Asymmetric C–H Functionalization

DOI: 10.1002/anie.201400147

Cationic Ir/Me-BIPAM-Catalyzed Asymmetric Intramolecular Direct Hydroarylation of α-Ketoamides**

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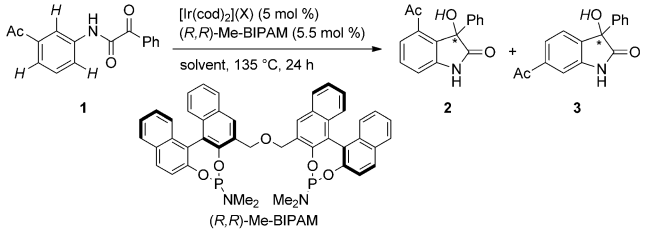
Abstract: *Asymmetric intramolecular direct hydroarylation of α-ketoamides gives various types of optically active 3-substituted 3-hydroxy-2-oxindoles in high yields with complete regioselectivity and high enantioselectivities (84–98% ee). This is realized by the use of the cationic iridium complex [Ir(cod)$_2$](BAr$^F_4$) and the chiral O-linked bidentate phosphoramidite (R,R)-Me-BIPAM.*

Oxindoles containing a chiral tetrasubstituted carbon at the 3-position are common structural motifs in many biologically active compounds.[1] Among them, 3-substituted 3-hydroxy-2-oxindoles are particularly noteworthy, and various methods for the synthesis of these chiral compounds have been developed in the past decade.[2–6] Transition-metal-catalyzed asymmetric nucleophilic addition reactions of organoboronic acid derivatives to isatins are powerful and straightforward approaches.[7] In this field, we have already reported that a chiral bidentate phosphoramidite ligand (Me-BIPAM), previously developed for the enantioselective 1,4-addition of arylbonic acids to enones,[8] the arylation of imines[9] and carbonyl compounds,[10] and the hydrogenation of α-dehydroaminoesters,[11] was efficient for ruthenium-catalyzed addition reactions of arylboronic acids to isatins.[10d] Transition-metal-catalyzed C–H functionalization has emerged in recent years as a powerful tool for the formation of carbon–carbon bonds from simple starting materials.[12,13] Very recently, it was shown that direct nucleophilic addition to imines or carbonyls through transition-metal-catalyzed C–H bond activation provides a concise and highly efficient pathway to synthesize amines and alcohols.[14–17] Intramolecular cyclizations by C–H bond activation have been reported for the synthesis of oxindoles.[18] Iridium complexes have also been shown to be efficient catalysts for C–H bond functionalization.[13e,19,20] In 2009, Shibata and co-workers reported cationic Ir/(*S*)-H$_8$-BINAP-catalyzed enantioselective synthesis of a chiral 4-acetyl-3-hydroxy-3-methyl-2-oxindole with 72% *ee* using the method of direct C–H bond functionalization.[20a] Although this reaction is the first example of enantioselective direct addition of a C–H bond to ketones, there is still room for improvement in terms of the enantioselectivity. In the course of our study on bidentate phosphoramidites as chiral ligands for enantioselective bond-forming reactions, we achieved direct synthesis of chiral 3-substituted 3-hydroxy-2-oxindoles through a highly enantioselective intramolecular hydroarylation reaction of α-ketoamides by the use of a cationic iridium and chiral O-linked bidentate phosphoramidite ((*R*,*R*)-Me-BIPAM).

We first examined the use of an α-ketoamide (**1**) for the asymmetric intramolecular direct hydroarylation reaction in the presence of a cationic iridium complex with (*R*,*R*)-Me-BIPAM as the catalyst (Table 1). Our initial screening of counteranions for the cationic iridium complex indicated that the [Ir(cod)$_2$](BAr$^F_4$) (cod = cyclooctadiene, BAr$^F_4$ = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate) complex would be more favorable than other counteranions (BF_4^-, SbF_6^-, TfO^-, ClO_4^-, and Cl^-), although the yield and enantioselectivity were moderate (62%, 71% *ee*) (entries 1–6). All reactions selectively gave 4-acetyl-3-hydroxy-3-phenyl-2-oxindole (**2**) with complete regioselectivity by enantioselective direct addition at the C–H bond in the more hindered *ortho* position to a carbonyl group. Further optimization of reaction conditions was performed using [Ir(cod)$_2$](BAr$^F_4$). As a result of screening several solvents, the highest efficiency with regard to the reaction was

Table 1: Optimization of reaction conditions.[a]



Entry	Catalyst (mol%)	Solvent	Yield of **2**/**3** [%]	*ee* of **2**/**3** [%]
1	[Ir(cod)$_2$](BAr$^F_4$) (5)	C_6H_5Cl	62/trace	71/–
2	[Ir(cod)$_2$](BF$_4$) (5)	C_6H_5Cl	37/trace	53/–
3	[Ir(cod)$_2$](SbF$_6$) (5)	C_6H_5Cl	12/trace	38/–
4	[Ir(cod)$_2$](OTf) (5)	C_6H_5Cl	15/trace	29/–
5	[Ir(cod)$_2$](ClO$_4$) (5)	C_6H_5Cl	3/trace	29/–
6	[Ir(cod)$_2$]Cl (5)	C_6H_5Cl	n.r.	–
7	[Ir(cod)$_2$](BAr$^F_4$) (5)	THF	94/trace	66/–
8	[Ir(cod)$_2$](BAr$^F_4$) (5)	DME	90/trace	88/–
9	[Ir(cod)$_2$](BAr$^F_4$) (5)	dioxane	28/trace	77/–
10	[Ir(cod)$_2$](BAr$^F_4$) (5)	diglyme	19/trace	58/–
11[b]	[Ir(cod)$_2$](BAr$^F_4$) (5)	diglyme	21/27	57/20

[a] Reaction conditions: α-ketoamides (0.25 mmol), iridium catalyst (5 mol%), and (*R*,*R*)-Me-BIPAM (1.1 equiv to Ir) in solvent (1 mL), stirred for 24 h at 135°C. [b] Run at 150°C. n.r. = no reaction.

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[**] This work was financially supported by the MEXT (Japan) program "Strategic Molecular and Materials Chemistry through Innovative Coupling Reactions" of Hokkaido University.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201400147.

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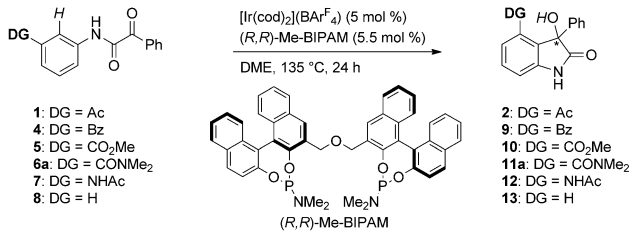
Table 2: Optimization of reaction conditions.[a]



1: DG = Ac
4: DG = Bz
5: DG = CO_2Me
6a: DG = $CONMe_2$
7: DG = NHAc
8: DG = H

2: DG = Ac
9: DG = Bz
10: DG = CO_2Me
11a: DG = $CONMe_2$
12: DG = NHAc
13: DG = H

Entry	DG	Ir precatalyst (mol %)	Ligand	Yield [%]	*ee*[b] [%]
1	Ac	$[Ir(cod)_2](BAr^F_4)$ (5)	(*R*,*R*)-Me-BIPAM	90	88
2	Bz	$[Ir(cod)_2](BAr^F_4)$ (5)	(*R*,*R*)-Me-BIPAM	90	88
3	CO_2Me	$[Ir(cod)_2](BAr^F_4)$ (5)	(*R*,*R*)-Me-BIPAM	37	95
4	$CONMe_2$	$[Ir(cod)_2](BAr^F_4)$ (5)	(*R*,*R*)-Me-BIPAM	>99	98 (*S*)
5[c]	**$CONMe_2$**	**$[Ir(cod)_2](BAr^F_4)$ (5)**	**(*R*,*R*)-Me-BIPAM**	**>99**	**98 (*S*)**
6	$CONMe_2$	$[Ir(cod)_2](BAr^F_4)$ (3)	(*R*,*R*)-Me-BIPAM	96	97 (*S*)
7	NHAc	$[Ir(cod)_2](BAr^F_4)$ (5)	(*R*,*R*)-Me-BIPAM	63	82
8	H	$[Ir(cod)_2](BAr^F_4)$ (5)	(*R*,*R*)-Me-BIPAM	n.r.	–
9	$CONMe_2$	$[Ir(cod)_2](BAr^F_4)$ (5)	(*R*)-BINAP	91	49
10	$CONMe_2$	$[Ir(cod)_2](BAr^F_4)$ (5)	(*R*)-MONOPHOS	32	45

[a] Reaction conditions: α-ketoamides (0.25 mmol), $[Ir(cod)_2](BAr^F_4)$ (5 mol %), and (*R*,*R*)-Me-BIPAM (1.1 equiv to Ir) in DME (1 mL), stirred for 24 h at 135 °C. [b] The absolute configuration of the chiral center within the product is given in parentheses. [c] Reaction mixture was stirred at 135 °C, 16 h. Bz = benzoyl.

observed in 1,2-dimethoxyethane (DME) at 135 °C (90 %, 88 % *ee*; entry 8). When the reaction carried out at 150 °C in diglyme, the corresponding 3-hydroxy-3-phenyl-2-oxindole **2** and **3** were obtained as a mixture of two regioisomers (entry 11).

We next examined the directing group attached to the aromatic ring of the aniline side (Table 2). The dimethyl amino carbonyl group was most effective and the enantioselectivity additionally improved to 98 % *ee* (entry 4). The reaction with substrate **8** gave no desired product, suggesting that a directing group is indispensable in this reaction. When the reaction time was 16 h, there was no change in yield or selectivity (entry 5). Moreover, it is notable that catalyst loading can be reduced to 3 mol % without loss of enantioselectivity (entry 6). Among the chiral ligands screened, the use of analogous C_2-symmetric (*R*)-BINAP (entry 9) and monodentate phosphoramidite, (*R*)-MONOPHOS (entry 10) resulted in lower selectivities, 49 % *ee* and 45 % *ee*, respectively. The absolute configuration of the product was assigned as the *S* enantiomer based on X-ray crystallographic analysis of the compound of **11a** (Figure 1).[21]

With these optimized conditions established, we next investigated the substrate scope of this reaction using 5 mol % of catalyst. As shown in Table 3, the reactions are applicable

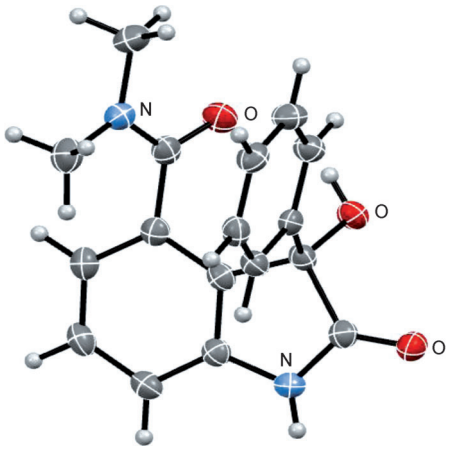
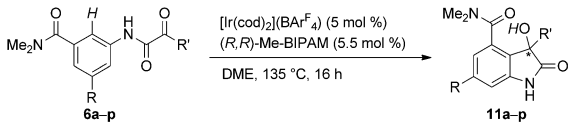


Figure 1. ORTEP diagram of **11a**, with thermal ellipsoids set at 50 %.

to a variety of α-ketoamides. In most cases, complete regioselectivity, high yield, and excellent *ee* values were obtained. Both electron-donating and electron-withdrawing substituents on the aromatic ring at the ketone side of the substrates were tolerated. In some cases (entries 9 and 12), the enantioselectivity decreased slightly. However, the enantioselectivity was improved by using preformed [Ir(cod)-((*R*,*R*)-Me-bipam)](BAr^F_4). These phenomena indicated that the cationic iridium catalyst precursor, $[Ir(cod)_2](BAr^F_4)$, sometimes slightly catalyzed this chemical transformation under our standard conditions.

Table 3: Asymmetric intramolecular direct hydroarylation of α-ketoamides.[a]



Entry	R	R′	Yield [%]	*ee*[b] [%]
1	H	C_6H_5 (**6a**)	>99 (**11a**)	98 (*S*)
2	H	4-$CF_3C_6H_4$ (**6b**)	98 (**11b**)	98
3	H	4-FC_6H_4 (**6c**)	99 (**11c**)	90
4	H	4-BrC_6H_4 (**6d**)	80 (**11d**)	98
5	H	4-PhC_6H_4 (**6e**)	94 (**11e**)	91
6	H	4-$PhOC_6H_4$ (**6f**)	73 (**11f**)	84
7[c]	H	4-$PhOC_6H_4$ (**6f**)	97 (**11f**)	84
8	H	3-$CF_3C_6H_4$ (**6g**)	97 (**11g**)	97
9	H	3-$CH_3C_6H_4$ (**6h**)	98 (**11h**)	86
10[c]	H	3-$CH_3C_6H_4$ (**6h**)	90 (**11h**)	92
11	H	2-FC_6H_4 (**6i**)	87 (**11i**)	97
12	H	2-naphthyl (**6j**)	91 (**11j**)	88
13[c]	H	2-naphthyl (**6j**)	88 (**11j**)	94
14	H	3,5-$(CF_3)_2C_6H_3$ (**6k**)	97 (**11k**)	98
15	H	3,4-$(CH_2O_2)C_6H_3$ (**6l**)	69 (**11l**)	84
16[c]	H	3,4-$(CH_2O_2)C_6H_3$ (**6l**)	85 (**11l**)	80
17	CF_3	C_6H_5 (**6m**)	96 (**11m**)	91
18	H	CH_3 (**6n**)	96 (**11n**)	94
19	H	CH_2CH_3 (**6o**)	95 (**11o**)	92
20	H	$CH(CH_3)_2$ (**6p**)	93 (**11p**)	90

[a] Reaction conditions: α-ketoamides (0.25 mmol), $[Ir(cod)_2](BAr^F_4)$ (5 mol %), and (*R*,*R*)-Me-BIPAM (1.1 equiv to Ir) in DME (1 mL) was stirred for 16 h at 135 °C. [b] The absolute configuration of the chiral center within the product is given in parentheses. [c] 5 mol % of [Ir(cod)((*R*,*R*)-Me-bipam)](BAr^F_4) was used as the catalyst.

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Furthermore, in the reaction of α-ketoamides having a disubstituted aromatic ring at the ketone side, the corresponding 3-aryl-3-hydroxy-2-oxindoles were also obtained with high enantioselectivities (entries 12–16). High enantioselectivity was maintained even when the aromatic ring of the aniline side has a substituent, such as a CF_3 group (91% *ee*; entry 17). The method was easily extended to a variety of aliphatic α-ketoamides and afforded the corresponding 3-alkyl-3-hyroxy-2-oxindoles in high enantioselectivities (90–94% *ee*; entries 18–20).

Finally, a plausible catalytic cycle and enantioselection mechanisms are proposed in Figures 2 and 3, based on the X-ray structure of **11a** (Figure 1) and previous reports.[3c,20a] First, [Ir((*R*,*R*)-Me-bipam)](BAr^F_4) ([Ir], **14**) is formed by an iridium catalyst precursor, [Ir(cod)$_2$](BAr^F_4), and (*R*,*R*)-Me-BIPAM in situ. Subsequently, **14** reacts with substrate **6** to afford aryl iridium complex **15**, which is coordinated with the two carbonyl groups of the amide. Asymmetric hydroarylation of the ketone carbonyl group would proceed from **16**, thus producing enantiomerically enriched iridium alkoxide species **17**. Finally, reductive elimination to product **11** from **17** occurs and regenerates the active iridium catalyst **14**. On the basis of a previous report,[9a] the enantioselective insertion can be rationalized by intermediate **16**-favored, which exhibits less steric congestion (Figure 3), and thus explains why the carbonyl group is attacked preferentially on its *si* face to produce the (*S*)-enantiomer.

In conclusion, we have developed a cationic iridium/(*R*,*R*)-Me-BIPAM-catalyzed highly enantioselective intramolecular direct hydroarylation of α-ketoamides through C–H functionalization. (*R*,*R*)-Me-BIPAM gave various types of optically active 3-substituted 3-hydroxy-2-oxindoles in high yields with complete regioselectivity and excellent enantioselectivities by enantioselective direct addition at the C–H bond in the more hindered *ortho* position to a carbonyl group. Further studies of this method toward expansion of the substrate scope are in progress.

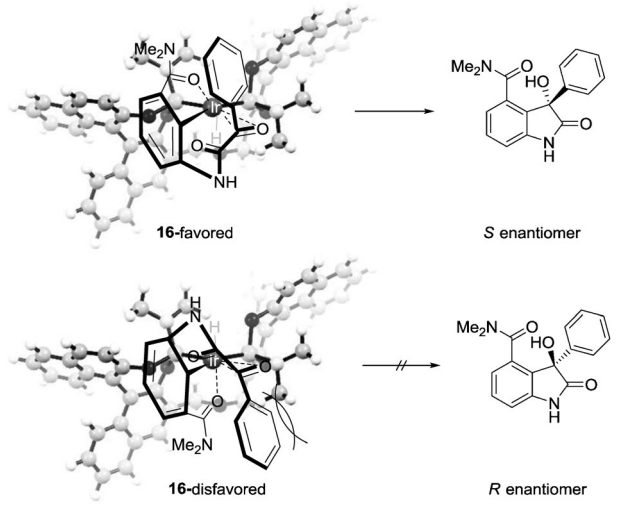

Figure 3. Plausible models for reaction enantioselectivity.

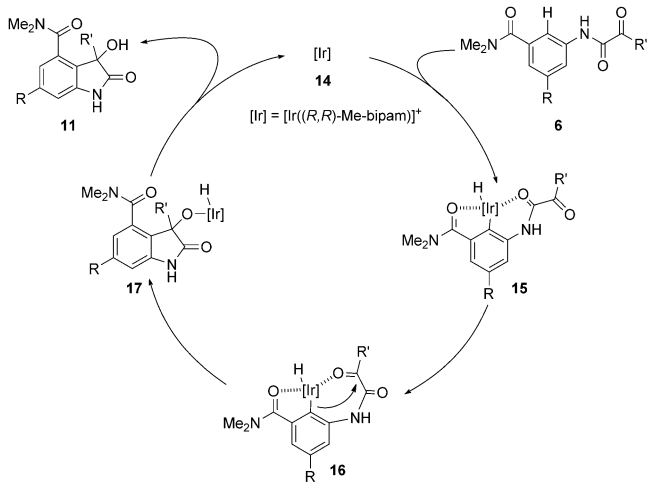

Figure 2. Proposed catalytic cycle.

Experimental Section

General procedure: To a flame-dried flask, [Ir(cod)$_2$](BAr^F_4) (0.0125 mmol, 5 mol%) and (*R*,*R*)-Me-BIPAM (0.0138 mmol, 5.5 mol%) and dry dimethoxyethane (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 α-ketoamide (0.25 mmol). The reaction mixture was then heated at 135°C. After being stirred for 16 h, the mixture was purified with silica gel column chromatography (eluent: *n*-hexane/ethyl acetate) to afford pure 3-substituted-3-hydroxy-2-oxindole.

Received: January 7, 2014

Keywords: asymmetric catalysis · C-H functionalization · iridium · oxindoles · phosphoramidites

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[21] CCDC 980114 (**11a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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