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Iridium-Catalyzed Direct Asymmetric Alkylation of Aniline Derivatives using 2-Norbornene

Tomohiko Shirai ^[a], Takakazu Okamoto ^[a], and Yasunori Yamamoto ^[b]

Abstract: We investigate an efficient and highly enantioselective direct alkylation process for acetanilides that use 2-norbornene with a bis(phosphoramidite)-cationic Ir catalytic system (up to 99% ee). This methodology allows the facile preparation of enantiomerically enriched *exo*-2-(bicyclo[2.2.1]heptan-2-yl)aniline, which can be readily transformed into other functionalities.

Enantioselective transformations through the activation of C–H bond depict a potential to become an ideal tool for the synthesis of chiral building blocks.^[1] Recently, transition-metal-catalyzed asymmetric direct additions of C–H bond have become impressive synthetic methods for building useful functionalized molecules from ubiquitous chemicals.^[2–5] Our research group has already demonstrated that the cationic Ir(I)/Me-BIPAM complexes can catalyze the asymmetric direct addition of C(sp²)–H bonds to unsaturated compounds such as C=O and C=C.^[6] In 2015, we reported the first highly enantioselective intermolecular direct addition of C(sp²)–H bonds to bicycloalkenes (Scheme 1).^[6b] In our reaction, an amide-based directing group (DG) depicted a better performance than that depicted ketone based DG. However, it is difficult to convert tertiary amides to form other functionalities.^[7] In this context, aniline derivatives, such as acetanilide, can be conventionally prepared and readily transformed into other functional groups. To the best of our knowledge, very few examples of aniline derivatives-directed asymmetric C–C bond formation through C–H bond activation have been reported. Shibata and co-workers developed the first acetanilide directed cationic iridium/chiral bis(phosphine) complex-catalyzed enantioselective C–H conjugate addition to the α,β -unsaturated carbonyl compounds. However, the products were only obtained in moderate yields with good enantioselectivity.^[3h] Therefore, no systems are observed to exist for the aniline derivatives-directed intermolecular asymmetric C–H addition to alkenes with high efficiency and high enantioselectivity. In this study, we describe the iridium/(*R,R*)-S-Me-BIPAM-catalyzed direct asymmetric alkylation of acetanilides using 2-norbornene.

We initiated our investigations by studying the reaction parameters, such as the precursors, chiral ligands and solvents

in asymmetric direct alkylation of 2-methylacetanilide (**1a**) with 2-norbornene (Table 1). **1a** was selected to be the model substrate in order to avoid the complication of overalkylation.

Scheme 1. Enantioselective intermolecular alkylation with bicycloalkenes.

Table 1. Optimization of the reaction conditions.^[a]

entry	Precursor	L*	Solvent	Yield [%] ^[b]	ee [%] ^[c]
1	[Ir(cod)Cl] ₂	L1	DCE	n.r.	-
2	Ir(cod) ₂ (BF ₄)	L1	DCE	39	99
3	Ir(cod) ₂ (BAr ^F ₄)	L1	DCE	89	97
4	Ir(cod) ₂ (BAr ^F ₄)	L2	DCE	52	73
5 ^[d]	Ir(cod) ₂ (BAr ^F ₄)	L*	DCE	8	12
6 ^[e]	Ir(cod) ₂ (BAr ^F ₄)	L*	DCE	77	20
7	Ir(cod) ₂ (BAr ^F ₄)	L1	Toluene	90	93
8	Ir(cod) ₂ (BAr ^F ₄)	L1	DME	69	97
9	Ir(cod) ₂ (BAr ^F ₄)	L1	THF	71	99
10	Ir(cod) ₂ (BAr ^F ₄)	L1	Dioxane	92	97
11 ^[f]	Ir(cod) ₂ (BAr ^F ₄)	L1	Dioxane	83	97

[a] Reaction conditions: **1a** (0.25 mmol), **2** (3.5 equiv), Ir cat. (5 mol%), and chiral ligand (1.1 equiv to Ir) in solvent, stirred for 21 h at 135 °C. [b] Isolated yield. n.r. = no reaction. [c] Determined by HPLC analysis. [d] (*R*)-

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BINAP was used. [e] (*R*)-Monophos was used. [f] At 100 °C.

As shown in the entries 1–3 of Table 1, alkylation in the presence of 5 mol% $[\text{Ir}(\text{cod})\text{Cl}]_2$ and (*R,R*)-S-Me-BIPAM in DCE at 135 °C did not yield **2a**. When $[\text{Ir}(\text{cod})_2](\text{BARF}_4)$ was used, the reaction proceeded smoothly to afford the alkylated product in high yield and excellent enantioselectivity (entry 3, 89%, 97% ee). However, the use of (*R*)-BINAP or (*R*)-Monophos caused reduced yields and low enantioselectivities (entries 5–6). The solvent had some effect on the yield and enantioselectivity (entries 7–10), and the highest yields could be obtained using 1,4-dioxane (entry 10). Lowering the reaction temperature from 135 °C to 100 °C slightly decreased the yield; however, excellent enantioselectivity was obtained. (entry 11, 83%, 97% ee).

We further explored the applicability of the optimized asymmetric alkylation conditions to various aniline derivatives (**1a–1n**), (Table 2). Differently substituted aniline derivatives (**1a–1d**) furnished the corresponding products (**2a–2d**) in good yields with high enantioselectivities. Hydrocarbon substituents, such as the ethyl, isopropyl, and *t*-butyl groups, on the amide structure did not interfere with the enantioselectivity. At the current level of development, carbamates and other tertiary amides were observed to be not suitable to serve as DGs (**2e**, **2f**). On the arene moiety, an extensive range of substituents, including Me, OMe, Cl, and CO_2Me , were tolerated (**2g–2j**; see supporting information for additional details).

Table 2. Iridium/S-Me-BIPAM-catalyzed asymmetric alkylation of aniline derivatives **1a–1n**.^[a]

[a] Reaction conditions: **1a** (0.25 mmol), **2** (3.5 equiv), $[\text{Ir}(\text{cod})_2](\text{BARF}_4)$ (5 mol%), and (*R,R*)-S-Me-BIPAM (1.1 equiv to Ir) in 1,4-dioxane, stirred for 21 h at 135 °C. [b] Isolated yield. n.r. = no reaction. [c] Determined by HPLC analysis.

The reaction of 2,3- or 2,4-disubstituted acetanilides (**1k–1m**) with 2-norbornene also produced the desired products (**2k–2m**) in good yields with high enantioselectivities. Unfortunately, 2-chloroacetanilide was not suitable for this reaction. In contrast to our previous study, dialkylation was only observed in case of the unsubstituted acetanilide (**2o**, 86%, the enantioselectivity could not be determined). These results suggest that the *mono*- or *di*-alkylation selectivity is dependent on the ease of bond rotation in the DG.

The acetamido group of product **2g** was readily eliminated by treat with aqueous NaOH to produce the corresponding aniline (**3**) in a yield of 84% (Scheme 2).^[8]

Scheme 2. Hydrolysis of **2g** with aqueous NaOH.

A catalytic cycle involving C–H activation, insertion of the C=C bond into the Aryl–Ir bond, and formation of the C–H bond causing reductive elimination has been already proposed in our previous study.^[6b] To gain an additional insight into the reaction mechanism, we performed D_2O experiments (Scheme 3). Exposure of 3-methylacetanilide (**1g**) to $[\text{Ir}(\text{cod})_2](\text{BARF}_4)/(\text{R,R})\text{-S-Me-BIPAM}$ with D_2O in the absence of 2-norbornene caused a deuterium-incorporation of 78% in the C6 position and of <5% in the C2 position. Furthermore, the same reaction was conducted with D_2O in the presence of 2-norbornene, and a deuterium-incorporation of 67% was observed in C6 position. The observation of H/D scrambling may illustrate that the C–H activation step is reversible (Figure 1). A similar deuterium experiment was conducted using 2-chloroacetanilide (**1n**). No deuterium incorporation was observed in the *ortho* position under catalytic conditions, which suggested that the chloro group negatively affects the C–H bond activation.

Scheme 3. Deuterium-incorporation in substrate **1g**.

Thus, we developed a highly *exo*-selective^[9] and enantioselective direct alkylation of aniline derivatives using 2-

norbornene catalyzed with the cationic Ir(*R,R*)-S-Me-BIPAM complex. Efforts to extend the scope of the enantioselective alkylation of aniline derivatives with unstrained alkenes and mechanistic investigations are currently underway.

Figure 1. The proposed catalytic cycle.

Experimental Section

General procedure: To a flame-dried flask, $[Ir(cod)_2](BAR^F_4)$ (0.0125 mmol, 5 mol%), (*R,R*)-S-Me-BIPAM (0.0138 mmol, 5.5 mol%), and 1,4-dioxane (1.0 mL) were added under an N_2 -atmosphere. The solution was stirred at room temperature for 30 min. Thereafter, acetanilide (0.25 mmol) and 2-norbornene (3.5 equiv.) were added. The reaction mixture was further heated to 135 °C and stirred for 24 h. The cooled mixture was purified using silica gel column chromatography (eluent: hexane/AcOEt) to afford pure hydroarylated product.

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COMMUNICATION

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