Asymmetric C–H Functionalization

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Cationic Iridium/S-Me-BIPAM-Catalyzed Direct Asymmetric Intermolecular Hydroarylation of Bicycloalkenes**

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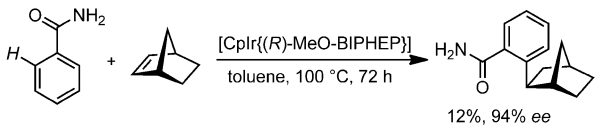
Abstract: *Highly enantioselective cationic iridium-catalyzed hydroarylation of bicycloalkenes, by carbonyl-directed C–H bond cleavage, was accomplished using a newly synthesized sulfur-linked bis(phosphoramidite) ligand (S-Me-BIPAM). The reaction provides alkylated acetophenone or benzamide derivatives in moderate to excellent yields and good to excellent enantioselectivities. Notably, the hydroarylation reaction of 2-norbornene with N,N-dialkylbenzamide proceeds with excellent enantioselectivity (up to 99% ee) and high selectivity for the mono-ortho-alkylation product.*

Transition-metal-catalyzed C–C bond-forming reactions by C–H bond activation are the ultimate atom-economical processes which feature high cost-efficiency and environmental harmony. In particular, direct additions of arenes to multiple bonds such as C=O,[1] C=N,[2] and C=C,[3] called hydroarylation reactions, are highly desirable because of their complete atom economy. Recently, highly enantioselective hydroheteroarylation reactions by a C–H activation/migratory insertion sequence have been developed.[4] Although some effort has been made to develop efficient catalytic systems for direct asymmetric intermolecular additions of arenes to alkenes, there have been no reports showing high levels of enantioselectivity, catalytic activity, and generality.[5,6] In 2000, Togni et al. reported cyclopentadienyl/iridium(I)-catalyzed asymmetric hydroarylation of 2-norbornene with benzamide (Scheme 1). Their study was a pioneering work on the direct intermolecular asymmetric addition of an arene C–H bond to alkenes. Although the reaction provides the hydroarylated product with 94% *ee*, their system displayed a very low catalytic activity and lack of substrate generality (12% yield, only one example).

Recently, we developed a cationic iridium/Me-BIPAM catalyst system for a direct enantioselective intramolecular hydroarylation reaction of α-ketoamides as one of the rare examples of asymmetric hydroarylation of ketones by a C–H bond cleavage/migratory insertion sequence.[7] Thus we became interested in developing asymmetric hydroarylation of alkenes. Herein we describe the highly enantioselective intermolecular hydroarylation of bicycloalkenes with high enantioselectivity by directed C–H bond cleavage of arenes.

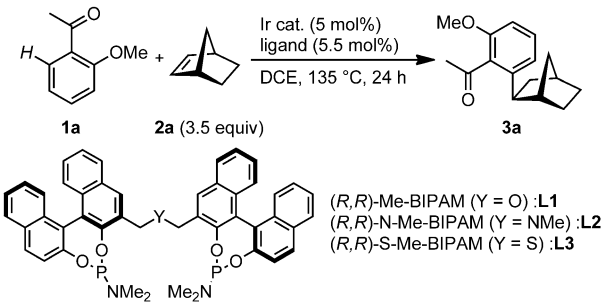
Our initial studies were focused on the development of reaction conditions, including the iridium precursor, chiral ligand, and solvent for the asymmetric hydroarylation of 2-norbornene (**2a**) with 2′-methoxyacetophenone (**1a**), thus giving the *ortho*-alkylated product **3a** (Table 1). Because our previously developed asymmetric hydroarylation of ketones

● Togni et al.



Scheme 1. Amide-assisted asymmetric hydroarylation of **1a**. BIPHEP = 2,2′-bis(diphenylphosphino)-1,1′-biphenyl.

Table 1: Optimization of reaction conditions.[a]



Entry	Precursor	Ligand	Solvent	Yield [%][b]	*ee* [%]
1	$[Ir(cod)_2](BAr^F_4)$	**L1**	DCE	93	52
2	$[Ir(cod)_2](BAr^F_4)$	**L2**	DCE	35	73
3	$[Ir(cod)_2](BAr^F_4)$	**L3**	DCE	82	88
4	$[Ir(cod)_2](SbF_6)$	**L3**	DCE	79	87
5	$[Ir(cod)_2](BF_4)$	**L3**	DCE	trace	–
6	$[Ir(cod)Cl]_2$	**L3**	DCE	n.r.	–
7	$[Ir(cod)_2](BAr^F_4)$	**L3**	DME	58	89
8	$[Ir(cod)_2](BAr^F_4)$	**L3**	PhCl	71	80
9	$[Ir(cod)_2](BAr^F_4)$	**L3**	toluene	87	86
10	$[Ir(cod)_2](BAr^F_4)$	BINAP	DCE	44	13
11	$[Ir(cod)_2](BAr^F_4)$	MonoPhos	DCE	96	21

[a] Reaction conditions: arene (0.25 mmol), iridium catalyst (5 mol%), and ligand (1.1 equiv to Ir) in solvent (1 mL) was stirred for 24 h at 135 °C. [b] Yield of isolated product. BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, cod = 1,5-cyclooctadiene, DCE = 1,2-dichloroethane, DME = 1,2-dimethoxyethane, MonoPhos = (−)-(*R*)-(3,5-dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a*']dinaphthalen-4-yl)dimethylamine, n.r. = no reaction.

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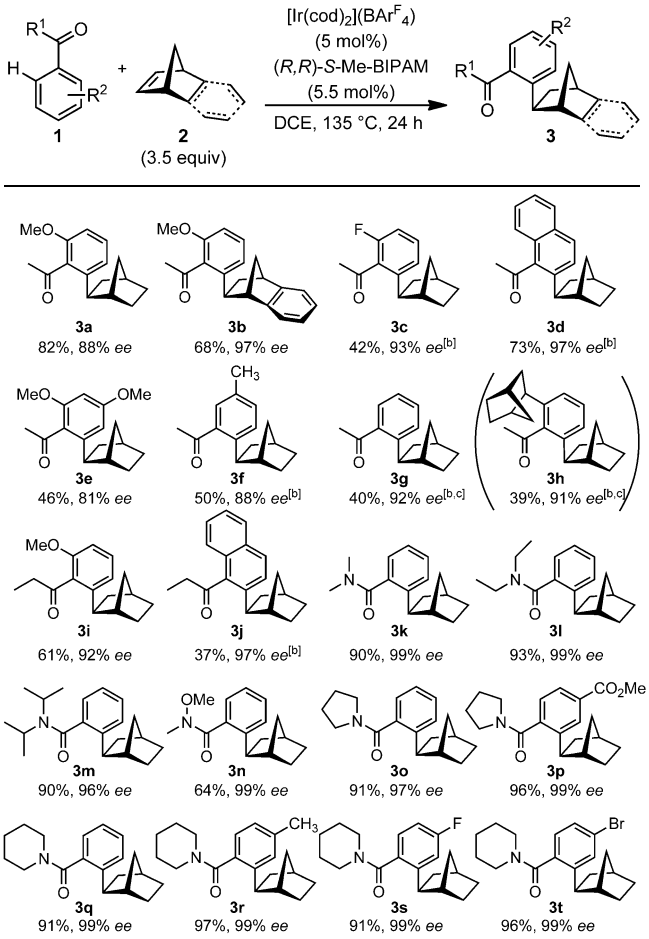
was effectively catalyzed by an $[Ir(cod)_2](BAr^F{}_4)$/bidentate bis(phosphoramidite) (Me-BIPAM) complex, we examined several chiral BIPAM ligands (entries 1–3). The use of (*R,R*)-Me-BIPAM (**L1**) as the ligand gave **3a** in 93% yield with 52% *ee*, and a higher *ee* value was achieved by changing the linker atom of the linked BINOL unit from oxygen to nitrogen [(*R,R*)-*N*-Me-BIPAM (**L2**); entry 2]. Substantial improvement of the enantioselectivity was achieved by using a sulfur-linked bis(phosphoramidite) ligand [(*R,R*)-S-Me-BIPAM (**L3**); entry 3].[8] Further optimization showed that the counteranion of the cationic iridium complex significantly affected the product yield (entries 4 and 5). A neutral iridium complex did not promote the hydroarylation reaction (entry 6). The solvent had some influence on both the yield and enantioselectivity (entries 7–9). Among the chiral ligands screened, the use of (*R*)-BINAP (entry 10) and the monodentate phosphoramidite (*R*)-MonoPhos (entry 11) resulted in lower selectivities of 13 and 21% *ee*, respectively.

With the optimized catalytic conditions (Table 1, entry 3) in hand, we next explored the substrate scope for asymmetric hydroarylation (Table 2). Various substituents including, OMe, F, and Me, on the arene moiety were tolerated (**3a**–**f**). The hydroarylated products were obtained in moderate to good yields with high enantioselectivities. Furthermore, hydroarylation of the benzene-fused bicyclic alkene **2b** with **1a** proceeded to produce **3b** in a synthetically useful yield with excellent enantioselectivity (97% *ee*). In the case of hydroarylation with unfunctionalized acetophenone as a substrate, a mixture of mono- (**3g**) and di-*ortho*-alkylated products (**3h**) was formed. Both products were characterized by GC-MS and ^{1}H NMR analysis. Propiophenone could also be used as a viable directing group, and the products (**3i**,**j**) were isolated with high enantioselectivities, albeit in moderate yields. In some cases for the ketone-directed hydroarylation, it was necessary to adjust the reaction conditions (**3c**, **3d**, **3f**, **3g**, and **3j**). Next, the hydroarylation reaction of **1a** with various benzamides was examined under the optimized reaction conditions. The protocol tolerates a range of amide-based directing groups, including a diethyl amide (**3l**) and diisopropyl amide (**3m**). A Weinreb amide, which is a synthon for the formyl group, was also tolerated and gave the hydroarylated product **3n** in 64% yield. Pyrrolidine- and piperidine-derived amides were also used as directing groups to form the desired products **3o** and **3q**, respectively. We also examined the substituent effects using a range of substituted benzamides. Substituents *para* to the directing group are well-tolerated (**3p**, **3r**–**t**). Potentially reactive functional groups such as an aryl ester (**3p**) and bromide (**3t**) were applicable to this transformation. Gratifyingly, only the mono-*ortho*-alkylated products were obtained in the amide-directed hydroarylation. X-ray diffraction analysis of a single crystal of **3b** revealed that the absolute configuration of **3b** is *R* at C1 and *S* at C8 and C9 (Figure 1).[9] The acetyl group of **3b** is orthogonal to the phenyl ring, probably because of steric hindrance. This observation suggests that the bond rotation of a directing group is limited by a congested environment. Therefore, the mono-*ortho*-alkylated products may predominate in the hydroarylation with benzamides that have more hindered substituents.[10]

Table 2: Substrate scope of enantioselective hydroarylation.[a]



[a] Reaction conditions: **1** (0.25 mmol), **2** (3.5 equiv), iridium catalyst (5 mol%), and (*R,R*)-S-Me-BIPAM (1.1 equiv to Ir) in DCE (1 mL) was stirred for 24 h at 135°C. [b] Reaction conditions: **1** (2 equiv), **2** (0.25 mmol), iridium catalyst (5 mol%), and (*R,R*)-S-Me-BIPAM (1.1 equiv to Ir) in DCE (1 mL) was stirred for 24 h at 135°C. [c] 0.5 mL of DCE was used as solvent.

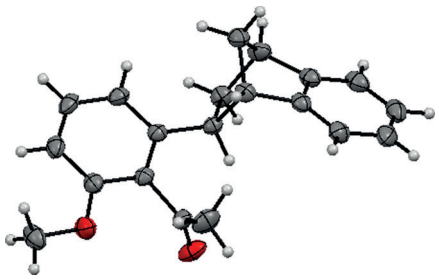
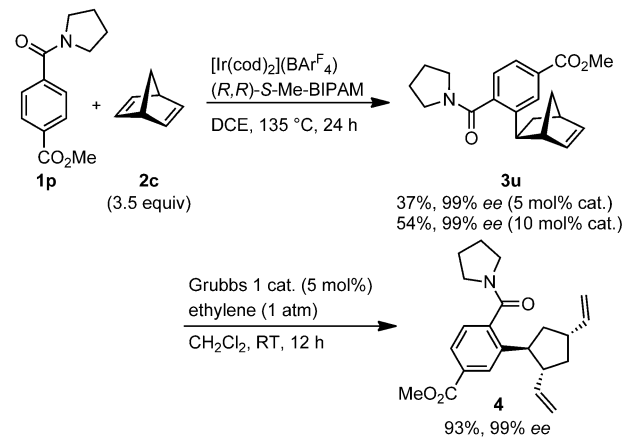


Figure 1. ORTEP diagram of **3h** with thermal ellipsoids set at 50%.

To demonstrate the synthetic utility of this protocol, we further transformed the products of asymmetric hydroarylation of bicycloalkenes. Enantioenriched norbornene could be used as a building block in organic synthesis for the preparation of functionalized chiral compounds. The highly functionalized cyclopentane (**4**) was successfully obtained, as a single diastereomer, by ring-opening metathesis of **3u** with



Scheme 2. Ring-opening metathesis of **3u** with ethylene.

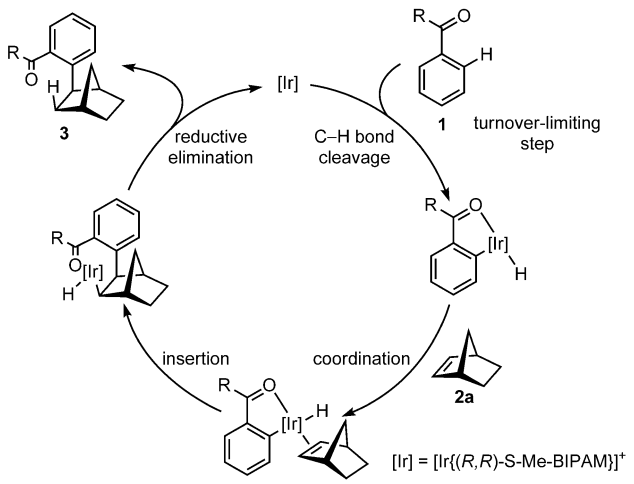
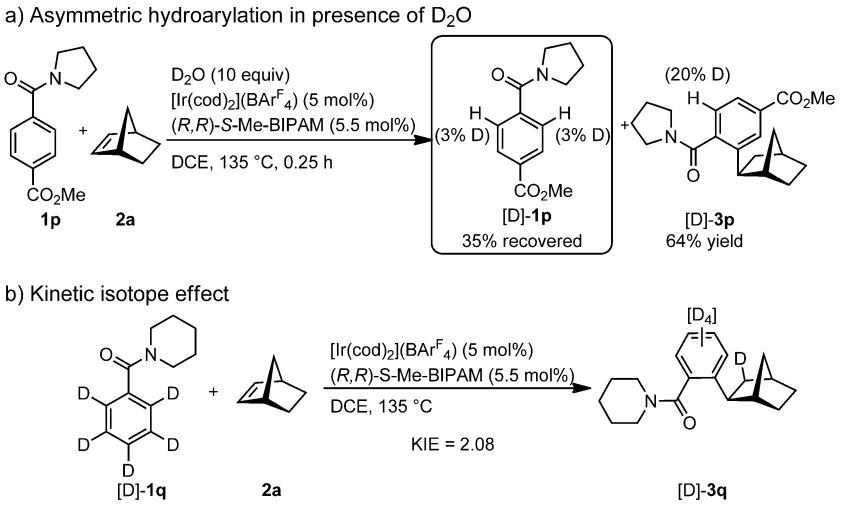


Figure 2. Proposed catalytic cycle.

ethylene and with no erosion of enantioselectivity (Scheme 2).

To obtain data for the reaction mechanism, we carried out an asymmetric hydroarylation of the substrate **1p** in the presence of D_2O (10 equiv) under the optimized reaction conditions (Scheme 3a). The reaction was quenched after



Scheme 3. Deuterium-labeling experiments.

0.25 hours, and the mixture was purified to obtain the unreacted substrate [D]-**1p** (35%) and product [D]-**3p** (64%). Deuterium incorporation was not observed at the *ortho* position of the amide group (3% D) in the substrate. This result may arise from the fact that C–H bond cleavage occurs in a non-reversible manner prior to the alkene insertion. In addition, deuterium-labeling studies were undertaken (Scheme 3b). Comparison of the initial rate constants for the addition of normal (**1q**) and deuterated *N*,*N*-piperidylbenzamide ([D]-**1q**) to **1a** in separate vessels revealed a kinetic isotope effect (KIE) of 2.08. These results indicate that the turnover-limiting step in our developed asymmetric hydroarylation includes the C–H bond cleavage step.[1h,j,4e]

Finally, a plausible catalytic cycle is shown in Figure 2. We propose a catalytic cycle involving chelation-assisted C–H bond cleavage, migratory insertion of a bicycloalkene into the Ir–C bond, and C–H bond-forming reductive elimination of the resulting organoiridium species.[11]

In conclusion, we have developed the first highly enantioselective intermolecular hydroarylation of bicycloalkene through arene C–H bond cleavage catalyzed by a cationic iridium/(*R*,*R*)-S-Me-BIPAM complex. Efforts to extend the scope of the enantioselective hydroarylation for other unstrained alkenes and mechanistic studies for the enantioselection are in progress.

Experimental Section

General procedure: To a flame-dried sealed tube, $[Ir(cod)_2](BAr^F_4)$ (0.0125 mmol, 5 mol%) and (*R*,*R*)-S-Me-BIPAM (0.0138 mmol, 5.5 mol%) and dry 1,2-dichloroethane (1.0 mL) were added under an N_2 atmosphere. The solution was stirred at room temperature for 30 min, followed by the addition of arene (0.25 mmol) and bicycloalkene (3.5 equiv). The reaction mixture was then heated at 135°C. After being stirred for 24 h, the mixture was purified by silica gel column chromatography (eluent: hexane/AcOEt) to afford a pure hydroarylated product.

Keywords: alkenes · alkylation · asymmetric synthesis · iridium · synthetic methods

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[9] CCDC 1400933 (**3h**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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