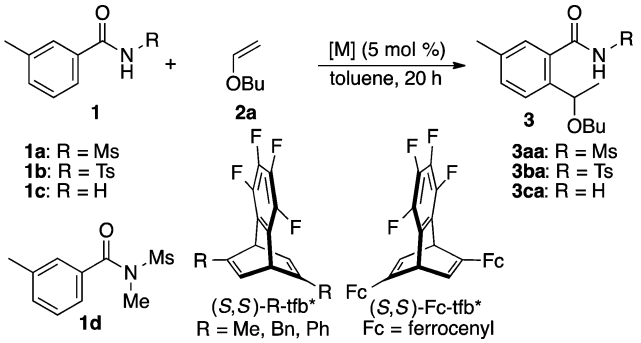
Table 1. Ir-Catalyzed Alkylation of 1 with 2a[a]



entry	[M]	1	yield (%)	ee (%)
1	$[Ir(OH)(cod)]_2$	**1a**	84	
2	$[IrCl(cod)]_2$	**1a**	0	
3[b]	$[IrCl(cod)]_2/NaBAr^F_4$	**1a**	0	
4	$[Rh(OH)(cod)]_2$	**1a**	0	
5	$[Ir(OH)((S,S)\text{-Me-tfb*})]_2$	**1a**	94	96
6	$[Ir(OH)((S,S)\text{-Bn-tfb*})]_2$	**1a**	71	95
7	$[Ir(OH)((S,S)\text{-Ph-tfb*})]_2$	**1a**	74	94
8	$[Ir(OH)((S,S)\text{-Fc-tfb*})]_2$	**1a**	93	94
9	$[Ir(OH)(cod)]_2/(R)\text{-binap}$	**1a**	11	42
10	$[Ir(OH)((S,S)\text{-Me-tfb*})]_2$	**1b**	6	97
11	$[Ir(OH)((S,S)\text{-Me-tfb*})]_2$	**1c**	0	
12	$[Ir(OH)(cod)]_2$	**1d**	0	

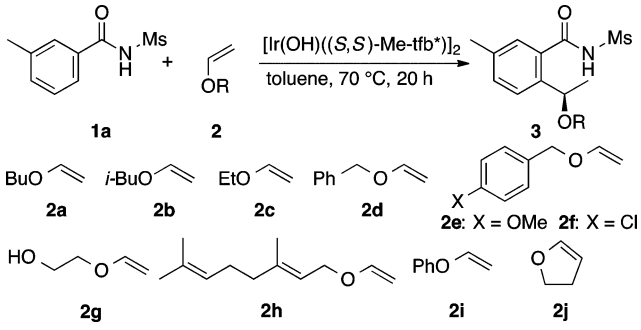
[a]Reaction conditions: **1** (0.10 mmol), **2a** (0.15 mmol), [M] (5 mol %) in toluene (0.40 mL) at 80 °C (entries 1−4) or at 70 °C (entries 5−12) for 20 h. [b]Performed with $NaBAr^F_4$ (10 mol %). Hydroxoiridium complexes $[Ir(OH)((S,S)\text{-R-tfb*})]_2$ were generated by pretreatment of the IrCl(diene) complexes with KOHaq. See the Supporting Information for details.

N−H proton of **1** that has a high acidity is essential for the formation of the amidoiridium species from the hydroxoiridium.

The hydroxoiridium/Me-tfb* complex displayed high catalytic activity and enantioselectivity in the alkylation of *N*-mesylbenzamide **1a** with diverse vinyl ethers (Table 2). Alkyl vinyl ethers **2a**−**h** participated in the alkylation of **1a** to give high yields of the corresponding products **3aa**−**3ah** with 83−97% ee (entries 1−8), where functional groups such as MeO (entry 5), Cl (entry 6), OH (entry 7), and internal alkene moieties (entry 8) were tolerated. The alkylation with phenyl vinyl ether (**2i**) gave **2ai** in 70% yield with 93% ee (entry 9). Cyclic ether **2j** was also applicable to the present alkylation to give the corresponding 2-aryltetrahydrofuran **3aj** in 97% yield with 92% ee (entry 10).[16] In contrast, no reaction of **1a** was observed with *tert*-butyl vinyl ether (**2k**), 1-octene, or styrene.

Table 3 summarizes the results obtained for the reaction of a variety of *N*-mesylbenzamides **1** with butyl vinyl ether (**2a**). The *ortho*-alkylation of benzamides substituted at the *meta*-position with MeO (**1e**), Br (**1f**), and Cl (**1g**) took place at the less sterically hindered position to give high yields of the corresponding adducts **3ea**−**3ga** with high enantioselectivity (entries 1−3). A similar regioselectivity of the C−H activation was observed in the reaction of **1h** having a less bulky fluoro group at the *meta*-position, although a small amount of the regioisomer, which is alkylated at the 2-position, was formed (entry 4). The alkylation of *meta*,*para*-disubstituted benzamides **1i**−**l** and *ortho*-substituted benzamides **1m**−**o** proceeded well to give the corresponding adducts **3ia**−**3oa** with high enantioselectivity (entries 5−11). Amides having naphthyl groups (**1p** and

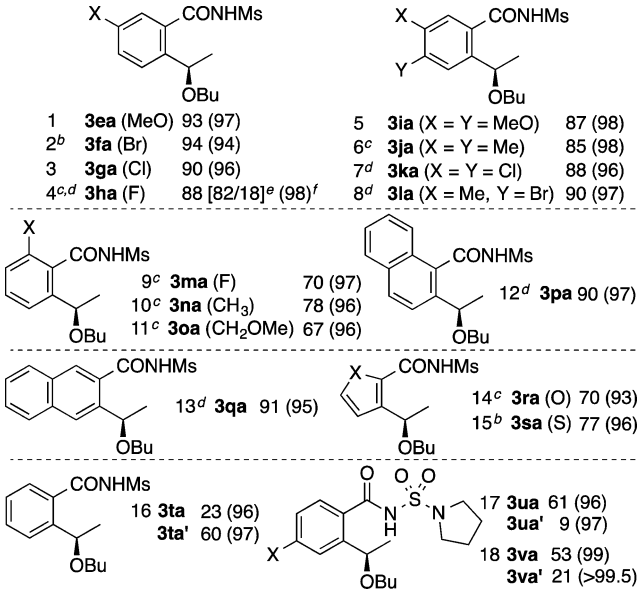
Table 2. Scope of Vinyl Ethers 2[a]



entry	2	3	yield (%)[b]	ee (%)[c]
1	**2a**	**3aa**	97	96
2	**2b**	**3ab**	89	97
3[d]	**2c**	**3ac**	96	96
4	**2d**	**3ad**	97	97
5	**2e**	**3ae**	91	97
6	**2f**	**3af**	94	96
7	**2g**	**3ag**	71	83
8[e]	**2h**	**3ah**	86	96
9[f]	**2i**	**3ai**	70	93
10	**2j**	**3aj**	97	92

[a]Reaction conditions: **1a** (0.20 mmol), **2a** (0.30 mmol), $[Ir(OH)((S,S)\text{-Me-tfb*})]_2$ (5 mol % of Ir) in toluene (0.80 mL) at 70 °C for 20 h. [b]Isolated yield. [c]Determined by HPLC analysis. For **3aa**−**3af** and **3ah**, the ee values were determined by HPLC analysis of *N*-mesyl-*N*-methylbenzamides **4** derived from **3**. [d]Performed with 3 equiv of **2c**. [e]For 48 h. [f]With 10 mol % of Ir.

Table 3. Asymmetric Alkylation of 1 with 2a[a]



[a]Reaction conditions: **1** (0.20 mmol), **2a** (0.30 mmol), $[Ir(OH)((S,S)\text{-Me-tfb*})]_2$ (5 mol % of Ir) in toluene (0.80 mL) at 70 °C for 20 h. Isolated yields (%) are shown. The ee values (%) are shown in parentheses. [b]For 48 h. [c]For 72 h. [d]The ee was determined by HPLC analysis of *N*-mesyl-*N*-methylbenzamides **4** derived from **3**. [e]The ratio of regioisomers (6- and 2-alkyl). [f]The ee of the major isomer.

1q) and heteroaromatic rings (**1r** and **1s**) are also good substrates to give the corresponding adducts **3pa**−**3sa** with 93−97% ee (entries 12−15). In the alkylation of *N*-mesylbenzamide (**1t**), the formation of a considerable amount (60%) of *ortho*-

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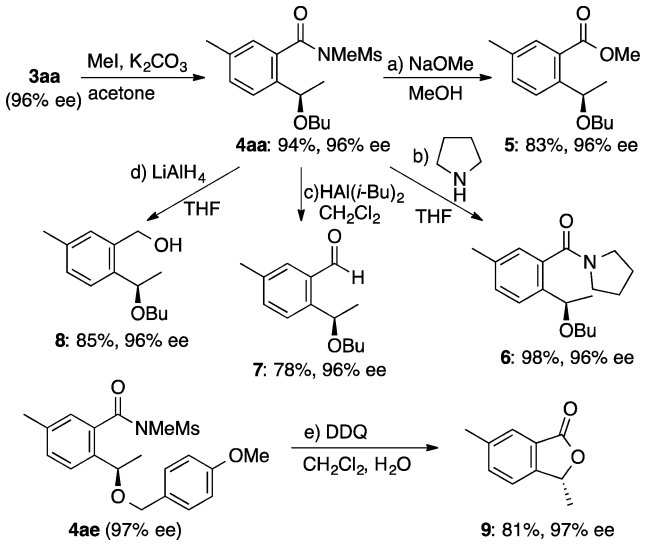
dialkylation product **3ta**′ was observed (entry 16). The reaction of amide **1u** having an *N*-(pyrrolidin-1-ylsulfonyl) group with **2a** under the standard reaction conditions gave monoalkylation product **3ua** in 61% yield with 96% ee with the formation of an 9% yield of dialkylation product **3ua**′ (entry 17). The alkylation of *p*-methylbenzamide **1v** gave monoalkylation product **3va** in 53% yield with 99% ee as well as a 21% yields of dialkylation product **3va**′ (entry 18).

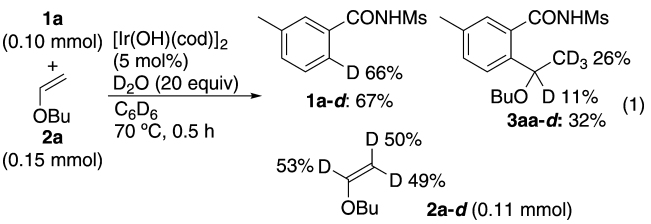
The *ortho*-alkylated *N*-mesylbenzamide obtained here with high enantioselectivity can be converted into several chiral compounds (Scheme 2). Thus, an introduction of a methyl

Scheme 2. Transformations of *N*-Mesylamides



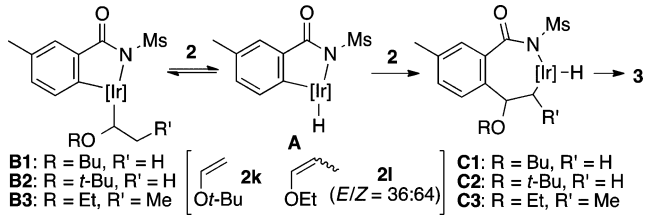
group on the nitrogen atom of **3aa** (96% ee) gave **4aa**, and the amide **4aa** was led to ester **5**, amide **6**, aldehyde **7**, and alcohol **8** without loss of the enantiomeric purity (Scheme 2a–d). Treatment of **4ae** with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) gave lactone **9** in 81% yield (Scheme 2e).

The results of deuterium-labeling experiments (Schemes S1–S6, eq 1) provided us with mechanistic insights. Thus, the



reaction of **1a** with butyl vinyl ether (**2a**) in the presence of $[Ir(OH)(cod)]_2$ (5 mol %) and D_2O (20 equiv) at 70 °C for 0.5 h gave alkylation product **3aa** (32%), where deuterium incorporation was observed for **3aa** and recovered **1a** and **2a** (eq 1). The result indicates that C–H activation and hydrometalation steps (from **A** to **B1**, Scheme 3) are reversible. The reaction of *tert*-butyl vinyl ether (**2k**) did not give the alkylation product **3ak**, but deuterium incorporation into the alkene moiety of **2k** was detected, indicating that species **A** undergoes reversible hydrometalation to **2k** (from **A** to **B2**). Ethyl 1-propenyl ether (**2l**) had a similar reactivity to **2k**. If reductive elimination from species **B1** took place to give the alkylation product **3aa**, the adducts **3ak** and **3al** will also be formed because there should not be a significant difference on the reactivities of species **B1**–**3**. As

Scheme 3. Key Step Leading to the Alkylation Product



an alternative pathway leading to the alkylation product, an irreversible carbometalation is presumably involved in the reaction (from **A** to **C**).[17] It is likely that a less bulky vinyl ether **2a** undergoes carbometalation to give the alkylation product via intermediate **C1**, but the carbometalation to more bulky vinyl ethers **2k** and **2l** is inhibited (from **A** to **C2** and **C3**).

In summary, we have developed the Ir-catalyzed asymmetric alkylation of *N*-sulfonylbenzamides with vinyl ethers via C–H bond activation. The asymmetric reaction with high enantioselectivity was achieved by use of the hydroxoiridium/chiral diene catalyst.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01591.

Experimental procedures (PDF)
Compound characterization data (CIF)
Compound characterization data (CIF)

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Notes

The authors declare no competing financial interest.

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(15) No reaction was also observed for 2-phenylpyridine.

(16) The absolute configurations of **3ai** and **3aj** were determined by X-ray crystallographic analysis. For others, they were assigned by analogy with **3ai** and **3aj**.

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