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# FMPhos: Expanding the Catalytic Capacity of Small-Bite-Angle Bisphosphine Ligands in Regioselective Alkene Hydrofunctionalizations

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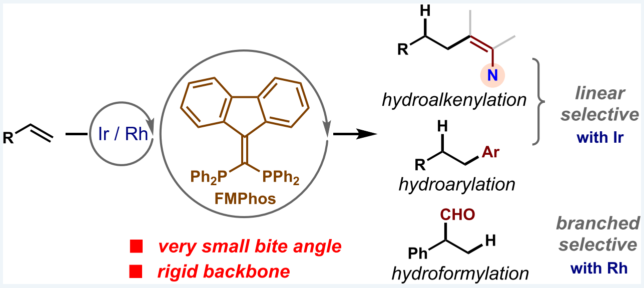
**ABSTRACT:** In contrast to the plethora of large-bite-angle bisphosphine ligands available to transition-metal catalysis, the development of small-bite-angle bisphosphine ligands has suffered from the limited structural variations accessible on their single-atom-containing backbones. Herein, we report the design and applications of a discrete very small bite-angle bisphosphine ligand, namely, FMPhos. Featuring a fluorene−methylene unit appended on the single-carbon linker, the ligand harbors an unusually rigid backbone that presumably stabilizes its complexation with transition metals during catalysis. Compared with the known dppm ligand, it exhibited superior reactivity and regioselectivity in a number of alkene hydrofunctionalization reactions, catalyzed by iridium and rhodium.



**KEYWORDS:** *bite angle, bisphosphine ligand, regioselectivity, alkene hydrofunctionalization*

## ■ INTRODUCTION

Ligands play an essential role in homogeneous catalysis through modulating reactivity and selectivity of transition-metal catalysts during the reactions.[1] Phosphines are among the most widely used ligands due to their robust $\sigma$-donating, $\pi$-accepting L-type coordination, as well as the systematic and predictable ways to alter their steric and electronic properties by varying the substituents on the phosphorus.[2] In particular, chelating phosphines, e.g., bidentate phosphines or bisphosphines, have found broad applications in chemical, pharmaceutical, and agrochemical industries. One key parameter for measuring steric and geometric properties of bisphosphines is bite angle, i.e., the ligand−metal−ligand bond angle of a coordination complex.[3] The merits of using *large-bite-angle* bisphosphine ligands in catalysis are well documented, such as acceleration of oxidative addition, migratory insertion, and reductive elimination processes.[4] Their pronounced impact on controlling reaction regioselectivity has also been recognized.[5] For example, the Rh-catalyzed alkene hydroformylation process,[6] which represents one of the largest volume applications with homogeneous catalysis and produces 14 billion pounds of aldehydes annually, benefits tremendously from using bisphosphines with extraordinarily large bite angles, as nearly perfect linear selectivity can be obtained with such ligands.

In contrast, much less attention has been paid to the advantages of using bisphosphines with *very small* bite angles. Considering that large- and small-bite-angle bisphosphine ligands may give complementary reactivity or selectivity, they could be equally important in the design and execution of new transition-metal-catalyzed reactions. Nevertheless, the development of these two classes of ligands has so far been highly disproportionate.[7] As depicted in Figure 1a, the backbone of large bite-angle ligands typically contains multiple carbon atoms, which gives plenty of space in incorporating a variety of functional linkers to set the two phosphine units apart. Such flexibility in ligand design accounts for the numerous privileged large bite-angle ligands developed to date, not to mention that many of them have been employed in enantioselective catalysis. On the other hand, the most common small-bite-angle ligand, bis(diphenylphosphino)methane (dppm), only has a single-carbon-atom spacer between the two phosphine units, leaving much less room for structural modifications (Figure 1b). Besides, the large ring strain associated with the four-member ring chelation could lead to dissociation of one of the phosphino groups of dppm from the metal center, known as "hemilability", which significantly diminishes its efficiency during catalysis.[8] Consequently, only a few catalytically competent small-bite-angle derivatives of dppm have been described in the literature,[9] stalling applications of this

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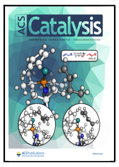

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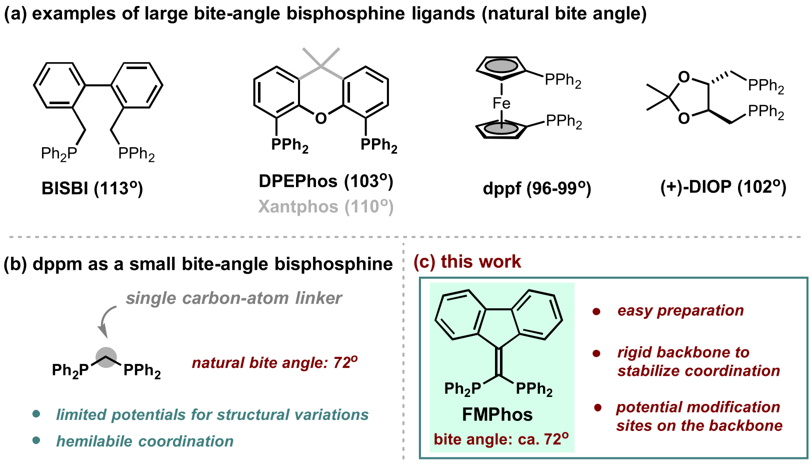


**Figure 1.** FMPhos as a discrete small-bite-angle bisphosphine ligand.

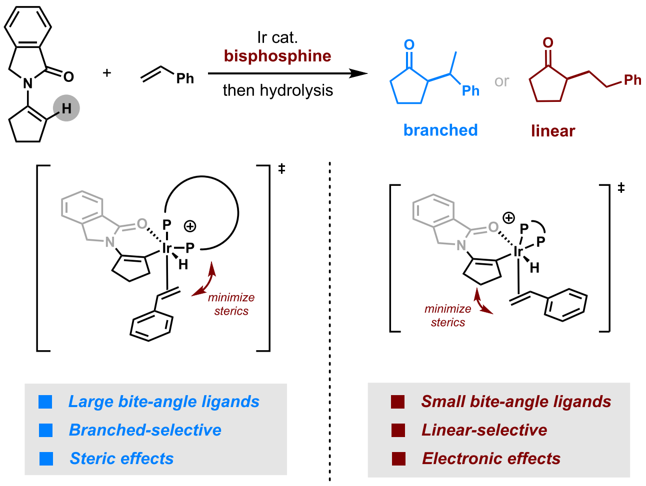
important class of bisphosphine ligands in transition-metal catalysis.

In this article, we wish to describe a full study of developing a discrete small-bite-angle bisphosphine ligand, namely, FMPhos, which contains a fluorene−methylene unit anchored onto the single-carbon linker between two phosphino groups (Figure 1c), as well as its applications in regioselective alkene hydrofunctionalizations. FMPhos features a very small calculated bite angle conferred by its unusually rigid backbone when complexed with transition metals and displays extraordinary reactivity and regioselectivity in three types of alkene hydrofunctionalization reactions. While not explicitly shown here, the incorporation of a fluorene moiety that conjugates with two phosphino groups could also create useful modification sites for fine-tuning the electronic property of the ligand.

## RESULTS AND DISCUSSION

**Ligand Discovery.** Our initial interest in exploring new small-bite-angle structural motifs in bidentate phosphine ligands was prompted by our previous research on the Ir(I)-catalyzed, branched-selective hydroalkenylation of alkenes with enamides as the coupling reagent, which provided an effective approach to realize branched-selective ketone $\alpha$-alkylation with olefins.[10] This study, along with pioneering works from the groups of Shibata,[11] Bower,[12] Hartwig,[13] Nishimura,[14] and others, capitalizes on the use of large bite-angle bisphosphine ligands to achieve branched selectivity (Scheme 1). Based on Huang and our mechanistic studies,[15] the large bite angle of the ligand promoted a rate-determining regioselective 1,2-Ir-C migratory insertion of the C−H activation intermediate into olefins, minimizing the steric interaction between the bulky metal center and the alkene substituent.[16] One intriguing question is whether *linear*-selective alkene hydroalkenylation could be realized using a *small*-bite-angle bisphosphine ligand, which, in turn, should provide a useful entry to access linear ketone-alkylation products. Our hypothesis is supported by a recent computational study performed by Huang and Liu on Ir-catalyzed hydroarylation of alkenes, which revealed that in the absence of steric repulsions from large bite-angle ligands, the linear/branched selectivity is predominantly controlled by the electronic nature of the alkene.[17] This implies that, using aryl alkenes or alkyl alkenes with electron-withdrawing groups (EWGs), high linear selectivity—i.e., 2,1-insertion—should be favorable due to the stabilization of the increasing negative charge at the $\alpha$ carbon during the Ir−C bond formation.

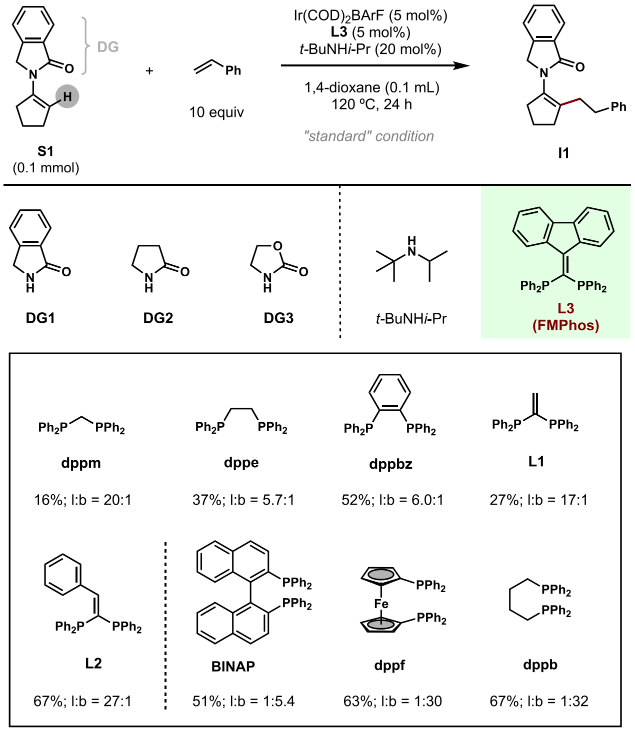
**Scheme 1. Hypothesis on the Ligand Bite-Angle Effect in the Regioselective Hydroalkenylation of Enamides**



To test this hypothesis, enamide **S1** was used as the model substrate and styrene was employed as the coupling partner (Table 1). A preliminary screening showed that, when Shibata's Ir(COD)$_2$BArF was used as the precatalyst,[11] reducing the bite angle of bisphosphine ligands was indeed accompanied by a great increase in linear selectivity. The use of dppm with a bite angle of 72.0°, though displaying excellent linear selectivity, resulted in a dramatic loss of reactivity (16% yield, entry 2). In contrast, lower linear selectivity but better yields were observed using dppe and dppbz, which have medium-sized bite angles.

We questioned if the reduced reactivity of dppm was due to the lack of stability of the resulting four-membered metallocycle (Figure 2). With a flexible methylene linker, one can imagine that the C−P bond could easily rotate away leading to a more labile mono-coordinated complex (Figure 2a).[8] Hence, we envisioned that using a more rigid linker the C−P bond rotation could be largely inhibited due to the buttressing effect, and such a "locked" conformation should result in a more stable catalyst (Figure 2b). Drawing inspiration from our prior use of the 1,1-bis(diphenylphosphino)ethylene (**L1**) ligand in the Ir-catalyzed deacylative transformations of ketones,[18] we

### Table 1. Control Experiments[a]



| entry | variation from the standard condition | yield of I1 (%)[b] | linear/branched ratio[c] |
|---|---|---|---|
| 1 | none | **70** | **27:1** |
| 2 | other L instead of **L3** | see above | see above |
| 3 | DG2 instead of DG1 | 50 | n/d[d] |
| 4 | DG3 instead of DG1 | 21 | n/d[d] |
| 5 | no *t*-BuNH*i*-Pr | 35 | 19:1 |
| 6 | in CPME | 68 | 27:1 |
| 7 | in toluene | 65 | 24:1 |
| 8 | **in DME** | **76** | **25:1** |
| 9 | in MeTHF | 67 | 24:1 |
| 10 | at 110 °C | 69 | 24:1 |
| 11 | at 130 °C | 70 | 20:1 |
| 12 | with 5 equiv of styrene | 54 | 27:1 |

[a] The reaction was performed with **S1** (0.1 mmol), styrene (1.0 mmol), Ir(COD)$_2$BArF (0.005 mmol), **L3** (0.005 mmol), and *t*-BuNH*i*-Pr (0.02 mmol) in 1,4-dioxane (0.1 mL) under a $N_2$ atmosphere at 120 °C for 24 h. [b] Determined by $^1$H NMR using $CH_2Br_2$ as the internal standard. [c] Determined by $^1$H NMR of the crude products. [d] Not determined. l:b = linear to branched ratio; DG = directing group; BArF = tetrakis(3,5-bis(trifluoromethyl)phenyl)-borate; COD = 1,5-cyclooctadiene; CPME = cyclopentyl methyl ether; DME = 1,2-dimethoxyethane; and MeTHF = 2-methyltetrahydrofuran.

wondered whether such a ligand scaffold with a more rigid backbone could deliver high linear-to-branched selectivity without compromising the efficiency of the reaction. While the use of simple methylene-bridged **L1** ligand only gave a slightly better yield with a decent linear/branched ratio (17:1), significantly improved efficiency and excellent linear/branched ratios were obtained with the ligands having substituents on the methylene backbones (**L2** and **L3**), which are expected to inhibit the undesired C−P bond rotation. Particularly, the use of FMPhos (**L3**), easily prepared in two steps from inexpensive 9-fluorenone, consistently provided a high yield and nearly complete linear selectivity (entry 1).

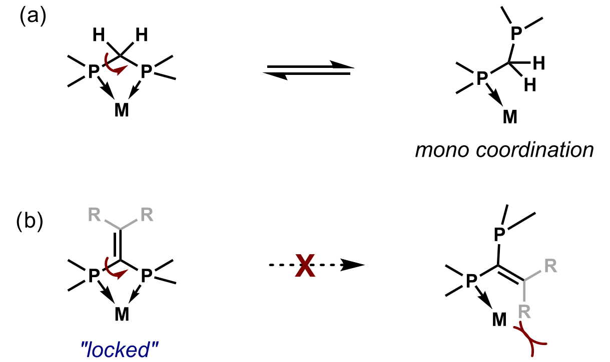
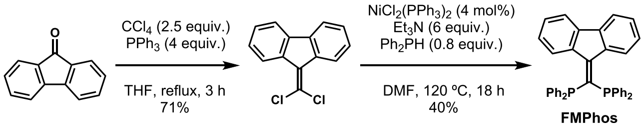


**Figure 2.** Linker effect in small-bite-angle ligands.

### Scheme 2. Synthesis of FMPhos



The synthesis of FMPhos is described in Scheme 2. Treatment of 9-fluorenone with carbon tetrachloride and $PPh_3$ under reflux in THF afforded 9-(dichloromethylene)-9*H*-fluorene in 71% yield,[19] which was subjected to a C−P cross-coupling reaction that employed $NiCl_2(PPh_3)_2$ as the catalyst, $Et_3N$ as the base, $Ph_2PH$ as the coupling reagent, and DMF as the solvent at 120 °C.[20] FMPhos was obtained as a yellow solid after column chromatography in 40% yield.

Crystal structures of **L1** and FMPhos have been obtained, and their corresponding bite angles with Ir have been calculated via DFT studies (Figure 3; for details, see the Supporting Information). Interestingly, the trend of bite angles indeed correlates well with the linear-to-branched selectivity (Figure 4), in which ligands with smaller bite angles give

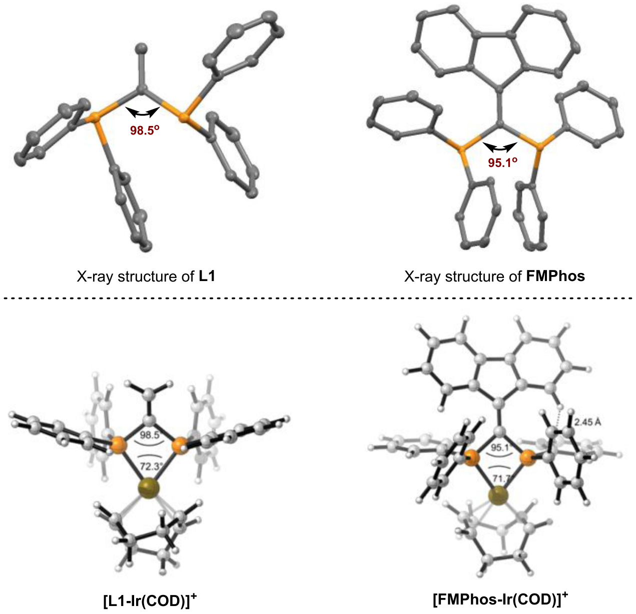


**Figure 3.** X-ray crystal structures of ligands **L1** (CCDC: 1992830) and **FMPhos** (CCDC: 1992831) and their computed bite angles with Ir via DFT studies.

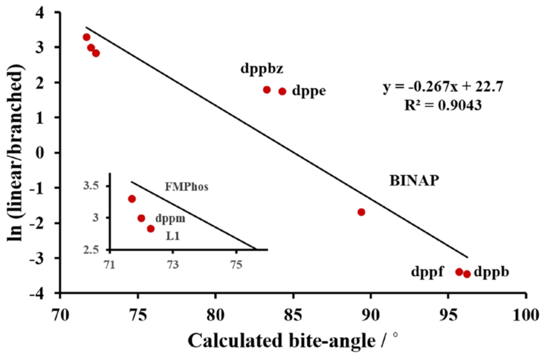


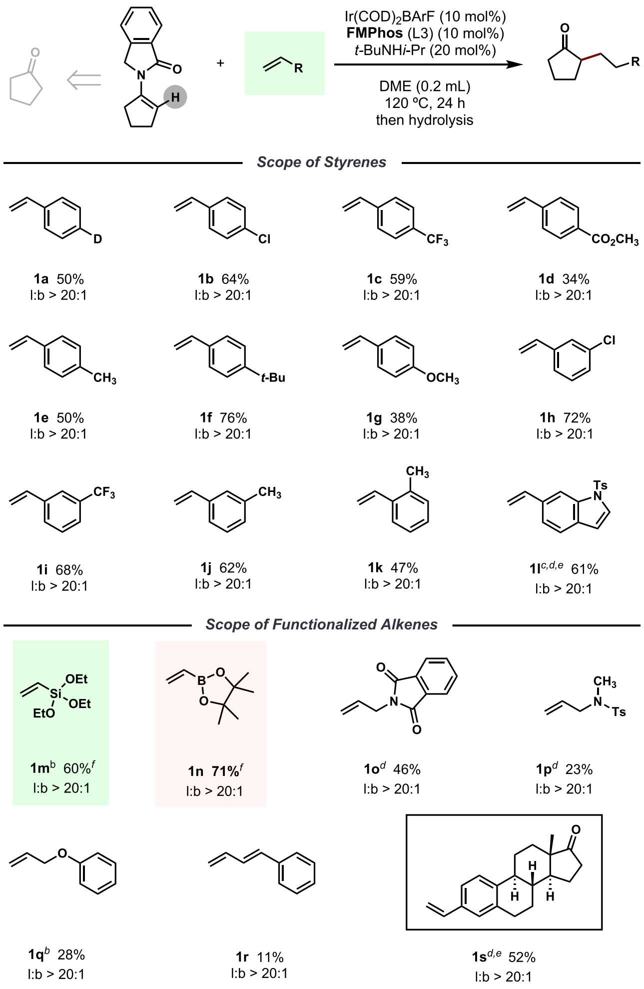
**Figure 4.** Correlation between calculated bite angles (based on Ir(I) complexes) and linear-to-branched selectivity in alkene hydroalkenylation.

higher linear selectivity and those with larger bite angles, as observed previously,[10−14] give higher branched selectivity instead. This trend is clearly opposite to the one found in the Rh-catalyzed hydroformylation of alkenes.[6] Among all of the ligands tested, FMPhos (**L3**) exhibits an equal or even smaller calculated bite angle (71.7°) than those of **L1** (72.3°) and dppm (72.0°) based on their coordination with Ir(I) complexes. This could likely be explained by the buttressing effect of the rigid coplanar fluorene linker that pushes the two phosphino groups closer to each other (Figure 3). Such an effect is reflected by the relatively small [C···H] distance (2.45 Å) between the phenyl group on phosphine and fluorene linker in the optimized structures (the sum of van der Waals radii of C and H is 2.90 Å).

With an understanding of the ligand effect, control experiments were subsequently conducted to probe the role of other reactants. Among the three five-membered lactam-derived enamide directing groups (DGs), isoindolin-1-one (**DG1**) displayed the highest reactivity (entries 1, 3, and 4, Table 1). A catalytic amount of *t*-BuNH*i*-Pr proved to be critical as it prevents hydrolysis of the enamide by adventitious water in the reaction (entry 5, Table 1).[10] Among a series of solvents evaluated, DME provided the highest reaction efficiency, i.e., 75% yield and 25:1 selectivity (entries 6−9, Table 1). The reaction was not improved when altering the reaction temperature (entries 10 and 11, Table 1). Finally, the reaction benefits from a high concentration of the alkene coupling partner as the migratory insertion of the Ir−C intermediate into the alkene is anticipated to be rate-determining based on the prior mechanistic studies.[15] Thus, a reduced amount of styrene lowered the reaction efficiency (entry 12, Table 1).

**Scope of Linear-Selective Hydroalkenylation.** With an optimized catalytic condition in hand, the scope of this linear-selective alkene hydroalkenylation was first investigated. It is noteworthy that upon completion of the hydroalkenylation reaction, a convenient one-pot enamide hydrolysis can be performed to afford the corresponding linear *α*-alkylated ketones.[21] As depicted in Scheme 3, styrenes bearing various electron-withdrawing groups, such as fluoro, chloro, trifluoromethyl, and ester groups, as well as electron-donating groups including methyl, *tert*-butyl, and methoxy groups at the *para* position, could all undergo the reaction smoothly to deliver the desired linear alkylation products in moderate-to-good yields with excellent linear-to-branched selectivity (**1a−g**). It was also possible to introduce a diverse set of functional groups at the *meta* position of styrene, such as chloro, trifluoromethyl, and methyl groups, without any erosion in the reaction performance (**1h−j**). This reaction was also amenable to an *ortho*-substituted styrene as well as an indole-derived olefin, in which cases consistently good yields and linear-to-branched selectivity were observed (**1k**, **1l**).

**Scheme 3. Scope of Alkenes**[a]

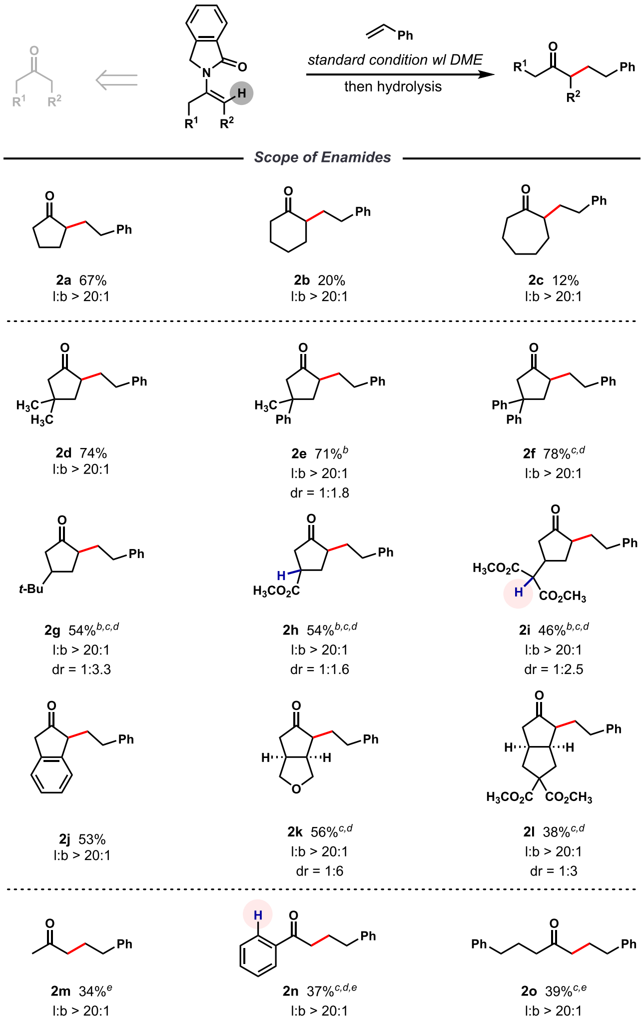


[a] Unless otherwise noted, all reactions were performed on a 0.2 mmol scale; the linear/branched ratio was determined by $^1$H NMR of the crude enamide products; and yields are isolated yields of the corresponding ketones after hydrolysis. [b] **L2** was used as the ligand. [c] 15 mol % Ir(COD)$_2$BArF and FMPhos. [d] 5 equiv of the alkene was used. [e] Toluene was used as the solvent. [f] Yield was based on the enamide product.

The scope of functionalized alkenes was also explored. Olefins containing a synthetically versatile functional group, such as silyl and pinacol-boryl (Bpin) groups, turned out to be excellent substrates, delivering the desired products in good yields with complete linear-to-branched selectivity (**1m**, **1n**).[22] While attempts to use unfunctionalized aliphatic alkenes, i.e., 1-octene, as the coupling reagent proved fruitless,[23] moderate reactivity and excellent linear-to-branched selectivity were restored when alkenes bearing an electronegative N or O substituent at the allylic position were employed (**1o−q**). It is possible that the inductive effect caused by these EWGs stabilizes the transition state of the 2,1-insertion, as predicted by the prior DFT studies.[16] Conjugated dienes were competent for this reaction, albeit in a low yield (**1r**). Finally, a steroid-derived alkene could also be ligated with decent reactivity and complete linear selectivity (**1s**).

Having shown that hydroalkenylation with various alkenes was possible, we next sought to evaluate the performance of structurally diverse enamides in this reaction (Scheme 4).

### Scheme 4. Scope of Enamides[a]

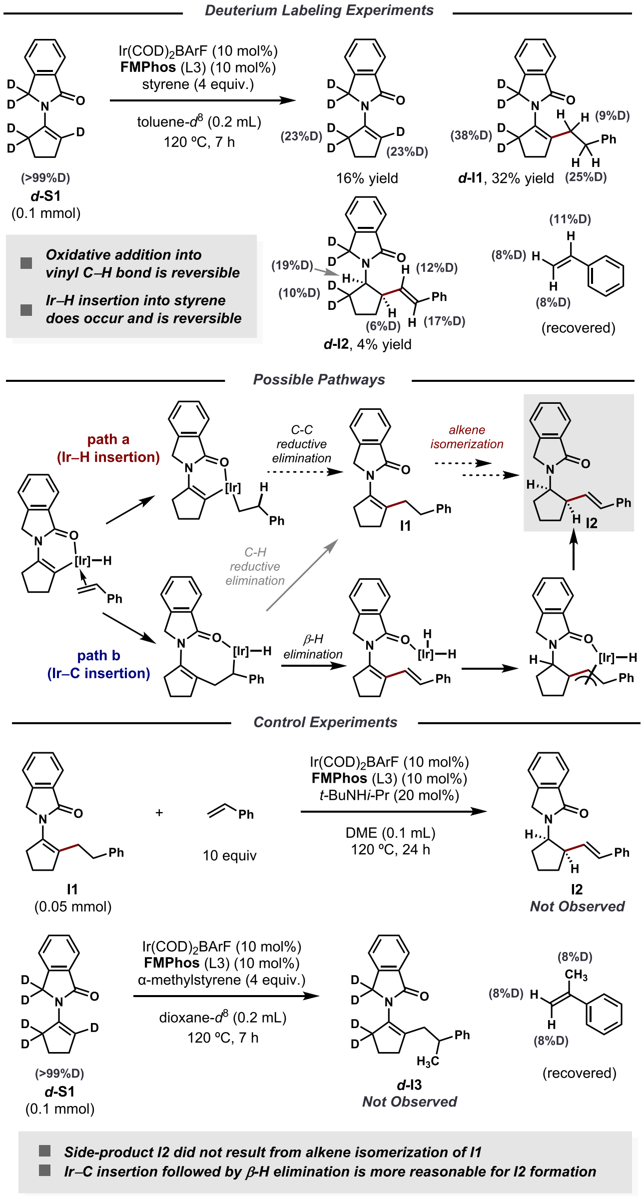


[b]Toluene was used as the solvent with 5 mol % mesitylenesulfonic acid dihydrate as an additive. [c]15 mol % Ir(COD)$_2$BArF and FMPhos. [d]72 h. [e]The hydrolyzed crude product was treated with Pd/C under $H_2$ (balloon). [a]Unless otherwise noted, all reactions were performed on a 0.2 mmol scale; linear/branched ratio was determined by $^1$H NMR of the crude enamide products; and yields are isolated yields of the corresponding ketones after hydrolysis.

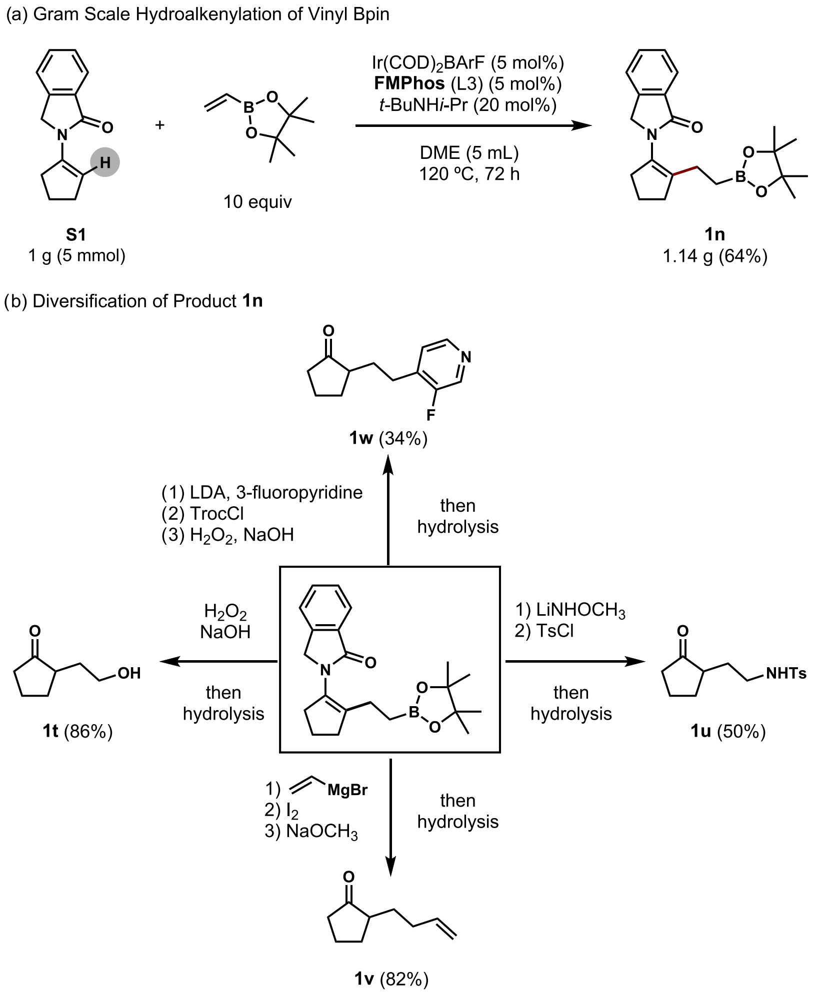
Typically, enamides were prepared via condensing **DG1** with a slight excess (1.3 equiv) of dimethyl ketals of the corresponding ketones in excellent yields (with just a few exceptions; see SI for details). While enamides derived from cyclohexanones (**2b**) and cycloheptanones (**2c**) exhibited low reactivity, substrates based on cyclopentanones generally gave good yields of the corresponding linear alkylation products following enamide hydrolysis. For example, mono- and di-*β*-substituted cyclopentanones are good to excellent substrates (**2d–i**), including those with a more acidic malonate moiety (**2i**). Unsurprisingly, selective mono-alkylation occurred at the less hindered side of cyclopentanones. In addition, benzo-fused and bicyclic ketones with an oxygen or a carbon linker are also suitable substrates (**2j–l**). Finally, the reaction also accommodated several acyclic substrates, affording the desired mono-alkylated acetone, acetophenone, and 5-phenylpentan-2-one in moderate yields (**2m–o**). Notably, the *ortho* C–H bond of acetophenone was untouched under the reaction conditions (**2n**), a result that is complementary to Murai's seminal study on the *ortho* C–H alkylation of aromatic ketones.[24] In all cases, complete linear selectivity was observed.

**Mechanistic Studies.** To gain some insights into the reaction mechanism, deuterated cyclopentanone-derived enamide (***d*-S1**) was treated with a *reduced* amount of styrene in toluene under the standard reaction condition for 7 h. As shown in Scheme 5, the deuterium ratio at the vinyl hydrogen of the recovered enamide substrate was significantly reduced. Meanwhile, incorporation of deuterium at the *α* and *β* positions of the recovered styrene was observed. These H/D scrambling phenomena implied that (1) oxidative addition of the Ir(I) species into the enamide vinyl C–H bond is

### Scheme 5. Mechanistic Studies



Scheme 6. Synthetic Utility



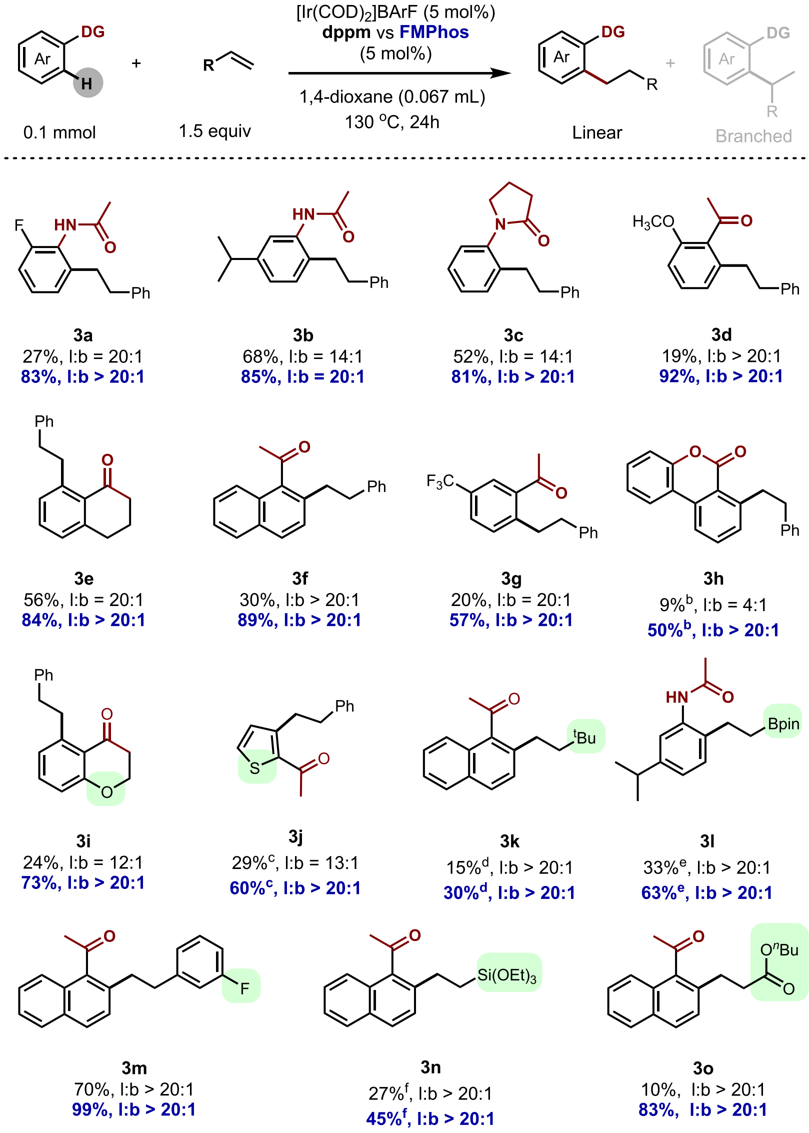
reversible and (2) Ir—H migratory insertion into styrene does occur and is also reversible. Further analysis of the desired hydroalkenylation product (***d*-I1**) revealed that a significant amount of deuterium was introduced at the benzylic position (25% D). Moreover, a small amount of the alkenylation side product (***d*-I2**) was also isolated, in which the enamide alkene was hydrogenated, with concomitant deuterium incorporation at the $\alpha$-nitrogen and allylic carbons.

Two pathways could possibly explain the formation of product ***d*-I2**. Path a involves an Ir—H insertion into styrene followed by C—C reductive elimination, and ***d*-I2** is formed via isomerization of the enamide alkene. Alternatively, if the reaction proceeds via an Ir—C insertion mechanism (path b), the hydroalkenylation product would be formed via a C—H reductive elimination. However, if $\beta$-H elimination takes place instead of C—H reductive elimination, the resulting Ir dihydride could insert into the enamide alkene (likely directed by the amide carbonyl) to give a stabilized $\pi$-allyl species, which undergoes C—H reductive elimination to provide ***d*-I2**.[25]

Two control experiments were carried out to probe the Ir—H vs Ir—C insertion pathway. First, the subjection of product **I1** to the standard reaction condition led to no alkene isomerization to product **I2** (Scheme 5). This indicates that path a is less likely to be responsible for forming **I2**. Second, while the reaction of ***d*-S1** with $\alpha$-methylstyrene did not give the desired hydroalkenylation product (***d*-I3**), deuterium was incorporated at all of the three $\beta$ positions of the recovered $\alpha$-methylstyrene. This result implied that Ir—H migratory insertion likely occurred with $\alpha$-methylstyrene but did not lead to a successful C—C reductive elimination. Given the success of coupling with simple styrene, the result of $\alpha$-methylstyrene is also *inconsistent* with the pathway of Ir—H insertion/C—C reductive elimination (path a). Taken together with the computational results from Huang and Liu,[17] it is reasonable to propose that the Ir—C migratory insertion into styrene (path b) is the main productive reaction pathway.

**Synthetic Utility.** To highlight the utility of this hydroalkenylation process, a gram-scale reaction between **S1** and vinyl-Bpin was performed. Using a reduced loading of Ir(COD)$_2$BArF and FMPhos, the desired hydroalkenylation product (**1n**) was isolated in a good yield (Scheme 6a). Most importantly, the Bpin group can then be easily transformed into a wide range of other functional moieties that would otherwise be difficult to obtain through direct coupling methods (Scheme 6b). For example, the boron moiety can be converted to an alcohol (**1t**) or a protected amine (**1u**) using Morken's method,[26] where the corresponding enol and enamine are *not* suitable alkene partners for this reaction. In addition, different coupling strategies could be adopted to introduce a terminal alkene through Zweifel olefination[27] or a pyridine group under Aggarwal's conditions[28] (**1v** and **1w**).

**Scheme 7. Ir-Catalyzed Linear-Selective Alkene Hydroarylation Reaction**[a]



**3a**
27%, l:b = 20:1
**83%, l:b > 20:1**

**3b**
68%, l:b = 14:1
**85%, l:b = 20:1**

**3c**
52%, l:b = 14:1
**81%, l:b > 20:1**

**3d**
19%, l:b > 20:1
**92%, l:b > 20:1**

**3e**
56%, l:b = 20:1
**84%, l:b > 20:1**

**3f**
30%, l:b > 20:1
**89%, l:b > 20:1**

**3g**
20%, l:b = 20:1
**57%, l:b > 20:1**

**3h**
9%$^{b}$, l:b = 4:1
**50%$^{b}$, l:b > 20:1**

**3i**
24%, l:b = 12:1
**73%, l:b > 20:1**

**3j**
29%$^{c}$, l:b = 13:1
**60%$^{c}$, l:b > 20:1**

**3k**
15%$^{d}$, l:b > 20:1
**30%$^{d}$, l:b > 20:1**

**3l**
33%$^{e}$, l:b > 20:1
**63%$^{e}$, l:b > 20:1**

**3m**
70%, l:b > 20:1
**99%, l:b > 20:1**

**3n**
27%$^{f}$, l:b > 20:1
**45%$^{f}$, l:b > 20:1**

**3o**
10%, l:b > 20:1
**83%, l:b > 20:1**

[b] 10 mol % Ir(COD)$_2$BArF and ligand at 155 °C. [c] 4.5 Equiv of alkene and 10 mol % Ir(COD)$_2$BArF and ligand in toluene (0.067 mL). [d] 2.0 Equiv of alkene and 10 mol % Ir(COD)$_2$BArF and ligand without solvent. [e] 4.5 Equiv of alkene. [f] 4.5 Equiv of alkene and 10 mol % Ir(COD)$_2$BArF and ligand. [a] Unless otherwise noted, all reactions were performed on a 0.1 mmol scale; the linear/branched ratio was determined by $^1$H NMR of the crude products; yields are based on isolated yields of the corresponding arene; black color means dppm was used as the ligand; and blue color means FMPhos was used as the ligand.

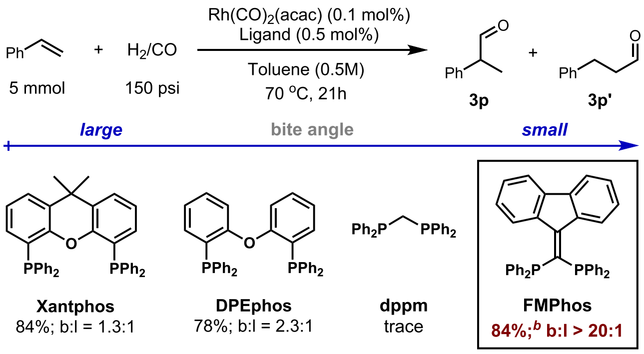
**Linear-Selective Hydroarylation and Branched-Selective Hydroformylation.** Having demonstrated that FMPhos is an effective small-bite-angle ligand in the linear-selective hydroalkenylation of alkenes with enamides, we next sought to examine its performance in other alkene hydrofunctionalization reactions. While FMPhos has a similar small bite angle to dppm, the rigid 9-fluorenone backbone is expected to reinforce and stabilize the chelating ($\kappa^2$) coordination mode, presumably preventing one phosphino group from slipping off the metal center. Thus, we may anticipate that FMPhos could perform better than dppm in either the reactivity or regioselectivity or both in other mechanistically related alkene hydrofunctionalization processes. For example, in the case of Ir-catalyzed alkene hydroarylation reaction, first discovered by Shibata,[11] the control of its regioselectivity has not been trivial. In 2014, Bower developed a novel large-bite-angle d$^F$ppb ligand to achieve general high branched selectivity.[12] However, the corresponding general and efficient linear-selective alkene hydroarylation with Ir catalysis has been elusive.

As depicted in Scheme 7, even though small-bite-angle ligands were predicted to give predominantly the linear hydroarylation product in this transformation,[17] dppm failed to induce high levels of linear-to-branched selectivity in many cases (**3b**, **3c**, **3h**−**j**). By contrast, the use of FMPhos led to a great increase in regioselectivity without any compromise in reactivity. In cases where satisfactory linear-to-branched selectivity was achieved with subpar reaction performance in the presence of dppm (**3a**, **3d**−**g**, **3k**−**o**), the use of FMPhos also raised the reaction efficiency to synthetically useful levels (over 50% yields in most cases). Of particular note is the broad substrate scope of this linear-selective hydroarylation process: a variety of weakly coordinating functionalities can be used as the DGs on the arene coupling partner, such as amides (**3a**, **3b**,

**3l**), lactams (**3c**), cyclic or acyclic ketones (**3d−g**, **3i−k**, **3m−o**), and lactones (**3h**).

Finally, we evaluated the performance of FMPhos in the venerable Rh-catalyzed alkene hydroformylation reaction. Unlike the above hydroalkenylation and hydroarylation processes, the hydroformylation reaction proceeds via a Rh−H rather than a Rh−C insertion pathway.[29] Hence, one would expect that under the same ligand environment, the branched/linear selectivity would be the *opposite* with respect to the two Ir-catalyzed reactions. Using styrene as the substrate and large-bite-angle Xantphos/DPEPhos as the ligand, the hydroformylation reaction took place with poor branched/linear selectivity (b:l = 1.3:1/2.3:1) in the presence of catalytic $Rh(CO)_2(acac)$ and pressurized syngas (150 psi) (Scheme 8).

**Scheme 8. Small-Bite-Angle Effect in Rh-Catalyzed Branched-Selective Hydroformylation of Styrene**[a]



[b] Isolated yield: 81%. [a] Yields and the linear/branched ratio were determined by $^1$H NMR of the crude products using tetrachloroethane as the internal standard.

This observation is consistent with the experimental results from van Leeuwen,[5b] who showed that even at elevated temperatures, there was little improvement to the branched/linear selectivity (b:l = 1:2.3) under similar reaction conditions. By contrast, the reaction proceeded with high efficiency (84% yield of the branched product) and excellent branched/linear selectivity (b:l > 20:1) when employing FMPhos as the bisphosphine ligand. As a sharp comparison, the use of dppm again gave almost no reactivity in this reaction (<1% combined yields). Taken together, these results demonstrated that FMPhos can achieve highly efficient and regioselective alkene hydrofunctionalization processes, complementary to large-bite-angle bisphosphines, which would otherwise be difficult with dppm.

## CONCLUSIONS

In summary, a unique small-bite-angle bisphosphine ligand, namely, FMPhos, has been developed to steer the regioselective outcome of alkene hydrofunctionalization reactions involving metal-hydride species. Compared to the known dppm ligand, FMPhos exhibits a rigid backbone and an equal or even smaller bite angle. The utility of FMPhos has been demonstrated in the linear-selective hydroalkenylation with enamides, linear-selective hydroarylation with diverse arene coupling partners, and the branched-selective hydroformylation of styrene. Given the complementary regioselectivity provided by FMPhos to large-bite-angle bisphosphines, we anticipate that the evolution of this new class of small-bite-angle ligands should expand our repertoire in achieving regiodivergent functionalizations of unactivated olefins. Efforts on developing a chiral version of FMPhos for enantioselective transformations are ongoing.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c04199.

Experimental procedures; spectral data; DFT calculation data; and X-ray crystallographic data (PDF)
X-ray crystallographic data (CIF)
X-ray crystallographic data (CIF)

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### Notes

The authors declare no competing financial interest.

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## REFERENCES

(1) (a) Hartwig, J. F. *Organotransition Metal Chemistry: From Bonding to Catalysis*; University Science Books: Sausalito, CA, 2010. (b) Dursch, T. J. Transition-Metal Complexes: Simple(r) Solutions to Complex Chemistry. *Trends Chem.* **2019**, *1*, 455−456.

(2) (a) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauff, D. J. Asymmetric hydrogenation with a complex of rhodium and a chiral bisphosphine. *J. Am. Chem. Soc.* **1975**, *97*, 2567−2568. (b) Miyaura, N.; Yamada, K.; Suzuki, A. A new stereospecific cross-coupling by the palladium-catalyzed reaction of 1-alkenylboranes with 1-alkenyl or 1-alkynyl halides. *Tetrahedron Lett.* **1979**, *20*, 3437−3440. (c) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. Asymmetric hydrogenation of.beta.-keto carboxylic esters. A practical, purely chemical access to.beta.-hydroxy esters in high enantiomeric purity. *J. Am. Chem. Soc.* **1987**, *109*, 5856−5858. (d) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. An Improved Catalyst System for Aromatic Carbon−Nitrogen Bond Formation: The Possible Involvement of Bis(Phosphine) Palladium Complexes as Key Intermediates. *J. Am. Chem. Soc.* **1996**, *118*, 7215−

7216. (e) Driver, M. S.; Hartwig, J. F. a second-generation catalyst for aryl halide amination: mixed secondary amines from aryl halides and primary amines catalyzed by (DPPF)PdCl2. *J. Am. Chem. Soc.* **1996**, *118*, 7217−7218. (f) Niemeyer, Z. L.; Milo, A.; Hickey, D. P.; Sigman, M. S. Parameterization of phosphine ligands reveals mechanistic pathways and predicts reaction outcomes. *Nat. Chem.* **2016**, *8*, 610−617. (g) Wu, K.; Doyle, A. G. Parameterization of phosphine ligands demonstrates enhancement of nickel catalysis via remote steric effects. *Nat. Chem.* **2017**, *9*, 779−784. (h) Zhao, S.; Gensch, T.; Murray, B.; Niemeyer, Z. L.; Sigman, M. S.; Biscoe, M. R. Enantiodivergent Pd-catalyzed C−C bond formation enabled through ligand parameterization. *Science* **2018**, *362*, 670−674.

(3) (a) Casey, C. P.; Whiteker, G. T. The Natural Bite Angle of Chelating Diphosphines. *Isr. J. Chem.* **1990**, *30*, 299−304. (b) Dierkes, P.; van Leeuwen, P. W. N. M. The bite angle makes the difference: a practical ligand parameter for diphosphine ligands. *J. Chem. Soc., Dalton Trans.* **1999**, 1519−1530. (c) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H. The bite angle makes the catalyst. *Pure Appl. Chem.* **1999**, *71*, 1443. (d) Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. Wide Bite Angle Diphosphines: Xantphos Ligands in Transition Metal Complexes and Catalysis. *Acc. Chem. Res.* **2001**, *34*, 895−904. (e) Freixa, Z.; van Leeuwen, P. W. N. M. Bite angle effects in diphosphine metal catalysts: steric or electronic? *Dalton Trans.* **2003**, 1890−1901.

(4) (a) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. Ligand Bite Angle Effects in Metal-catalyzed C−C Bond Formation. *Chem. Rev.* **2000**, *100*, 2741−2770. (b) Birkholz, M.-N.; Freixa, Z.; van Leeuwen, P. W. N. M. Bite angle effects of diphosphines in C−C and C−X bond forming cross coupling reactions. *Chem. Soc. Rev.* **2009**, *38*, 1099−1118.

(5) (a) Casey, C. P.; Whiteker, G. T.; Melville, M. G.; Petrovich, L. M.; Gavney, J. A.; Powell, D. R. Diphosphines with natural bite angles near 120.degree. increase selectivity for n-aldehyde formation in rhodium-catalyzed hydroformylation. *J. Am. Chem. Soc.* **1992**, *114*, 5535−5543. (b) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. New Diphosphine Ligands Based on Heterocyclic Aromatics Inducing Very High Regioselectivity in Rhodium-Catalyzed Hydroformylation: Effect of the Bite Angle. *Organometallics* **1995**, *14*, 3081−3089. (c) Casey, C. P.; Paulsen, E. L.; Beuttenmueller, E. W.; Proft, B. R.; Petrovich, L. M.; Matter, B. A.; Powell, D. R. Electron Withdrawing Substituents on Equatorial and Apical Phosphines Have Opposite Effects on the Regioselectivity of Rhodium Catalyzed Hydroformylation. *J. Am. Chem. Soc.* **1997**, *119*, 11817−11825. (d) van der Veen, L. A.; Boele, M. D. K.; Bregman, F. R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J.; Schenk, H.; Bo, C. Electronic Effect on Rhodium Diphosphine Catalyzed Hydroformylation: The Bite Angle Effect Reconsidered. *J. Am. Chem. Soc.* **1998**, *120*, 11616−11626. (e) van der Veen, L. A.; Keeven, P. H.; Schoemaker, G. C.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Lutz, M.; Spek, A. L. Origin of the Bite Angle Effect on Rhodium Diphosphine Catalyzed Hydroformylation. *Organometallics* **2000**, *19*, 872−883. (f) Bronger, R. P. J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. Influence of the Bite Angle on the Hydroformylation of Internal Olefins to Linear Aldehydes. *Organometallics* **2003**, *22*, 5358−5369.

(6) Franke, R.; Selent, D.; Börner, A. Applied Hydroformylation. *Chem. Rev.* **2012**, *112*, 5675−5732.

(7) Mansell, S. M. Catalytic applications of small bite-angle diphosphorus ligands with single-atom linkers. *Dalton Trans.* **2017**, *46*, 15157−15174.

(8) Chaudret, B.; Delavaux, B.; Poilblanc, R. Bisdiphenylphosphinomethane in dinuclear complexes. *Coord. Chem. Rev.* **1988**, *86*, 191−243.

(9) (a) Hansen, S. M.; Volland, M. A. O.; Rominger, F.; Eisenträger, F.; Hofmann, P. A New Class of Ruthenium Carbene Complexes: Synthesis and Structures of Highly Efficient Catalysts for Olefin Metathesis. *Angew. Chem., Int. Ed.* **1999**, *38*, 1273−1276. (b) Yamanoi, Y.; Imamoto, T. Methylene-Bridged P-Chiral Diphosphines in Highly Enantioselective Reactions. *J. Org. Chem.* **1999**, *64*, 2988−2989. (c) Dossett, S. J.; Gillon, A.; Orpen, A. G.; Fleming, J. S.; Pringle, P. G.; Wass, D. F.; Jones, M. D. Steric activation of chelate catalysts: efficient polyketone catalysts based on four-membered palladium(ii) diphosphine chelates. *Chem. Commun.* **2001**, 699−700. (d) Gridnev, I. D.; Yasutake, M.; Higashi, N.; Imamoto, T. Asymmetric Hydrogenation of Enamides with Rh-BisP* and Rh-MiniPHOS Catalysts. Scope, Limitations, and Mechanism. *J. Am. Chem. Soc.* **2001**, *123*, 5268−5276. (e) Carter, A.; Cohen, S. A.; Cooley, N. A.; Murphy, A.; Scutt, J.; Wass, D. F. High activity ethylene trimerisation catalysts based on diphosphine ligands. *Chem. Commun.* **2002**, 858−859. (f) Bollmann, A.; Blann, K.; Dixon, J. T.; Hess, F. M.; Killian, E.; Maumela, H.; McGuinness, D. S.; Morgan, D. H.; Neveling, A.; Otto, S.; Overett, M.; Slawin, A. M. Z.; Wasserscheid, P.; Kuhlmann, S. Ethylene Tetramerization: A New Route to Produce 1-Octene in Exceptionally High Selectivities. *J. Am. Chem. Soc.* **2004**, *126*, 14712−14713. (g) Hoge, G.; Wu, H.-P.; Kissel, W. S.; Pflum, D. A.; Greene, D. J.; Bao, J. Highly Selective Asymmetric Hydrogenation Using a Three Hindered Quadrant Bisphosphine Rhodium Catalyst. *J. Am. Chem. Soc.* **2004**, *126*, 5966−5967. (h) Gridnev, I. D.; Imamoto, T.; Hoge, G.; Kouchi, M.; Takahashi, H. Asymmetric Hydrogenation Catalyzed by a Rhodium Complex of (R)-(tert-Butylmethylphosphino)(di-tert-butylphosphino)methane: Scope of Enantioselectivity and Mechanistic Study. *J. Am. Chem. Soc.* **2008**, *130*, 2560−2572. (i) Chaplin, A. B.; Hooper, J. F.; Weller, A. S.; Willis, M. C. Intermolecular Hydroacylation: High Activity Rhodium Catalysts Containing Small-Bite-Angle Diphosphine Ligands. *J. Am. Chem. Soc.* **2012**, *134*, 4885−4897. (j) Castaing, M.; Wason, S. L.; Estepa, B.; Hooper, J. F.; Willis, M. C. 2-Aminobenzaldehydes as Versatile Substrates for Rhodium-Catalyzed Alkyne Hydroacylation: Application to Dihydroquinolone Synthesis. *Angew. Chem., Int. Ed.* **2013**, *52*, 13280−13283. (k) Murphy, S. K.; Bruch, A.; Dong, V. M. Substrate-Directed Hydroacylation: Rhodium-Catalyzed Coupling of Vinylphenols and Nonchelating Aldehydes. *Angew. Chem., Int. Ed.* **2014**, *53*, 2455−2459.

(10) Xing, D.; Dong, G. Branched-Selective Intermolecular Ketone $\alpha$-Alkylation with Unactivated Alkenes via an Enamide Directing Strategy. *J. Am. Chem. Soc.* **2017**, *139*, 13664−13667.

(11) (a) Tsuchikama, K.; Kasagawa, M.; Hashimoto, Y.-K.; Endo, K.; Shibata, T. Cationic iridium−BINAP complex-catalyzed addition of aryl ketones to alkynes and alkenes via directed C−H bond cleavage. *J. Organomet. Chem.* **2008**, *693*, 3939−3942. (b) Pan, S.; Ryu, N.; Shibata, T. Ir(I)-Catalyzed C−H Bond Alkylation of C2-Position of Indole with Alkenes: Selective Synthesis of Linear or Branched 2-Alkylindoles. *J. Am. Chem. Soc.* **2012**, *134*, 17474−17477.

(12) (a) Crisenza, G. E. M.; McCreanor, N. G.; Bower, J. F. Branch-Selective, Iridium-Catalyzed Hydroarylation of Monosubstituted Alkenes via a Cooperative Destabilization Strategy. *J. Am. Chem. Soc.* **2014**, *136*, 10258−10261. (b) Crisenza, G. E. M.; Sokolova, O. O.; Bower, J. F. Branch-Selective Alkene Hydroarylation by Cooperative Destabilization: Iridium-Catalyzed ortho-Alkylation of Acetanilides. *Angew. Chem., Int. Ed.* **2015**, *54*, 14866−14870. (c) Grélaud, S.; Cooper, P.; Feron, L. J.; Bower, J. F. Branch-Selective and Enantioselective Iridium-Catalyzed Alkene Hydroarylation via Anilide-Directed C−H Oxidative Addition. *J. Am. Chem. Soc.* **2018**, *140*, 9351−9356.

(13) Sevov, C. S.; Hartwig, J. F. Iridium-Catalyzed Oxidative Olefination of Furans with Unactivated Alkenes. *J. Am. Chem. Soc.* **2014**, *136*, 10625−10631.

(14) (a) Ebe, Y.; Nishimura, T. Iridium-Catalyzed Branch-Selective Hydroarylation of Vinyl Ethers via C−H Bond Activation. *J. Am. Chem. Soc.* **2015**, *137*, 5899−5902. (b) Ebe, Y.; Onoda, M.; Nishimura, T.; Yorimitsu, H. Iridium-Catalyzed Regio- and Enantioselective Hydroarylation of Alkenyl Ethers by Olefin Isomerization. *Angew. Chem., Int. Ed.* **2017**, *56*, 5607−5611. (c) Yamauchi, D.; Nishimura, T.; Yorimitsu, H. Asymmetric hydroarylation of vinyl ethers catalyzed by a hydroxoiridium complex: azoles as effective directing groups. *Chem. Commun.* **2017**, *53*, 2760−2763.

(15) (a) Li, X.; Wu, H.; Lang, Y.; Huang, G. Mechanism, selectivity, and reactivity of iridium- and rhodium-catalyzed intermolecular ketone $\alpha$-alkylation with unactivated olefins via an enamide directing strategy. *Catal. Sci. Technol.* **2018**, *8*, 2417−2426. (b) Xing, D.; Qi, X.; Marchant, D.; Liu, P.; Dong, G. Branched-Selective Direct $\alpha$-Alkylation of Cyclic Ketones with Simple Alkenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 4366−4370.

(16) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. Transition-Metal-Catalyzed C−H Alkylation Using Alkenes. *Chem. Rev.* **2017**, *117*, 9333−9403.

(17) Huang, G.; Liu, P. Mechanism and Origins of Ligand-Controlled Linear Versus Branched Selectivity of Iridium-Catalyzed Hydroarylation of Alkenes. *ACS Catal.* **2016**, *6*, 809−820.

(18) Xu, Y.; Qi, X.; Zheng, P.; Berti, C. C.; Liu, P.; Dong, G. Deacylative transformations of ketones via aromatization-promoted C−C bond activation. *Nature* **2019**, *567*, 373−378.

(19) Rezaei, H.; Normant, J. F. Preparation of 1-Bromo-1-chloro-, 1,1-Dibromo- or 1,1-Dichloroalk-1-enes from Ketones. *Synthesis* **2000**, *2000*, 109−112.

(20) Shulyupin, M. O.; Chirkov, E. A.; Kazankova, M. A.; Beletskaya, I. P. Nickel-Catalyzed Cross-Coupling of Diphenylphosphine with Vinyl Bromides and Chlorides as a Route to Diphenylvinylphosphines. *Synlett* **2005**, *2005*, 658−660.

(21) (a) Mo, F.; Dong, G. Regioselective ketone $\alpha$-alkylation with simple olefins via dual activation. *Science* **2014**, *345*, 68−72. (b) Wang, Z.; Reinus, B. J.; Dong, G. Catalytic Intermolecular C-Alkylation of 1,2-Diketones with Simple Olefins: A Recyclable Directing Group Strategy. *J. Am. Chem. Soc.* **2012**, *134*, 13954−13957. (c) Rodriguez, A. L.; Bunlaksananusorn, T.; Knochel, P. Potassium tert-Butoxide Catalyzed Addition of Carbonyl Derivatives to Styrenes. *Org. Lett.* **2000**, *2*, 3285−3287. (d) Nakamura, M.; Hatakeyama, T.; Nakamura, E. $\alpha$-Alkylation of Ketones by Addition of Zinc Enamides to Unactivated Olefins. *J. Am. Chem. Soc.* **2004**, *126*, 11820−11825. (e) Majima, S.; Shimizu, Y.; Kanai, M. Cu(I)-catalyzed $\alpha$-alkylation of ketones with styrene derivatives. *Tetrahedron Lett.* **2012**, *53*, 4381−4384. (f) Iwahama, T.; Sakaguchi, S.; Ishii, Y. Catalytic radical addition of ketones to alkenes by a metal−dioxygen redox system. *Chem. Commun.* **2000**, 2317−2318.

(22) (a) Pan, S.; Ryu, N.; Shibata, T. Iridium(I)-Catalyzed Direct C-H Bond Alkylation of the C-7 Position of Indolines with Alkenes. *Adv. Synth. Catal.* **2014**, *356*, 929−933. (b) Lahm, G.; Opatz, T. Unique Regioselectivity in the C(sp3)−H $\alpha$-Alkylation of Amines: The Benzoxazole Moiety as a Removable Directing Group. *Org. Lett.* **2014**, *16*, 4201−4203. (c) Ilies, L.; Zhou, Y.; Yang, H.; Matsubara, T.; Shang, R.; Nakamura, E. Iron-Catalyzed Directed Alkylation of Carboxamides with Olefins via a Carbometalation Pathway. *ACS Catal.* **2018**, *8*, 11478−11482.

(23) Electronically-unbiased alkenes, such as 1-octene, gave low yields (<20%) with poor linear-to-branched selectivity (typically 1:1).

(24) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. Efficient catalytic addition of aromatic carbon-hydrogen bonds to olefins. *Nature* **1993**, *366*, 529.

(25) Bai, X.-Y.; Wang, Z.-X.; Li, B.-J. Iridium-Catalyzed Enantioselective Hydroalkynylation of Enamides for the Synthesis of Homopropargyl Amides. *Angew. Chem., Int. Ed.* **2016**, *55*, 9007−9011.

(26) Mlynarski, S. N.; Karns, A. S.; Morken, J. P. Direct Stereospecific Amination of Alkyl and Aryl Pinacol Boronates. *J. Am. Chem. Soc.* **2012**, *134*, 16449−16451.

(27) (a) Zweifel, G.; Arzoumanian, H.; Whitney, C. C. A convenient stereoselective synthesis of substituted alkenes via hydroboration-iodination of alkynes. *J. Am. Chem. Soc.* **1967**, *89*, 3652−3653. (b) Sonawane, R. P.; Jheengut, V.; Rabalakos, C.; Larouche-Gauthier, R.; Scott, H. K.; Aggarwal, V. K. Enantioselective Construction of Quaternary Stereogenic Centers from Tertiary Boronic Esters: Methodology and Applications. *Angew. Chem., Int. Ed.* **2011**, *50*, 3760−3763.

(28) Llaveria, J.; Leonori, D.; Aggarwal, V. K. Stereospecific Coupling of Boronic Esters with N-Heteroaromatic Compounds. *J. Am. Chem. Soc.* **2015**, *137*, 10958−10961.

(29) Breit, B.; Seiche, W. Recent Advances on Chemo-, Regio- and Stereoselective Hydroformylation. *Synthesis* **2001**, 1−36.