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Cationic Iridium/Chiral Bisphosphine-Catalyzed Enantioselective Hydroacylation of Ketones

Tomohiko Shirai,^[a] Tomoya Iwasaki,^[b] Kazuya Kanemoto,^[c] and Yasunori Yamamoto^[d]

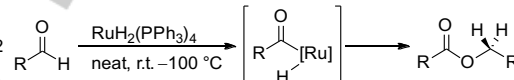
Abstract: A facile and convenient synthesis of the chiral phthalide framework catalyzed by cationic iridium was developed. The method utilized cationic iridium/bisphosphine-catalyzed asymmetric intramolecular carbonyl hydroacylation of 2-keto benzaldehydes to furnish the corresponding optically active phthalide products in good to excellent enantioselectivities (up to 98% ee). The mechanistic studies using a deuterium-labelled substrate suggested that the reaction involved an intramolecular carbonyl insertion mechanism to iridium hydride intermediate. In addition, we investigated the kinetic isotope effect (KIE) of intramolecular hydroacylation with deuterated substrate and determined that the C–H activation step is not included in the turnover-limiting step.

Transition metal-catalyzed hydroacylation, which is the formal direct addition of aldehyde to multiple C–C or C–O bonds, is a powerful atom economical method for the synthesis of ketones and esters.^[1] Although there have been many examples of the hydroacylation of unsaturated bonds, such as alkenes and alkynes using rhodium, ruthenium, or cobalt catalysts,^[2] there are only sporadic examples of the hydroacylation of carbonyl compounds (**Scheme 1**).^[3] The first approach was demonstrated in 1978 by the Yamamoto group on ruthenium-catalyzed Tishchenko-type ester formation.^[3a] In this case, it is assumed that this reaction proceeds via the generation of acylruthenium species by the oxidative addition of aldehyde to ruthenium. In addition, the intermolecular Cannizzaro-type reaction of 1,4-dicarbonyl compounds has been reported by Bosnich group in 1990.^[3b] However, the recent efforts in asymmetric variants have further enlarged the scope of this research field. In 2008, Dong et al. have first reported an enantioselective approach to lactones by rhodium-catalyzed intramolecular hydroacylation and achieved high yields and excellent enantioselectivities.^[3c] In addition, they

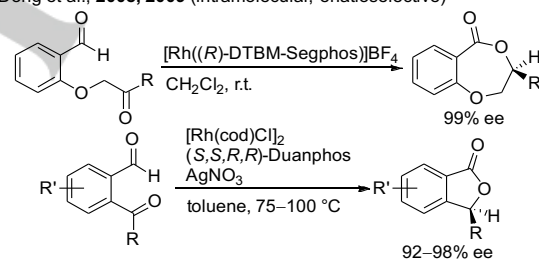
also extended this methodology to the chiral phthalides synthesis.^[3d] Phthalide moieties are widespread in a number of biologically active compounds.^[4] Although considerable efforts have been made toward the phthalide synthesis,^[5] there have been few reports of atom-economical hydroacylation.^[3f, 5d] The ruthenium-^[6] and cobalt-catalyzed^[7] variants of this transformation have been also reported, however, the development of a new catalytic system for the highly enantioselective carbonyl hydroacylation involving C–H bond activation is still challenging because the valuable chiral scaffolds can be directly assembled and toxic by-products derived from reagents are not formed.

Related literature examples:

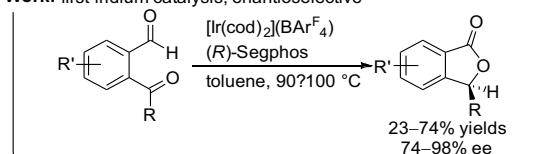
- Yamamoto et al., 1978 (first carbonyl hydroacylation)



- Dong et al., 2008, 2009 (intramolecular, enantioselective)



This Work: first iridium catalysis, enantioselective



Scheme 1. Catalytic carbonyl hydroacylations.

Recently, we reported the cationic iridium-bisphosphine-catalyzed decarbonylation of aldehydes through aldehydic C–H bond activation and their preliminary application to carbonyl hydroacylation.^[8] Thus, we became interested in developing new highly enantioselective carbonyl hydroacylation using a cationic iridium catalyst. Herein, we report that cationic iridium complexes catalyze the asymmetric intramolecular carbonyl hydroacylation of 2-keto benzaldehydes. The reaction affords the optically active 3-substituted phthalides in moderate to good yields with a good level of enantioselectivities.

In our initial studies using 2-acetylbenzaldehyde (**1a**) with a catalytic amount of $[\text{Ir}(\text{cod})_2](\text{BAR}^{\text{F}}_4)$ ($\text{Ar}^{\text{F}} = 3,5\text{-bis}(\text{trifluoromethyl})\text{phenyl}$) and (*R*)-BINAP in toluene at 90 °C, we observed the formation of phthalide, 3-methylisobenzofuran-1(3*H*)-one (**2a**) in low yield (18%) with good enantioselectivity

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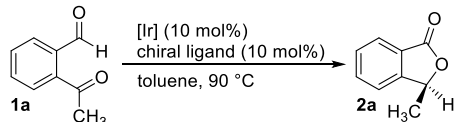
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Supporting information for this article is given via a link at the end of the document.

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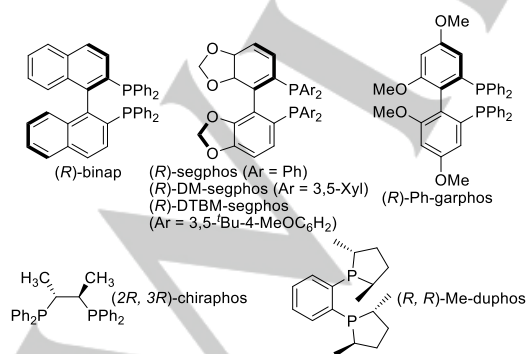
(86% ee, **Table 1**, entry 1). However, when the reaction was performed in the presence of (*R*)-SEGPHOS, the catalyst worked efficiently and afforded the desired phthalide **2a** in the 59% yield and 92% ee (*S*) (entry 2).^[9] The application of sterically crowded SEGPHOS type ligands led to a decrease in the yield and enantioselectivity (entries 3 and 4). Chiraphos, Me-Duphos, and Ph-Garphos showed low reactivity (entries 5–7). The comparative experiments showed that the BAR^{F4} counterion is crucial for reactivity, no desired product is obtained when [Ir(cod)₂](BF₄) or

Table 1. Optimization of the enantioselective cationic iridium(I)-catalyzed hydroacylation of **1a**.



entry	[Ir]	ligand	yield (%) ^[a]	ee (%) ^[b]
1	[Ir(cod) ₂](BAR ^{F4})	(<i>R</i>)-binap	18	86
2	[Ir(cod) ₂](BAR ^{F4})	(<i>R</i>)-segphos	59	92
3	[Ir(cod) ₂](BAR ^{F4})	(<i>R</i>)-DM-segphos	45	88
4	[Ir(cod) ₂](BAR ^{F4})	(<i>R</i>)-DTBM-segphos	26	83
5	[Ir(cod) ₂](BAR ^{F4})	(2 <i>S</i> , 3 <i>S</i>)-chiraphos	n.r.	-
6	[Ir(cod) ₂](BAR ^{F4})	(<i>R</i> , <i>R</i>)-Me-duphos	9	80
7	[Ir(cod) ₂](BAR ^{F4})	(<i>R</i>)-Ph-garphos	27	93
8	[Ir(cod) ₂](BF ₄)	(<i>R</i>)-segphos	trace	-
9	[IrCl(cod)] ₂	(<i>R</i>)-segphos	trace	-
10 ^[c]	[Ir(cod) ₂](BAR ^{F4})	(<i>R</i>)-segphos	17	80
11 ^[d]	[Ir(cod) ₂](BAR ^{F4})	(<i>R</i>)-segphos	trace	-
12 ^[e]	[Ir(cod) ₂](BAR ^{F4})	(<i>R</i>)-segphos	61	89
13 ^[f]	[Ir(cod) ₂](BAR ^{F4})	(<i>R</i>)-segphos	42	92

[a] Determined by ¹H NMR using ethoxybenzene as internal standard. [b] Determined by HPLC analysis with a chiral column. [c] In 1,2-dichloroethane. [d] In 1,2-dimethoxyethane. [e] At 100 °C. [f] At 80 °C.

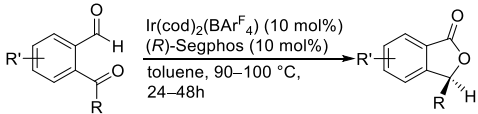


[IrCl(cod)]₂ are used as a precursor (entries 8 and 9). By subsequent solvent screening, we determined that a better yield was achieved in toluene than in other solvents (entries 10 and 11), and the reaction was completed at 100 °C to afford the desired product **2a** in a 61% isolated yield with 89% ee (entry 12). A decrease in the reaction temperature to 80 °C did not improve this result (entry 13). Unfortunately, the undesired decarbonylation of aldehydes to form simple arenes has been always observed.^[10, 11]

Then, the scope of cationic iridium-catalyzed enantioselective hydroacylation was investigated under the optimized conditions of entries 2 or 12 in **Table 1**. Differently substituted keto benzaldehydes **1** furnished the corresponding products **2** in moderate to good yields with good enantioselectivities (**Table 2**). The catalytic system proved to be tolerant of valuable functionality such as alkyl, halogen, ester or ether substituents. The Ketones bearing butyl substituent underwent hydroacylation to give the (*S*)-butylphthalide **2b** with high enantioselectivity, which is known to exhibit aduldicidal activity^[4] (entry 2). The methyl-bearing product **3b** is obtained in excellent enantioselectivity (98% ee, entry 3), albeit with a lower yield. 2-Acetylbenzaldehydes with sterically bulky tertiary butyl, fluoro, chloro and ester substituents at the 5-position react in good yield to give products **2d–2g** with high enantioselectivities (entries 4–7). 2-Acetyl-4-methoxybenzaldehyde (**1h**) provides a good yield of phthalide **2h** albeit with modest enantioselectivity (entry 8). Unfortunately, the substituent at the 3 or 6 position of substrate were inappropriate for our hydroacylation, and only the decarbonylated product was obtained (see Supporting Information (SI)).

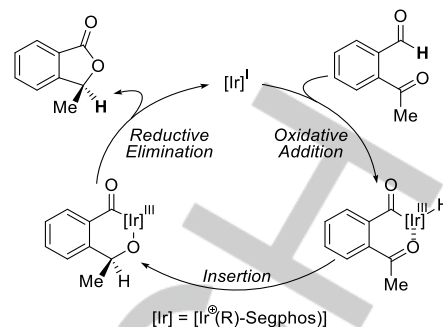
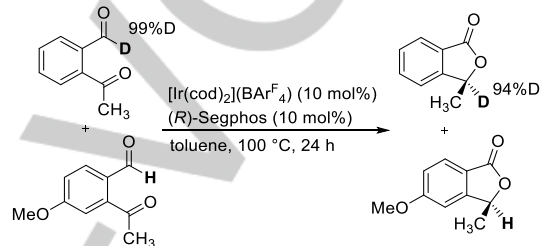
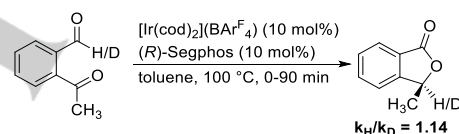
In addition, this system can be applied to the asymmetric hydroacylation of 2-benzoylbenzaldehydes. The reaction of substituted benzoyl substrates afforded the corresponding phthalides **2i–2n** in moderate to good yields with good enantioselectivities (entries 9–14). No reaction of ortho-substituted 2-benzoylbenzaldehydes was observed (see Supporting Information (SI)). When the aromatic ring of the ketone side has an electron-donating methoxy substituent (**1n**), the reaction gave the corresponding product **2n** in low yield (entry 14). Overall, it is notable that the cationic iridium complex was determined to be superior in the asymmetric hydroacylation of some 2-keto benzaldehyde substrates (entries 3, 7, 9, 11, 12 in Table 2) when compared to the reported catalysts.^[3f, 6, 7]

On the basis of pioneering mechanistic investigations by Dong^[3f] and Yoshikai,^[7] we proposed a catalytic cycle that proceeded via an oxidative addition/insertion/reductive elimination pathway (**Scheme 2**). To obtain an additional insight into the hydroacylation mechanism, we performed the competition experiments (**Scheme 3**). By subjecting of **1a–d** and **1h** to the competitive hydroacylation conditions, **2a–d** was formed without the erosion of deuterium and without deuterium incorporation at the benzyl position in **2h**. This result implies that the carbonyl insertion into the Ir–H bond presumably proceeds in an intramolecular manner under the conditions used.^[7] Next, kinetic isotope effect (KIE) experiments were undertaken for reactions using substrates **1a** and **1a–d** as the starting material (**Scheme 4**). Thus, the *k_H*/*k_D* ratio of 1.14 was observed, which suggested that the formyl C–H bond activation was not included in the turnover-limiting step in our developed cationic iridium-catalyzed enantioselective carbonyl hydroacylation.

Table 2. Substrate scope of the enantioselective hydroacylation of 2-keto benzaldehydes.^[a]


entry	substrate	product	time (h)	yield (%) ^[b]	ee (%) ^[c]
1			24	59 61 ^[d]	92 89 ^[d]
2			48	52	96
3			48	38	98
4			48	71 ^[d]	95 ^[d]
5			48	69	90
6			48	70	93
7			48	64	97
8			48	68	74
9			48	74	95
10			48	63 ^[d]	84 ^[d]
11			24	64 ^[d]	90 ^[d]
12			24	71 ^[d]	94 ^[d]
13			48	46	89
14			24	23 ^[e]	80

^[a] Reaction conditions: 1a (0.25 mmol), [Ir(cod)₂](BArF₄) (10 mol%), and (*R*)-Segphos (1 equiv to Ir) in toluene, stirred at 90 °C under a N₂ atmosphere. ^[b] Isolated yield. ^[c] Determined by HPLC analysis with a chiral column. ^[d] At 100 °C. ^[e] Determined by ¹H NMR using ethoxybenzene as internal standard.

**Scheme 2.** Proposed catalytic cycle.**Scheme 3.** Competitive hydroacylation with isotopically labeled compound.**Scheme 4.** Kinetic isotope effect.

In summary, we demonstrated the feasibility of the highly enantioselective atom-economical carbonyl hydroacylation of 2-keto benzaldehydes by iridium catalysis. The mechanistic experimental data allowed us to propose that carbonyl insertion proceeds via intramolecular pathway involving an iridium-hydride intermediate. In addition, the kinetic isotope studies revealed that the formyl C–H activation step was not involved in the turnover-limiting step of carbonyl hydroacylation. Overall, this study demonstrates that the iridium-catalyzed direct enantioselective formyl C–H addition to ketones provides new examples of asymmetric carbonyl hydroacylation to synthesize optically active molecules. Efforts to extend the scope of enantioselective reactions, which encompass various double bonds, are in progress.

Experimental Section

General procedure: All reactions were carried out in a dry solvent under a nitrogen atmosphere. To a dried flask, [Ir(cod)₂](BArF₄) (31.8 mg, 10 mol%), (*R*)-Segphos (15.3 mg, 10 mol%) and toluene (2.0 mL) were added under N₂ atmosphere. The solution was stirred at 50 °C for 30 min. Thereafter, 2-keto benzaldehyde (37.0 mg, 0.25 mmol) was added. The reaction mixture was further heated to 90 °C and stirred for 24 h. After removal of the solvent in vacuo, the mixture was purified using silica gel column

chromatography (eluent: Hexane/AcOEt) to afford a pure phthalide product.

Acknowledgements

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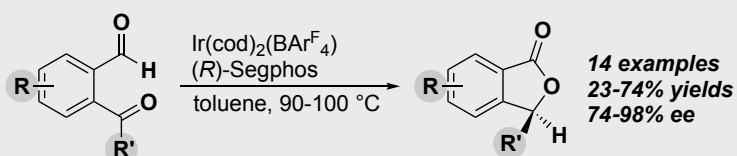
Keywords: hydroacylation • ketone • C–H activation • cationic iridium • enantioselective

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- [8] T. Shirai, K. Sugimoto, M. Iwasaki, R. Sumida, H. Fujita, Y. Yamamoto, *Synlett* **2019**, *30*, 972–976.
- [9] Absolute Configuration of product **2a** was determined to be (S) by the specific rotation reported for (S)-isomer and retention times of two enantiomers in HPLC analysis, See: ref. 3f)
- [10] When the hydroacylation reaction was carried out under an atmosphere of carbon monoxide (1.0 atm), a desired product was not obtained and the starting materials **1a** was recovered quantitatively.
- [11] To study the catalytic intermediates formed during the hydroacylation with competitive decarbonylation by cationic iridium, IR study under the standard decarbonylation conditions was carried out (see supporting information for details). The reaction mixture obtained by decarbonylation was vacuum dried, IR spectroscopy of the remaining solid residue revealed a strong band at 2090–2100 cm⁻¹ corresponding to a carbonyl ligand. Thus, this indicated that the carbon monoxide generated by competitive decarbonylation of the aldehyde may serve as a carbonyl ligand to iridium center.

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Entry for the Table of Contents

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Tomohiko Shirai*, Tomoya Iwasaki,
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Hydroacylation of Ketones**

A facile and convenient synthesis of the chiral phthalide framework catalyzed by cationic iridium was developed. The method utilized cationic iridium/bisphosphine-catalyzed asymmetric intramolecular carbonyl hydroacylation of 2-keto benzaldehydes to furnish the corresponding optically active phthalide products in good to excellent enantioselectivities (up to 98% ee).