ORGANOMETALLICS

Article

pubs.acs.org/Organometallics

Iridium-Catalyzed Asymmetric Allylic Amination Reactions with *N*-Aryl Phosphoramidite Ligands

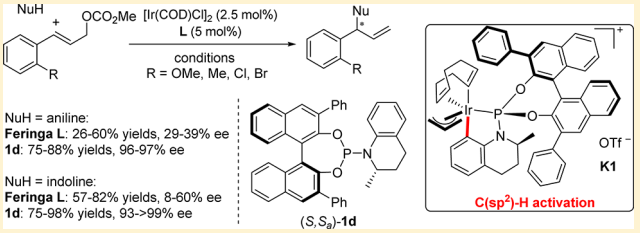
Xiao Zhang, Wen-Bo Liu, Qiang Cheng, and Shu-Li You*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, People's Republic of China

Collaborative Innovation Center of Chemical Science and Engineering, Tianjin, People's Republic of China

Supporting Information

ABSTRACT: A series of *N*-aryl phosphoramidite ligands were synthesized, and the iridium complexes derived from these novel ligands were proven to be efficient catalysts for asymmetric intermolecular allylic amination reactions. This C−N bond forming process readily accommodates a diverse range of amines and allylic carbonates, especially for the previously challenging ortho-substituted cinnamyl substrates. Moreover, isolation and characterization of the corresponding (π-allyl)−iridium complex **K1** reveal that the active iridacycle is generated through a C(sp^2)−H bond insertion of tetrahydroquinoline of the ligand.



INTRODUCTION

Iridium-catalyzed asymmetric allylic substitution reactions have become a powerful tool to construct chiral centers in organic synthesis.[1] A literature survey shows that many catalytic systems involving chiral ligands such as oxazolinyl-phosphine ligands,[1h] binaphthol-derived phosphoramidites,[2] phosphoramidite-olefin ligands,[3] and others[4] have been successfully demonstrated in this transformation.

In particular, Ir complexes derived from Feringa type ligands usually provide excellent regio- and enantioselectivity for a variety of substrates.[5] Subsequent mechanistic studies by the Hartwig group and the Helmchen group reveal that the active iridacycle catalyst is generated by cyclometalation of a methyl group of the ligand (Figures 1 and 2a).[6] Although the $[Ir(COD)Cl]_2$/**1a** combination is widely appreciated for its reactivity and selectivity, its sensitivity to steric hindrance somehow limits its application. For example, ortho-substituted phenyl allylic substrates were found to lead to a decrease in either yield or enantioselectivity in many cases (Scheme 1).[7] Recently, our group has developed a series of *N*-aryl phosphoramidite ligands, which offer high regio- and enantioselective control with a broad substrate scope involving sterically congested nucleophiles.[8] Moreover, these types of ligands were found to be superior to previously established systems in asymmetric allylic alkylation of ortho-substituted cinnamyl carbonates.[8a,b] One possibility for the high reactivity with sterically bulky substrates has been rationalized by the fact that the iridacycle catalyst, formed through C(sp^2)−H

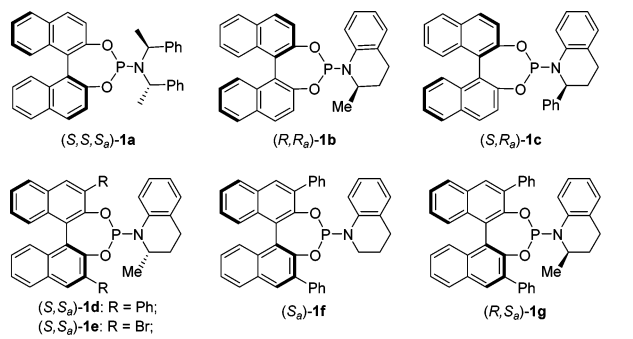


Figure 1. Phosphoramidite ligands.

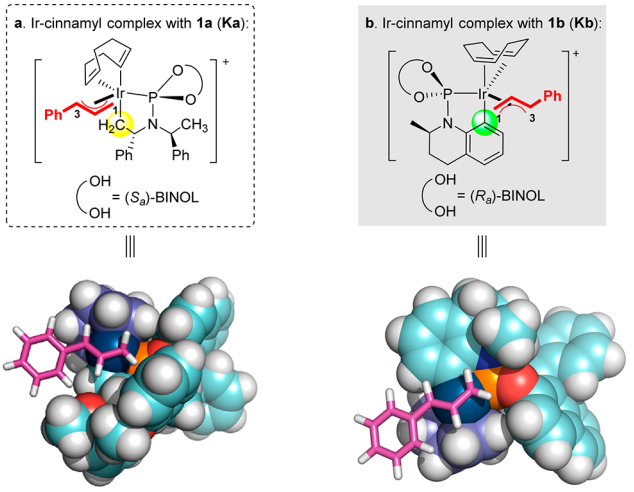
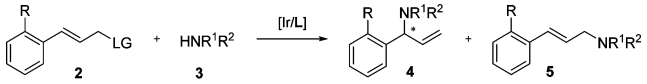


Figure 2. Structures and CPK models of iridium cinnamyl complexes (anions are omitted).

Received: April 26, 2016

DOI: 10.1021/acs.organomet.6b00339
Organometallics XXXX, XXX, XXX−XXX

Scheme 1. Ir-Catalyzed Allylic Amination with Ortho-Substituted Substrates

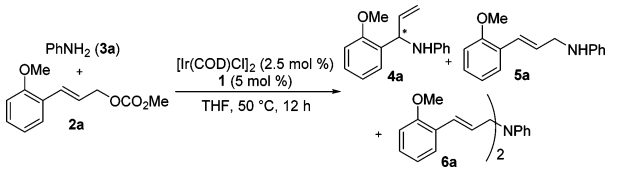


Challenge:
with [Ir]/**1a** system: lack of enantiocontrol (derease in the ee of **4**)
with [Ir]/**1b** system: loss of regiochemical control (decrease in the ratio of **4**:**5**)

activation of Me-THQphos (**1b**) with $[Ir(COD)Cl]_2$, is less sterically embraced in comparison with those derived from Feringa type ligands (Figure 2b).

We went on to apply Me-THQphos (**1b**) in asymmetric allylic aminations, with the hope of overcoming the low yield and enantioselectivity obtained from the reactions between ortho-substituted cinnamyl substrates and nitrogen-containing nucleophiles in previous studies.[7b,h] With 2-methoxylphenyl allylic carbonate and aniline as model substrates, Me-THQphos (**1b**) as a ligand resulted in a significantly increased enantioselectivity in comparison with **1a** (from 36% to 97% ee; Table 1, entries 1 and 2). To our surprise, the corresponding regioselectivity (branched to linear) decreased dramatically from 99/1 to 83/17. The C3 terminus of the allyl fragment of **Kb** (Figure 2b) is more electrophilic than the C1 terminus, which principally drives the branched selectivity as we reported previously.[9] However, by comparing the CPK models (Figure 2), we found that the C1 terminus of **Kb** is much less sterically surrounded than that of **Ka**. Thus, for the small but highly reactive nucleophiles (i.e., amines), although the branched product is still the major outcome, there are increased chances to attack the C1 terminus to form a linear product. We sought to improve the regioselectivity by engineering new ligands to create a crowded environment close by the C1 terminus in order to prevent it from being attacked. With these ideas in mind, several new *N*-aryl phosphoramidite ligands (**1c**–**g**), designed by the installment of substituents at the 3,3′-positions of the BINOL scaffold or increase in the size of the 2-substituent of tetrahydroquinoline, were synthesized and applied in the allylic amination reactions. We herein wish to report the results from this study.

Table 1. Investigation of Ligands in the Ir-Catalyzed Allylic Amination Reaction[a]



entry	1	4a/5a/6a[b]	yield of 4a (%)[c]	ee of 4a (%)[d]
1	**1a**	99/1/0	60	36 (*S*)
2	**1b**	83/14/3	61	97 (*S*)
3	**1c**	90/10/0	64	85 (*S*)
4	**1d**	99/1/0	88	97 (*R*)
5	**1e**	22/78/0	20	91 (*R*)
6	**1f**	99/1/0	87	55 (*R*)
7	**1g**	99/1/0	88	97 (*R*)
8[e]	**1d** + **1g**	99/1/0	88	97 (*R*)

[a]Reaction conditions: $[Ir(COD)Cl]_2$ (2.5 mol %), ligand **1** (5.0 mol %), **2a** (100 mol %), $PhNH_2$ (**3a**) (200 mol %) in THF at 50 °C unless noted otherwise. [b]Determined by ^1H NMR of the crude reaction mixture. [c]Isolated yield. [d]The ee of **4a** was determined by HPLC analysis. [e]A mixture of **1d** (2.5 mol %) and **1g** (2.5 mol %) was used.

RESULTS AND DISCUSSION

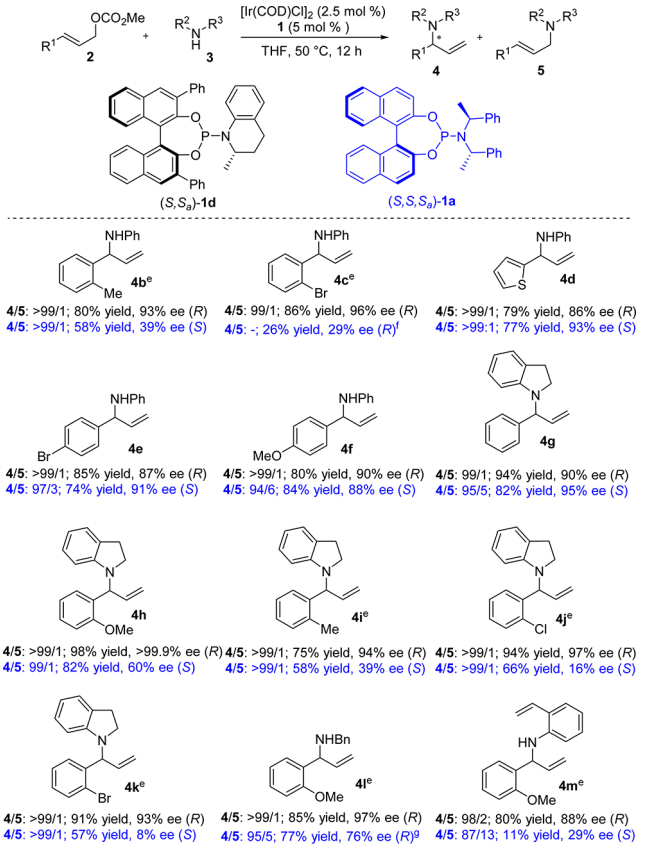
Optimization of the Reaction Conditions. We next investigated the efficiency of these *N*-aryl phosphoramidite ligands[10] in iridium-catalyzed allylic amination reactions (Table 1). The 2-phenyl-substituted ligand **1c** led to a slightly increased regioselectivity, but a decreased enantioselectivity (entry 3). To our delight, ligand **1d**,[8i] by introducing double phenyl substituents at the 3,3′-positions of BINOL, was found to be able to improve the branched selectivity dramatically (99/1), meanwhile maintaining the excellent enantioselectivity (97% ee, entry 4). In comparison, linear product was formed favorably when 3,3′-dibromo-substituted binaphthol derived ligand **1e** was used (**4a**/**5a**/**6a** = 22/78/0, entry 5). A sharp decrease in the enantioselectivity (55% ee) was observed when ligand **1f** without a methyl group in the amine part was employed (entry 6). Interestingly, employment of ligand **1g**, a diastereomer of **1d** with an opposite configuration in the amine part, provided results in terms of selectivity and yield identical with those of the reaction with **1d** (entry 4 vs entry 7). Given the same reactivity and selectivity of the catalysts derived from **1d** and **1g**, we envisioned that it was not necessrary for the 2-methyl-1,2,3,4-tetrahydroquinoline to be enantiopure in this case. Further evidence was obtained by the use of a combination of $[Ir(COD)Cl]_2$ with a mixture of identical amounts of **1d** and **1g**, affording the same yields and selectivities as expected (**4a**/**5a**/**6a** = 99/1/0, 88% yield, 97% ee, entry 8). Since the mixture of diastereomers is easily accessed from readily available enantiopure BINOL and racemic 2-methyltetrahydroquinoline directly, the utilization of this diastereomeric ligand mixture will provide an economic alternative for ligand **1d** or **1g**, especially for scale-up reactions.

Substrate Scope. With the optimized reaction conditions in hand, our efforts were focused on expanding the reaction substrate scope by exploring various nitrogen-containing nucleophiles and ortho-substituted phenyl allylic carbonates (Scheme 2). The results obtained with **1a** as ligand for comparison were adhered to (highlighted in blue). First, with aniline as the nucleophile, the cinnamyl carbonate with an electron-donating methyl group at the ortho position was tested (**1d** as the ligand), affording the desired product **4b** in good yield and excellent enantioselectivity (80% yield, 93% ee). In sharp contrast, only a moderate ee was obtained when **1a** was employed as the ligand (58% yield, 39% ee, **4b**; Scheme 2). It is worth noting that the reaction of 2-bromocinnamyl ethyl carbonate with aniline catalyzed by the chiral Ir complex derived from $[Ir(COD)Cl]_2$ and (R,R,R_a)-**1a** form product **4c** in 26% yield and 29% ee.[7i] Pleasingly, with a catalyst derived from $[Ir(COD)Cl]_2$ and ligand **1d**, 2-bromocinnamyl methyl carbonate was converted to its amination product **4c** in 86% yield and 96% ee. Moreover, non-ortho-substituted substrates including heteroaryl allyl carbonate and para-substituted cinnamyl carbonates proceeded smoothly, with ligand **1d** yielding **4d**–**f** with satisfactory results (79–85% yields, 86–90% ee) in comparison with those obtained from ligand **1a** (74–84% yields, 88–93% ee; Scheme 2), showcasing the generality of the current catalytic system.

To further test the potential of this Ir-catalyzed allylic amination reactions, we turned our attention toward other nucleophiles such as indoline due to its prevalence in natural products (**4g**–**k**, Scheme 2). While ligand **1a** could only give

DOI: 10.1021/acs.organomet.6b00339
Organometallics XXXX, XXX, XXX–XXX

Scheme 2. Substrate Scope of the Ir-Catalyzed Allylic Amination Reactions[a−d]



[a]Reaction conditions: $[Ir(COD)Cl]_2$ (2.5 mol %), ligand **1** (5.0 mol %), **2** (100 mol %), and **3** (200 mol %) in THF at 50 °C unless noted otherwise. The top results are from ligand **1d** (black), while the bottom results are from ligand **1a** (blue). [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Isolated yield. [d]ee of **4** was determined by HPLC analysis. [e]$[Ir(COD)Cl]_2$ (5.0 mol %) and ligand **1** (10.0 mol %) were used. [f]2-Bromocinnamyl ethyl carbonate was used as the substrate, and *ent*-**1a** was used as the ligand; see ref 7i. [g]*ent*-**1a** was used as the ligand; see ref 2c.

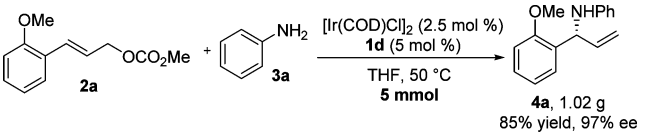
moderate ee values (8−60% ee) except for the non-ortho-substituted **4g** (95% ee), excellent enantioselectivity (90−99.9% ee) was obtained for the amination process with cinnamyl carbonates having varying substituents (H, OMe, Me, Cl, Br) at the ortho position of the phenyl group by ligand **1d**. In addition to the significant increase in enantioselectivity, the yields of products could be improved in most cases.

Finally, benzylamine and 2-vinylaniline were also proven to be suitable nucleophiles. The reactions with 2-methoxy cinnamyl methyl carbonate proceeded smoothly, leading to the desired products **4l**,**m** in better yields (85 and 80%, respectively) and ee value (97% and 88% ee, respectively) by utilizing ligand **1d** in comparison with ligand **1a** (77% and 11% yields and 76% and 29% ee, respectively; Scheme 2).

In order to demonstrate the robustness and practicality of the current method, a gram-scale reaction was carried out. The allylic amination reaction between aniline and 2-methoxy cinnamyl methyl carbonate was performed on a 5.0 mmol scale to give product **4a** in 85% yield and 97% ee (Scheme 3).

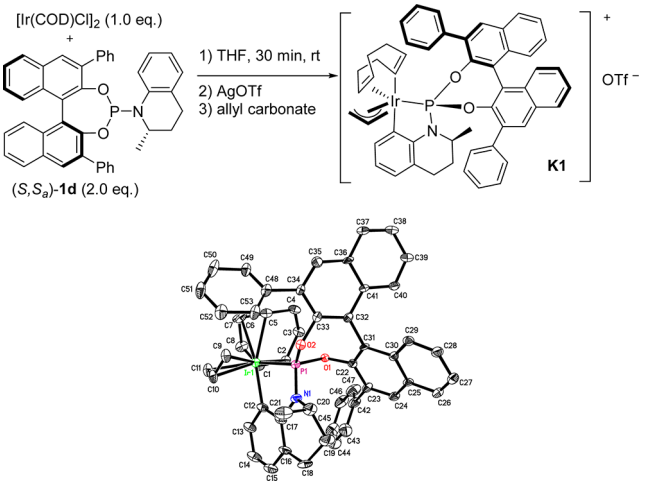
Preparation of the π-Allyl−Iridium Complex. Evaluation of the substrate scope led to the observation that the

Scheme 3. Gram-Scale Synthesis of 4a



configuration of the branched products is opposite by using **1d** and **1a**, although ligands **1d** and **1a** have the same chirality of binaphthol. The same phenomenon is also observed in the allylic alkylations.[8b] Consistent with C(sp^2)−H bond activation for ligand **1b**, it is likely that the active catalytic species of iridium complex is generated through C(sp^2)−H bond activation in ligand **1d** rather than C(sp^3)−H bond activation. To verify this hypothesis, π-allyl−iridium complex **K1** was synthesized according to a one-pot procedure[6c,d] developed by Helmchen and co-workers (Scheme 4). This complex was

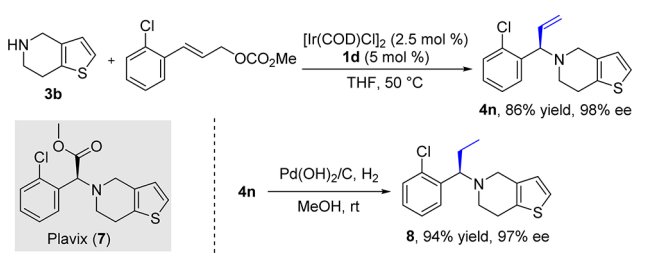
Scheme 4. Preparation and X-ray Structure of the (π-Allyl)−Ir−1d Complex K1



obtained as a mixture of endo and exo isomers in a ratio of 92:8. The C(sp^2)−H bond activation was confirmed unambiguously by an X-ray crystallographic analysis of a crystal of **K1**.[10]

Synthetic Application. Plavix (**7**) is an antiplatelet medication which is used in the prevention of blood clotting as well as reducing the risk of heart attack and stroke.[11] Compound **8** displays antithrombotic and anti-blood-platelet-aggregating activities.[12] As shown in Scheme 5, the reaction (or allylic alkylation, since we are talking about **3b**) of commercially available **3b** with 2-chloro cinnamyl methyl carbonate proceeded smoothly under the optimized conditions, delivering the desired product **4n** in 86% yield and 98% ee. Attempts to

Scheme 5. Transformation



DOI: 10.1021/acs.organomet.6b00339
Organometallics XXXX, XXX, XXX−XXX

convert **4n** to Plavix under various oxidation conditions have failed so far.[13] Subjecting compound **4n** (98% ee) to a $Pd(OH)_2$/C-catalyzed hydrogenation reaction afforded compound **8** in 94% yield and 97% ee.

CONCLUSION

In conclusion, various *N*-aryl phosphoramidite ligands were synthesized and demonstrated to be superior to the Feringa ligands in Ir-catalyzed allylic amination reactions, especially when ortho-substituted cinnamyl carbonates were used. High to excellent regio- and enantioselectivities could be achieved for several nitrogen-containing nucleophiles, including aniline, indoline, benzylamine, and 2-vinylaniline. X-ray analysis of a (π-allyl)−iridium complex revealed that the active Ir complex is formed via a C(sp^2)−H activation.

EXPERIMENTAL SECTION

General Procedure for Ir-Catalyzed Allylic Amination Reaction. In a dry Schlenk tube filled with argon, $[Ir(COD)Cl]_2$ (3.3 mg, 0.005 mmol, 2.5 mol %), phosphoramidite ligand **1d** (6.1 mg, 0.01 mmol, 5 mol %), and propylamine (0.5 mL) were dissolved in THF (0.5 mL). The reaction mixture was heated to 50 °C for 30 min and then the volatile solvents were removed in vacuum to give a yellow solid. In this tube, allylic carbonate **2** (0.20 mmol) and amine **3** (0.4 mmol, 2 equiv) were added and stirred at 50 °C until the reaction was complete. The solvent was evaporated and the regioselectivity (**4**/**5**) was determined by ^{1}H NMR of the crude reaction mixture. The residue was purified by silica gel column chromatography using PE/EA as the eluent to give desired product **4**.

Compound (*R*)-4a. Yellow oil, 37.7 mg, 88% yield, 97% ee (Daicel Chiralcel OD-H (0.46 cm × 25 cm), *n*-hexane/2-propanol 98/2, v = 0.8 mL min^{-1}, λ 230 nm, t(major) = 7.64 min, t(minor) = 8.56 min); $[\alpha]_D^{23}$ = +26.0 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H, OCH_3), 4.20 (br s, 1H, NH), 5.14−5.24 (m, 2H, CH_2), 5.33 (d, $^3J_{H-H}$ = 5.2 Hz, 1H, CH), 6.07 (ddd, $^3J_{H-H}$ = 5.6, $^3J_{H-H}$ = 10.4, $^3J_{H-H}$ = 17.2 Hz, 1H, CH), 6.60 (d, $^3J_{H-H}$ = 10.0 Hz, 2H, Ar-H), 6.66 (t, $^3J_{H-H}$ = 8.4 Hz, 1H, Ar-H), 6.89−6.94 (m, 2H, Ar-H), 7.10−7.14 (m, 2H, Ar-H), 7.24 (dt, $^4J_{H-H}$ = 2.0, $^3J_{H-H}$ = 7.6 Hz, 1H, Ar-H), 7.31 (dd, $^4J_{H-H}$ = 1.6, $^3J_{H-H}$ = 7.6 Hz, 1H, Ar-H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 54.6, 55.4, 110.7, 113.4, 115.1, 117.3, 120.8, 127.7, 128.4, 129.0, 129.7, 138.6, 147.3, 156.8. IR (thin film): ν_{max} (cm^{-1}) 3409, 3050, 2836, 1599, 1500, 1462, 1436, 1314, 1238, 1179, 1089, 1049, 1026, 992, 922, 870, 746, 691. HRMS (ESI): calcd for $C_{16}H_{18}NO$ [M + H]$^+$, 240.1383; found, 240.1374.

Compound (*R*)-4b. Yellow oil, 37.2 mg, 80% yield, 93% ee (Daicel Chiralpak AD-H (0.46 cm × 25 cm), *n*-hexane/2-propanol 100/1, v = 0.5 mL min^{-1}, λ 214 nm, t(major) = 15.53 min, t(minor) = 16.78 min); $[\alpha]_D^{20}$ = −6.5 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.38 (s, 3H, CH_3), 3.95 (br s, 1H, NH), 5.09 (d, $^3J_{H-H}$ = 4.8 Hz, 1H, CH), 5.23 (d, $^3J_{H-H}$ = 18.3 Hz, 1H, CH_2), 5.25 (d, $^3J_{H-H}$ = 9.0 Hz, 1H, CH), 6.04 (ddd, $^3J_{H-H}$ = 5.1, $^3J_{H-H}$ = 10.2, $^3J_{H-H}$ = 16.2 Hz, 1H, CH), 6.55 (d, $^3J_{H-H}$ = 7.5 Hz, 2H, Ar-H), 6.68 (t, $^3J_{H-H}$ = 7.2 Hz, 1H, Ar-H), 7.10−7.19 (m, 5H, Ar-H), 7.36−7.40 (m, 1H, Ar-H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 19.2, 56.9, 113.1, 116.4, 117.4, 126.4, 126.5, 127.3, 129.1, 130.6, 136.0, 137.8, 139.4, 147.3. IR (thin film): ν_{max} (cm^{-1}) 3410, 3051, 3020, 2962, 2920, 2852, 1602, 1502, 1461, 1428, 1316, 1261, 1090, 1019, 926, 868, 799, 749, 727, 692. HRMS (ESI): calcd for $C_{16}H_{18}N$ [M + H]$^+$, 224.1434; found, 224.1430.

Compound (*R*)-4c.[7i] Yellow oil, 50.2 mg, 86% yield, 96% ee (Daicel Chiralpak AD-H (0.46 cm × 25 cm), *n*-hexane/2-propanol 98/2, v = 1.0 mL min^{-1}, λ 220 nm, t(major) = 5.64 min, t(minor) = 6.94 min); $[\alpha]_D^{20}$ = −87.2 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.23 (br s, 1H, NH), 5.19−5.26 (m, 2H, CH_2), 5.40 (d, $^3J_{H-H}$ = 6.0 Hz, 1H, CH), 6.04 (ddd, $^3J_{H-H}$ = 5.6, $^3J_{H-H}$ = 10.4, $^3J_{H-H}$ = 17.2 Hz, 1H, CH), 6.54 (d, $^3J_{H-H}$ = 9.6 Hz, 2H, Ar-H), 6.67−6.70 (m, 1H, Ar-H), 7.10−7.14 (m, 2H, Ar-H), 7.19−7.23 (m, 2H, Ar-H), 7.37−7.40 (m, 1H, Ar-H), 7.43−7.46 (m, 1H, Ar-H).

Compound (*R*)-4d. Yellow oil, 30.3 mg, 79% yield, 86% ee (Daicel Chiralcel OJ-H (0.46 cm × 15 cm), *n*-hexane/2-propanol 80/20, v = 0.5 mL min^{-1}, λ 230 nm, t(minor) = 22.04 min, t(major) = 25.13 min); $[\alpha]_D^{20}$ = −64.9 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.05 (br s, 1H, NH), 5.21 (br s, 1H, CH), 5.25−5.38 (m, 2H, CH_2), 6.06 (ddd, $^3J_{H-H}$ = 6.0, $^3J_{H-H}$ = 10.4, $^3J_{H-H}$ = 17.2 Hz, 1H, CH), 6.65 (dd, $^4J_{H-H}$ = 1.2, $^3J_{H-H}$ = 8.8 Hz, 2H, Ar-H), 6.71−6.75 (m, 1H, Ar-H), 6.96−7.01 (m, 2H, Ar-H), 7.14−7.18 (m, 2H, Ar-H), 7.22 (dd, J = $^4J_{H-H}$ = 1.6, $^3J_{H-H}$ = 5.2 Hz, 1H, Ar-H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 56.3, 113.7, 116.5, 118.1, 124.6, 124.7, 126.9, 129.1, 138.2, 146.3, 146.7. IR (thin film): ν_{max} (cm^{-1}) 3663, 3401, 2969, 2903, 1599, 1500, 1428, 1312, 1256, 1228, 1179, 1068, 1038, 991, 926, 795, 748, 690. MS-EI: 215 [M]$^+$. HRMS-EI: m/z [M]$^+$ calcd for $C_{13}H_{13}NS$ (M$^+$), 215.0769; found, 215.0772.

Compound (*R*)-4e.[14] Yellow oil, 48.6 mg, 85% yield, 87% ee (Daicel Chiralpak AD-H (0.46 cm × 25 cm), *n*-hexane/2-propanol 98/2, v = 1.0 mL min^{-1}, λ 230 nm, t(major) = 7.85 min, t(minor) = 8.36 min); $[\alpha]_D^{20}$ = +1.5 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.01 (br s, 1H, NH), 4.89 (d, $^3J_{H-H}$ = 5.7 Hz, 1H, CH), 5.22 (d, $^3J_{H-H}$ = 11.1 Hz, 1H, CH_2), 5.23 (d, $^3J_{H-H}$ = 17.1 Hz, 1H, CH_2), 6.00 (ddd, $^3J_{H-H}$ = 6.0, $^3J_{H-H}$ = 9.9, $^3J_{H-H}$ = 16.8 Hz, 1H, CH), 6.55 (d, $^3J_{H-H}$ = 7.8 Hz, 2H, Ar-H), 6.70 (t, $^3J_{H-H}$ = 7.5 Hz, 1H, Ar-H), 7.13 (t, $^3J_{H-H}$ = 7.8 Hz, 2H, Ar-H), 7.25 (d, $^3J_{H-H}$ = 8.1 Hz, 2H, Ar-H), 7.46 (d, $^3J_{H-H}$ = 8.4 Hz, 2H, Ar-H).

Compound (*R*)-4f.[14] Yellow oil, 35.1 mg, 80% yield, 90% ee (Daicel Chiralcel OD-H (0.46 cm × 25 cm), *n*-hexane/2-propanol 100/1, v = 0.5 mL min^{-1}, λ 214 nm, t(major) = 31.78 min, t(minor) = 37.58 min); $[\alpha]_D^{20}$ = +18.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 (s, 3H, OCH_3), 3.98 (br s, 1H, NH), 4.88 (d, $^3J_{H-H}$ = 5.1 Hz, 1H, CH), 5.21 (d, $^3J_{H-H}$ = 11.4 Hz, 1H, CH_2), 5.26 (d, $^3J_{H-H}$ = 18.3 Hz, 1H, CH_2), 6.01 (ddd, $^3J_{H-H}$ = 6.0, $^3J_{H-H}$ = 10.2, $^3J_{H-H}$ = 16.8 Hz, 1H, CH), 6.59 (d, $^3J_{H-H}$ = 8.1 Hz, 2H, Ar-H), 6.68 (t, $^3J_{H-H}$ = 7.2 Hz, 1H, Ar-H), 6.88 (d, $^3J_{H-H}$ = 8.7 Hz, 2H, Ar-H), 7.13 (d, $^3J_{H-H}$ = 7.5 Hz, 2H, Ar-H), 7.29 (d, $^3J_{H-H}$ = 9.0 Hz, 2H, Ar-H).

Compound (*R*)-4g.[15] Yellow oil, 44.3 mg, 94% yield, 90% ee (Agilent 1260 Infinity Analytical SFC system, Daicel Chiralpak IC (0.46 cm × 15 cm), CO_2/2-propanol 95/5, v = 1.3 mL min^{-1}, λ 214 nm, t(major) = 6.56 min, t(minor) = 6.90 min); $[\alpha]_D^{23}$ = +33.9 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.95 (t, $^3J_{H-H}$ = 8.8 Hz, 2H, CH_2), 3.30−3.40 (m, 2H, CH_2), 4.96 (d, $^3J_{H-H}$ = 7.6 Hz, 1H, CH), 5.28−5.32 (m, 2H, CH_2), 6.05−6.14 (m, 1H, CH), 6.30 (d, $^3J_{H-H}$ = 8.0 Hz, 1H, Ar-H), 6.62 (t, $^3J_{H-H}$ = 7.2 Hz, 1H, Ar-H), 6.95 (t, $^3J_{H-H}$ = 7.6 Hz, 1H, Ar-H), 7.06 (dd, $^4J_{H-H}$ = 0.8, $^3J_{H-H}$ = 7.2 Hz, 1H, Ar-H), 7.25−7.29 (m, 1H, Ar-H), 7.34 (t, $^3J_{H-H}$ = 7.2 Hz, 2H, Ar-H), 7.42 (d, $^3J_{H-H}$ = 8.8 Hz, 2H, Ar-H).

Compound (*R*)-4h. Yellow oil, 52.0 mg, 98% yield, > 99.9% ee (Daicel Chiralcel OD-H (0.46 cm × 25 cm), *n*-hexane/2-propanol 1000/1, v = 1.0 mL min^{-1}, λ 230 nm, t(minor) = 18.35 min, t(major) = 23.89 min); $[\alpha]_D^{20}$ = +35.9 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.88−2.94 (m, 2H, CH_2), 3.23−3.42 (m, 2H, CH_2), 3.79 (s, 3H, OCH_3), 5.19−5.28 (m, 2H, CH_2), 5.42 (d, $^3J_{H-H}$ = 6.3 Hz, 1H, CH), 6.05 (ddd, $^3J_{H-H}$ = 6.6, $^3J_{H-H}$ = 10.2, $^3J_{H-H}$ = 17.1 Hz, 1H, CH), 6.38 (d, $^3J_{H-H}$ = 7.8 Hz, 1H, Ar-H), 6.57 (t, $^3J_{H-H}$ = 7.2 Hz, 1H, Ar-H), 6.90 (t, $^3J_{H-H}$ = 8.7 Hz, 2H, Ar-H), 6.95 (t, $^3J_{H-H}$ = 8.7 Hz, 1H, Ar-H), 7.02 (d, $^3J_{H-H}$ = 7.5 Hz, 1H, Ar-H), 7.20−7.27 (m, 1H, Ar-H), 7.38 (dd, $^4J_{H-H}$ = 1.5, $^3J_{H-H}$ = 7.8 Hz, 1H, Ar-H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 28.3, 50.2, 55.5, 57.1, 107.6, 110.7, 116.3, 116.8, 120.4, 124.0, 127.0, 128.3, 128.6, 128.9, 129.9, 136.6, 151.8, 157.0. IR (thin film): ν_{max} (cm^{-1}) 2836, 1677, 1603, 1488, 1460, 1242, 1159, 1107, 1050, 1026, 922, 741, 685. HRMS (ESI): calcd for $C_{18}H_{20}NO$ [M + H]$^+$, 266.1539; found, 266.1541.

Compound (*R*)-4i. Yellow oil, 44.1 mg, 75% yield, 94% ee (Daicel Chiralcel OD-H (0.46 cm × 25 cm), *n*-hexane/2-propanol 98/2, v = 0.5 mL min^{-1}, λ 214 nm, t(minor) = 12.70 min, t(major) = 13.88 min); $[\alpha]_D^{23}$ = +64.2 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H, CH_3), 2.93 (t, $^3J_{H-H}$ = 8.7 Hz, 2H, CH_2), 3.15−3.23 (m, 1H, CH_2), 3.29−3.38 (m, 1H, CH_2), 5.07 (d, $^3J_{H-H}$ = 6.6 Hz, 1H, CH), 5.23 (d, $^3J_{H-H}$ = 17.1 Hz, 1H, CH_2), 5.26 (d, $^3J_{H-H}$ = 10.2 Hz, 1H, CH_2), 6.05 (ddd, $^3J_{H-H}$ = 6.9, $^3J_{H-H}$ = 10.2, $^3J_{H-H}$ = 17.1 Hz, 1H, CH), 6.24 (d, $^3J_{H-H}$ = 8.1 Hz, 1H, Ar-H), 6.60 (t, $^3J_{H-H}$ = 7.5 Hz, 1H,

DOI: 10.1021/acs.organomet.6b00339
Organometallics XXXX, XXX, XXX−XXX

Ar-H), 6.95 (t, $^3J_{H-H}$ = 7.8 Hz, 1H, Ar-H), 7.04 (d, $^3J_{H-H}$ = 6.9 Hz, 1H, Ar-H), 7.18−7.19 (m, 3H, Ar-H), 7.41−7.44 (m, 1H, Ar-H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 19.3, 28.2, 50.0, 60.8, 107.2, 116.99, 117.03, 124.2, 126.0, 127.1, 127.2, 127.6, 130.0, 130.5, 135.4, 136.6, 138.6, 151.5. IR (thin film): ν_{max} (cm^{-1}) 3022, 2845, 1748, 1639, 1605, 1485, 1458, 1332, 1260, 1158, 1024, 996, 921, 873, 740, 640. HRMS (ESI): calcd for $C_{18}H_{20}N$ $[M + H]^+$, 250.1590; found, 250.1584.

Compound (*R*)-4j. Yellow oil, 49.2 mg, 94% yield, 97% ee (Daicel Chiralcel OJ-H (0.46 cm × 25 cm), *n*-hexane/2-propanol 98/2, v = 0.5 mL min^{-1}, λ 214 nm, t(major) = 17.54 min, t(minor) = 22.71 min); $[\alpha]_D^{20}$ = −22.0 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 2.96 (t, $^3J_{H-H}$ = 8.1 Hz, 2H, CH_2), 3.35−3.41 (m, 2H, CH_2), 5.24−5.31 (m, 3H, CH and CH_2), 6.00 (ddd, $^3J_{H-H}$ = 6.9, $^3J_{H-H}$ = 10.2, $^3J_{H-H}$ = 17.4 Hz, 1H, CH), 6.22 (d, $^3J_{H-H}$ = 8.1 Hz, 1H, Ar-H), 6.61 (t, $^3J_{H-H}$ = 7.5 Hz, 1H, Ar-H), 6.94 (t, $^3J_{H-H}$ = 7.5 Hz, 1H, Ar-H), 7.05 (d, $^3J_{H-H}$ = 6.9 Hz, 1H, Ar-H), 7.18−7.27 (m, 2H, Ar-H), 7.38−7.41 (m, 1H, Ar-H), 7.52−7.55 (m, 1H, Ar-H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 28.3, 50.9, 61.5, 107.7, 117.5, 117.7, 124.2, 127.0, 127.1, 128.5, 129.2, 129.8, 130.0, 133.7, 135.3, 138.3, 151.4. IR (thin film): ν_{max} (cm^{-1}) 2962, 2847, 1606, 1486, 1441, 1261, 1089, 1025, 928, 871, 799, 745. HRMS (ESI): calcd for $C_{17}H_{17}ClN$ $[M + H]^+$, 270.1044; found, 270.1037.

Compound (*R*)-4k. Yellow oil, 67.5 mg, 91% yield, 93% ee (Daicel Chiralcel OJ-H (0.46 cm × 25 cm), *n*-hexane/2-propanol 98/2, v = 0.5 mL min^{-1}, λ 214 nm, t(major) = 18.29 min, t(minor) = 22.71 min); $[\alpha]_D^{20}$ = −20.6 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 2.97 (t, $^3J_{H-H}$ = 7.8 Hz, 2H, CH_2), 3.35−3.42 (m, 2H, CH_2), 5.24−5.33 (m, 3H, CH and CH_2), 5.99 (ddd, $^3J_{H-H}$ = 7.2, $^3J_{H-H}$ = 10.5, $^3J_{H-H}$ = 17.4 Hz, 1H, CH), 6.21 (d, $^3J_{H-H}$ = 7.8 Hz, 1H, Ar-H), 6.62 (t, $^3J_{H-H}$ = 7.5 Hz, 1H, Ar-H), 6.94 (t, $^3J_{H-H}$ = 8.1 Hz, 1H, Ar-H), 7.06 (d, $^3J_{H-H}$ = 7.2 Hz, 1H, Ar-H), 7.11−7.17 (m, 1H, Ar-H), 7.29 (t, $^3J_{H-H}$ = 7.5 Hz, 1H, Ar-H), 7.54 (d, $^3J_{H-H}$ = 7.8 Hz, 1H, Ar-H), 7.60 (d, $^3J_{H-H}$ = 8.1 Hz, 1H, Ar-H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 28.3, 50.9, 61.5, 107.7, 117.5, 117.7, 124.2, 127.0, 127.1, 128.5, 129.2, 129.8, 130.0, 133.7, 135.3, 138.3, 151.4. IR (thin film): ν_{max} (cm^{-1}) 3049, 2843, 1639, 1605, 1566, 1485, 1437, 1333, 1259, 1158, 1022, 994, 925, 872, 807, 741, 643. HRMS (ESI): calcd for $C_{17}H_{17}BrN$ $[M + H]^+$, 314.0539; found, 314.0532.

Compound (*R*)-4l.[2c] Yellow oil, 43.2 mg, 85% yield, 97% ee (Phenomenex Lu × 5u Amylose-2 (0.46 cm × 25 cm), *n*-hexane/2-propanol 85/15, v = 0.5 mL min^{-1}, λ 230 nm, t(minor) = 9.63 min, t(major) = 10.20 min); $[\alpha]_D^{20}$ = −1.5 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 1.96 (br s, 1H, NH), 3.66−3.76 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 4.58 (d, $^3J_{H-H}$ = 6.6 Hz, 1H, CH), 5.11 (d, $^3J_{H-H}$ = 9.6 Hz, 1H, CH_2), 5.21 (d, $^3J_{H-H}$ = 17.1 Hz, 1H, CH_2), 6.03 (ddd, $^3J_{H-H}$ = 6.9, $^3J_{H-H}$ = 10.5, $^3J_{H-H}$ = 17.1 Hz, 1H, CH), 6.87 (d, $^3J_{H-H}$ = 7.8 Hz, 1H, Ar-H), 6.95 (t, $^3J_{H-H}$ = 7.2 Hz, 1H, Ar-H), 7.21−7.36 (m, 7H, Ar-H).

Compound (*R*)-4m. Yellow oil, 47.3 mg, 80% yield, 88% ee (Daicel Chiralcel OJ-H (0.46 cm × 25 cm), *n*-hexane/2-propanol 95/5, v = 1.0 mL min^{-1}, λ 220 nm, t(minor) = 6.85 min, t(major) = 7.65 min); $[\alpha]_D^{20}$ = −38.5 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 3.85 (s, 3H, OCH_3), 4.43 (br s, 1H, NH), 5.15 (d, $^3J_{H-H}$ = 10.5 Hz, 1H, CH_2), 5.20 (d, $^3J_{H-H}$ = 18.0 Hz, 1H, CH_2), 5.30−5.37 (m, 2H, CH and CH_2), 5.62 (d, $^3J_{H-H}$ = 17.1 Hz, 1H, CH_2), 6.08 (ddd, $^3J_{H-H}$ = 5.4, $^3J_{H-H}$ = 10.2, $^3J_{H-H}$ = 16.8 Hz, 1H, CH), 6.55 (d, $^3J_{H-H}$ = 8.1 Hz, 1H, Ar-H), 6.67 (t, $^3J_{H-H}$ = 7.2 Hz, 1H, Ar-H), 6.77−6.94 (m, 3H, Ar-H), 7.06 (t, $^3J_{H-H}$ = 7.5 Hz, 1H, Ar-H), 7.21−7.30 (m, 3H, Ar-H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 54.8, 55.4, 110.8, 112.1, 115.1, 116.1, 117.2, 120.9, 124.3, 127.3, 127.7, 128.4, 128.7, 129.6, 133.1, 138.6, 144.2, 156.8. IR (thin film): ν_{max} (cm^{-1}) 2963, 1600, 1489, 1456, 1261, 1095, 1023, 917, 799, 748. HRMS (ESI): calcd for $C_{18}H_{20}NO$ $[M + H]^+$, 266.1539; found, 266.1536.

Compound (*R*)-4n. Colorless oil, 499.3 mg, 86% yield, 98% ee (Daicel Chiralcel OJ-H (0.46 cm × 25 cm), *n*-hexane/2-propanol 98/2, v = 0.5 mL min^{-1}, λ 230 nm, t(minor) = 15.92 min, t(major) = 17.96 min); $[\alpha]_D^{15}$ = −41.3 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 2.75−2.89 (m, 4H, CH_2 CH_2), 3.43 (d, $^2J_{H-H}$ = 14.7 Hz, 1H, CH_2), 3.69 (d, $^2J_{H-H}$ = 14.7 Hz, 1H, CH_2), 4.48 (d, $^3J_{H-H}$ = 9.0 Hz, 1H, CH), 5.10 (dd, $^2J_{H-H}$ = 1.2, $^3J_{H-H}$ = 9.9 Hz, 1H, CH_2), 5.39 (dd, $^2J_{H-H}$ = 0.6, $^3J_{H-H}$ = 17.1 Hz, 1H, CH_2), 5.82 (ddd, $^3J_{H-H}$ = 9.0, $^3J_{H-H}$ = 9.6, $^3J_{H-H}$ = 17.1 Hz, 1H, CH), 6.65 (d, $^3J_{H-H}$ = 5.1 Hz, 1H, Ar-H), 7.01 (d, $^3J_{H-H}$ = 5.1 Hz, 1H, Ar-H), 7.12 (dt, $^4J_{H-H}$ = 1.5, $^3J_{H-H}$ = 7.5 Hz, 1H, Ar-H), 7.23 (t, $^3J_{H-H}$ = 7.5 Hz, 1H, Ar-H), 7.33 (dd, $^4J_{H-H}$ = 1.2, $^3J_{H-H}$ = 7.8 Hz, 1H, Ar-H), 7.65 (dd, $^4J_{H-H}$ = 1.5, $^3J_{H-H}$ = 7.8 Hz, 1H, Ar-H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 25.4, 48.6, 51.5, 68.7, 116.7, 122.5, 125.3, 127.2, 127.9, 128.8, 129.6, 133.4, 133.6, 133.9, 138.9, 139.3. IR (thin film): ν_{max} (cm^{-1}) 3065, 2962, 2922, 2843, 1638, 2808, 2760, 1592, 1469, 1435, 1369, 1341, 1320, 1299, 1260, 1172, 1096, 1080, 1048, 1033, 1013, 923, 799, 756, 734, 702, 673. HRMS (ESI): calcd for $C_{16}H_{17}ClNS$ $[M + H]^+$, 290.0765; found, 290.0754.

General Procedure for the Preparation of (π-Allyl)−Ir Complex K1. In a flame-dried Schlenk tube were placed a solution of $[Ir(COD)Cl]_2$ (203.8 mg, 0.3 mmol) and ligand **1d** (378.9 mg, 0.6 mmol) in dry THF (20 mL) under an argon atmosphere. After the mixture was stirred for 30 min at room temperature, AgOTf (157.6 mg, 0.6 mmol) and allyl methyl carbonate (168.8 mg, 1.5 mmol) were added subsequently, and the reaction mixture was stirred overnight to afford a pale suspension. The precipitate was filtered, and the solvents were removed under reduced pressure. The residue was washed with diethyl ether (10 mL × 3) to give (π-allyl)−Ir complex **K1** (284.8 mg, 85%) as a pale yellow powder, existing as two isomers in a ratio of 92/8 as determined by ^{31}P NMR.

Full details can be found in the Supporting Information.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.6b00339.

Experimental procedures and analysis data for all new compounds (PDF)

Crystallographic data (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for S.-L.Y.: slyou@sioc.ac.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Basic Research Program of China (2016YFA0202900, 2015CB856600), the National Natural Science Foundation of China (21332009, 21421091, 21572252), and the Chinese Academy of Sciences for generous financial support.

■ REFERENCES

(1) For selected reviews, see: (a) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675−691. (b) Helmchen, G. In *Iridium Complexes in Organic Synthesis*; Oro, L. A., Claver, C., Eds.; Wiley-VCH: Weinheim, Germany, 2009; pp 211−250. (c) Hartwig, J. F.; Stanley, L. M. *Acc. Chem. Res.* **2010**, *43*, 1461−1475. (d) Hartwig, J. F.; Pouy, M. J. *Top. Organomet. Chem.* **2011**, *34*, 169−208. (e) Liu, W.-B.; Xia, J.-B.; You, S.-L. *Top. Organomet. Chem.* **2012**, *38*, 155−208. (f) Tosatti, P.; Nelson, A.; Marsden, S. P. *Org. Biomol. Chem.* **2012**, *10*, 3147−3163. (g) Liu, W.; Zhao, X. *Synthesis* **2013**, *45*, 2051−2069. For the first racemic example, see: (h) Takeuchi, R.; Kashio, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 263−265. For the first asymmetric example, see: (i) Janssen, J. P.; Helmchen, G. *Tetrahedron Lett.* **1997**, *38*, 8025−8026.

(2) For selected examples, see: (a) Bartels, B.; Helmchen, G. *Chem. Commun.* **1999**, 741−742. (b) Fuji, K.; Kinoshita, N.; Kawabata, T.;

DOI: 10.1021/acs.organomet.6b00339
Organometallics XXXX, XXX, XXX−XXX

Tanaka, K. *Chem. Commun.* **1999**, 2289−2290. (c) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164−15165. (d) Bartels, B.; García-Yebra, C.; Helmchen, G. *Eur. J. Org. Chem.* **2003**, 1097−1103. (e) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2426−2428. (f) Lipowsky, G.; Miller, N.; Helmchen, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4595−4597. (g) Leitner, A.; Shekhar, S.; Pouy, M. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15506−15514. (h) Onodera, G.; Watabe, K.; Matsubara, M.; Oda, K.; Kezuka, S.; Takeuchi, R. *Adv. Synth. Catal.* **2008**, *350*, 2725−2732.

(3) For early examples, see: (a) Roggen, M.; Carreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 11917−11919. (b) Roggen, M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 5568−5571. (c) Lafrance, M.; Roggen, M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3470−3473. (d) Roggen, M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 8652−8655. (e) Schafroth, M. A.; Sarlah, D.; Krautwald, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2012**, *134*, 20276−20278. (f) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. *J. Am. Chem. Soc.* **2013**, *135*, 994−997. (g) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7532−7535. (h) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. *Science* **2013**, *340*, 1065−1068.

(4) For use of diene ligands, see: (a) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628−1629. For use of Py-box ligands, see: (b) Miyabe, H.; Matsumura, A.; Moriyama, K.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 4631−4634. For use of chiral diaminophosphine oxides (DIAPHOXs), see: (c) Nemoto, T.; Sakamoto, T.; Fukuyama, T.; Hamada, Y. *Tetrahedron Lett.* **2007**, *48*, 4977−4981. For use of phosphorodiamidite ligands, see: (d) Kimura, M.; Uozumi, Y. *J. Org. Chem.* **2007**, *72*, 707−714.

(5) For a review, see: Teichert, J. F.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2486−2528. For the first application of a Feringa ligand in an Ir-catalyzed allylic substitution reaction, see ref 2c.

(6) (a) Kiener, C. A.; Shu, C.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14272−14273. (b) Madrahimov, S. T.; Markovic, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 7228−7229. (c) Spiess, S.; Raskatov, J. A.; Gnamm, C.; Brödner, K.; Helmchen, G. *Chem. - Eur. J.* **2009**, *15*, 11087−11090. (d) Raskatov, J. A.; Spiess, S.; Gnamm, C.; Brödner, K.; Rominger, F.; Helmchen, G. *Chem. - Eur. J.* **2010**, *16*, 6601−6615.

(7) (a) López, F.; Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 3426−3427. (b) Shu, C.; Leitner, A.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4797−4800. (c) Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrich, K. *Chem. - Eur. J.* **2006**, *12*, 3596−3609. (d) Yamashita, Y.; Gopalarathnam, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7508−7509. (e) Pouy, M. J.; Leitner, A.; Weix, D. J.; Ueno, S.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 3949−3952. (f) Liu, W.-B.; He, H.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2008**, *10*, 1815−1818. (g) Liu, W.-B.; Zheng, S.-C.; He, H.; Zhao, X.-M.; Dai, L.-X.; You, S.-L. *Chem. Commun.* **2009**, 6604−6606. (h) Stanley, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 8971−8983. (i) Madrahimov, S. T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 8136−8147.

(8) For the synthesis of ligands, see: (a) Liu, W.-B.; He, H.; Dai, L.-X.; You, S.-L. *Synthesis* **2009**, 2076−2082. (b) Liu, W.-B.; Zheng, C.; Zhuo, C.-X.; Dai, L.-X.; You, S.-L. *J. Am. Chem. Soc.* **2012**, *134*, 4812−4821. For the application of ligands in reactions with sterically congested nucleophiles, see: (c) Wu, Q.-F.; He, H.; Liu, W.-B.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 11418−11419. (d) Liu, W.-B.; Reeves, C. M.; Virgil, S. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2013**, *135*, 10626−10629. (e) Liu, W.-B.; Reeves, C. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2013**, *135*, 17298−17301. (f) Yang, Z.-P.; Wu, Q.-F.; You, S.-L. *Angew. Chem., Int. Ed.* **2014**, *53*, 6986−6989. (g) Zhang, X.; Liu, W.-B.; Tu, H.-F.; You, S.-L. *Chem. Sci.* **2015**, *6*, 4525−4529. (h) Yang, Z.-P.; Wu, Q.-F.; Shao, W.; You, S.-L. *J. Am. Chem. Soc.* **2015**, *137*, 15899−15906. (i) Cheng, Q.; Wang, Y.; You, S.-L. *Angew. Chem., Int. Ed.* **2016**, *55*, 3496−3499. (j) Liu, W.-B.; Okamoto, N.; Alexy, E. J.; Hong, A. Y.; Tran, K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2016**, *138*, 5234−5237. (k) Zhao, K.; Xu, S.; Pan, C.; Sui, X.; Gu, Z. *Org. Lett.* **2016**, DOI: 10.1021/acs.orglett.6b01790.

(9) The bond length for Ir−C3 is 2.400 Å and for Ir−1 is 2.227 Å; see ref 8b for details. Studies by Hartwig et al. revealed that the regioselectivity of the substitution process is usually high when the difference in Ir−C bond lengths is greater than 0.07 Å; see ref 7i for details. Recent computational studies suggested that interactions of H-bond acceptors with a vinyl C−H bond of the alkene ligand may determine the formation of the branched product. See: Madrahimov, S. T.; Li, Q.; Sharma, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2015**, *137*, 14968−14981.

(10) See the Supporting Information for details.

(11) (a) Boneu, B.; Destelle, G. *Thromb. Haemostasis* **1996**, *76*, 939−943. (b) Coukell, A. J.; Markham, A. *Drugs* **1997**, *54*, 745−750. (c) Yang, L. H.; Hoppensteadt, D.; Fareed, J. *Thromb. Res.* **1998**, *92*, 83−89. (d) Gurbel, P. A.; O'Connor, C. M.; Cummings, C. C.; Serebruany, V. L. *Pharmacol. Res.* **1999**, *40*, 107−111.

(12) Blanchard, J.; Panak, E. Therapeutic compositions having antithrombotic and anti-blood-platelet-aggregating activity . Canadian Patent CA 1147658 A1 19830607, 1983.

(13) For the dihydroxylation of alkenes in the presence of OsO_4, see: (a) Milas, N. A.; Sussman, S. *J. Am. Chem. Soc.* **1936**, *58*, 1302−1304. For palladium-catalyzed direct oxidation of alkenes with molecular oxygen, see: (b) Wang, A.; Jiang, H. *J. Org. Chem.* **2010**, *75*, 2321−2326 Wacker oxidation and ozonation were tested, leading to a mixture of unexpected compounds..

(14) Barluenga, J.; Rodríguez, F.; Álvarez-Rodrigo, L.; Zapico, J. M.; Fañanás, F. J. *Chem. - Eur. J.* **2004**, *10*, 109−116.

(15) Liu, W.-B.; Zhang, X.; Dai, L.-X.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 5183−5187.

DOI: 10.1021/acs.organomet.6b00339
Organometallics XXXX, XXX, XXX−XXX