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A Ligand Control of Palladium-Catalyzed Site-Selective α- and γ-Arylation of α,β-Unsaturated Ketones with (Hetero)aryl Halides

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Dedicated to Professor Albert Sun-Chi Chan on the occasion of his 70th birthday

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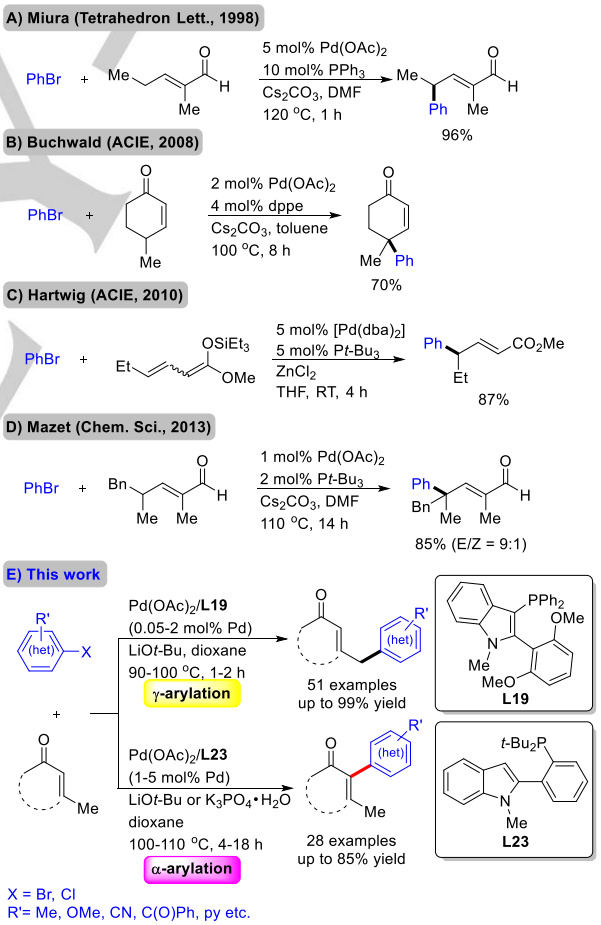
Abstract: This study describes the first palladium-catalyzed, site-selective α- and γ-arylation of α,β-unsaturated ketones with (hetero)aryl halides. A wide range of hetero(aryl)halides was coupled with α,β-unsaturated ketones and transformed to the arylated products with excellent-to-good yields. The site selectivity of the reaction is switchable via simply changing the phosphine ligands to access either α-arylated or γ-arylated products with good-to-excellent yields, low catalyst loading, and good functional group compatibility.

Direct C–H bond functionalization represents an attractive class of transformations. It can maximize the atom/step economy and simplify chemical synthesis.[1] However, site-selective C–H functionalization remains challenging,[2] as substrate-based control of selectivity through the directing groups or electronically biased substrates are required to achieve single site selectivity.[3] Besides the substrate-based control strategies, achieving the selective formation of different isomeric products by simply changing the ligands at the palladium center would be an extremely attractive approach, yet it is highly challenging to identify and rationalize the appropriate catalytic systems.

Palladium-catalyzed α-arylation of ketones and related carbonyl functional groups has become a very simple and dependable route to access α-aryl and α-vinyl ketones.[4] In contrast, the palladium-catalyzed arylation of α,β-unsaturated ketones has received less attention thus far. However, these ketones compose a class of interesting and useful compounds, which offer multiple active C–H bonds for the rapid construction of arylated α,β-unsaturated ketone motifs. Some important studies related to this aspect have been conducted by Miura, Buchwald, Hartwig, and Mazet. Miura and co-workers demonstrated that α,β-unsaturated ketones and aldehydes reacted with aryl bromides under basic conditions selectively at the γ-position using a $Pd(OAc)_2$/PPh_3-based catalyst (Scheme 1A).[5] Buchwald and co-workers developed a method for the selective γ-arylation of α,β- or β,γ-unsaturated ketones to generate γ-aryl-α,β-unsaturated ketones (Scheme 1B).[6] Hartwig and co-workers developed palladium-catalyzed coupling of aryl halides with silyl ketene acetals to form γ-arylated acyclic α,γ-unsaturated esters using P*t*-Bu_3 as the ligand (Scheme 1C).[7] Most recently, Mazet and co-workers reported the intermolecular palladium-catalyzed γ-arylation of α,β-unsaturated aldehydes with aryl bromides (Scheme 1D).[8]



Scheme 1. Palladium-catalyzed C–H arylation of α,β-unsaturated ketones.

Collectively, these studies showed that 1) the α- and γ- C–H bonds are active towards the direct arylation reaction, and this reaction can be controlled by appropriate ligands to give γ-arylated products; 2) The formation of the γ-arylated products may

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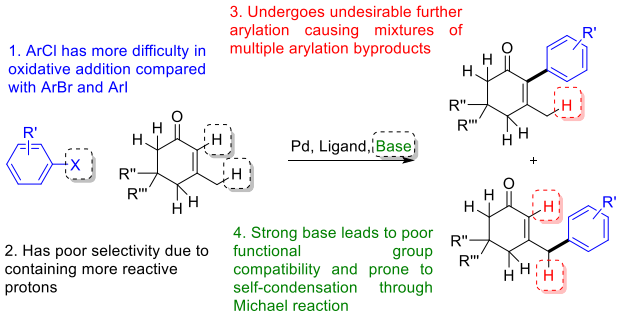
be thermodynamically and kinetically favored over the formation of the α-arylated products;[9] 3) The presence of an α-substituent may be necessary to prevent the formation of γ-arylation and the α,γ-bis-arylated mixture;[8] 4) the nature of the influence of ligand on the regioselectivity is still unclear, and a good regioselective α-arylation of α,β-unsaturated compounds has not yet been demonstrated.

Based on this prior research, we interested in the regioselective α- or γ-arylation of α,β-unsaturated ketones,[10] which is challenging because of the high possibility of the formation of regioisomeric products (Scheme 2).



Scheme 2. Persistent challenges of C–H arylation of α,β-unsaturated ketones.

We initially started our investigation of the site-selective arylation of α,β-unsaturated ketones by employing 4-chloroanisole and isophorone as the model substrates (Table 1). The reason for choosing isophorone is that isophorone and its derivatives are forms of α,β-unsaturated cyclic ketones, which have demonstrated importance in industry and medicinal chemistry.[11] Their widespread synthetic utility is highlighted by a myriad of possible transformations, including the synthesis of aldehydes, acids, amines, esters, and isocyanate (Figure 1).[11]

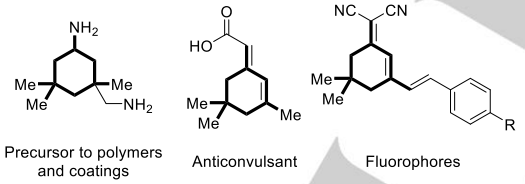
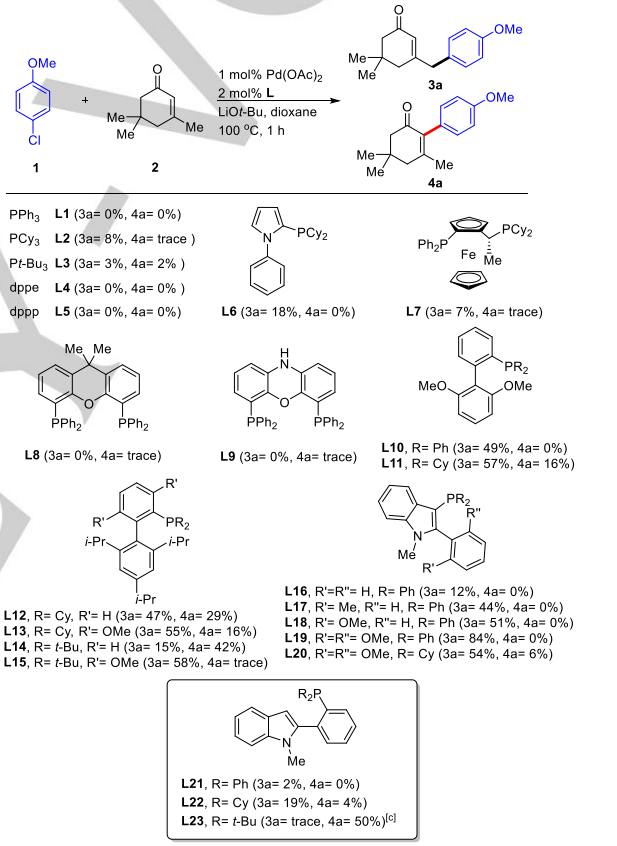


Figure 1. Examples of isophorone derivatives and their potential applications.

PPh_3 (**L1**), and bidentate ligands such as dppe (**L4**), dppp (**L5**), XantPhos (**L8**) and NiXantPhos (**L9**), which were active towards γ-arylation as reported by Buchwald,[6] were found to be ineffective in promoting this catalysis. PCy_3 (**L2**), CataCXium® PCy (**L6**), and Josiphos ligand (**L7**) gave the poor conversions in γ-arylation of isophorone. P*t*-Bu_3 (**L3**) gave both poor conversion and regioselectivity in the arylation reaction. A series of Buchwald type ligands (**L10**–**L15**) were then investigated. Less electron-donating PhSPhos (**L10**) promoted only γ-arylation reaction; meanwhile, electron-rich SPhos (**L11**) promoted both α-arylation and γ-arylation. Further increase of the steric bulkiness of the bottom ring, XPhos (**L12**) and BrettPhos (**L13**) further promoted α-arylation reaction. More electron-donating *t*-BuXPhos (**L14**) promoted α-arylation over γ-arylation reaction. However, the most electron-rich and bulky *t*-BuBrettPhos (**L15**) promoted only γ-arylation reaction. Based on these observations and our previous studies, we hypothesize that the γ-arylation of α,β-unsaturated ketones, which is similar to the direct α-arylation of ketones, maybe also a Csp^2–Csp^3 reductive elimination-demanding reaction.[10,12] From our and other authors' previous works on α-arylation of ketones,[10,13] palladium complexes containing strong, electron-donating ancillary ligands (e.g., –PCy_2) tend to undergo Csp^2–Csp^3 reductive elimination reaction more slowly than complexes containing weakly electron-donating ancillary ligands (e.g., –PPh_2). We believe that for ligand scaffold with an appropriate steric induced via the bottom ring, the alternation of electron density may provide a significant inference towards the regioselectivity and give the site-selective α- or γ-arylated product.

Table 1. Investigation of ligands on the selectivity of palladium-catalyzed arylation of isophorone with 4-chloroanisole between α- and γ- position[a]



[a] Reaction condition: 4-chloroanisole (1.0 mmol), isophorone (1.0 mmol), $Pd(OAc)_2$ (1 mol%), **L** (2 mol%), LiO*t*-Bu (2.5 mmol), and dioxane (3 mL) were stirred at 100 °C for 1 h under N_2. [b] The yields were calibrated by GC-FID using dodecane as the internal standard. [c] 24 h was conducted.

A series of indolyl phosphine ligands (**L16**–**L23**) that were previously found to be effective towards direct α-arylation of ketones were then investigated. Indolyl phosphine ligands, which bear the weakly electron-donating –PPh_2 group at the C3 position, were suitable ligands for γ-arylation of isophorone. It was found that the γ-arylated product yields were generally improved along with the increasing size of the substituted group at the *ortho*-position of the 2-aryl ring (H < Me < OMe < 2,6-di-OMe) (**L16**, **L17**, **L18,** and **L19**). **L19** was found to be a superior ligand for γ-arylation of isophorone. α-Arylated products appeared upon replacing the –PPh_2 group with the more electron-donating –PCy_2 (**L20**). Unfortunately, the installation of –P*t*-Bu_2 was not yet

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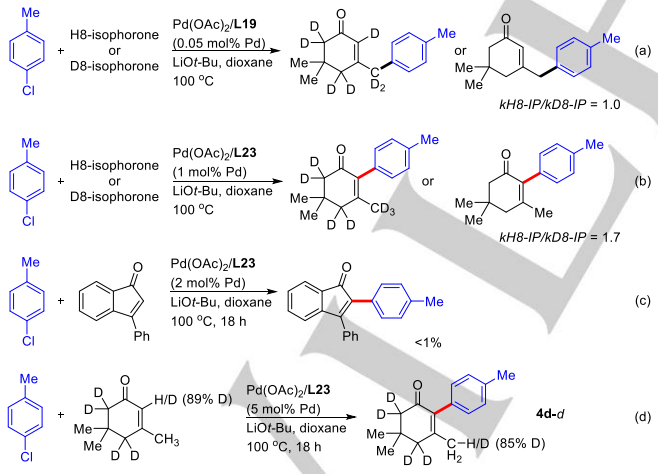
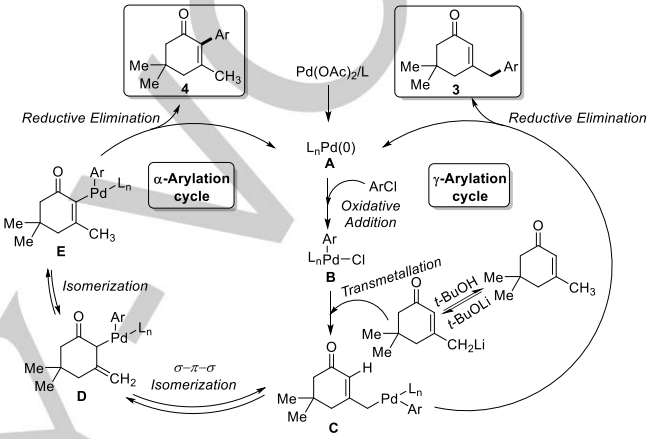
successful. Neither PhCM-Phos (**L21**) nor CM-Phos (**L22**) can effectively promote this reaction. However, the synthesis of the newly developed *t*-BuCM-Phos (**L23**) was successful, and we were delighted to observe that *t*-BuCM-Phos (**L23**) provided inverted and excellent regioselectivity toward the α-arylation reaction.

A series of experiments was conducted to investigate the origin of ligand effects on regioselectivity. *p*-Chloroanisole, *p*-chlorotoluene, and *p*-chlorobenzotrifluoride were selected to probe the electronic effect with respect to the initial rate of γ-arylation (see the Supporting Information, Scheme S1). Electron-deficient *p*-chlorobenzotrifluoride, which is more facial to oxidative addition, was found to proceed at the slower rate than the electron-rich *p*-chloroanisole and *p*-chlorotoluene. These results suggested that the γ-arylation of isophorone may still be a reductive elimination demanding reaction even with the less electron-donating ancillary phosphine ligand.[13a, 14] A set of isotope experiments was then carried out to investigate the dependence of the C–H bond cleavage. Using the Pd/**L19** catalytic system, the γ-arylation reaction was performed in two separate reaction vessels with H8-isophorone and D8-isophorone (Scheme 3a). The kH8-IP/kD8-IP was 1.0, which indicates that the deprotonation of γ-hydrogen is not the rate determinating step in γ-arylation reaction. In contrast, using the Pd/**L23** catalytic system, the reaction rate of α-arylation reaction with D8-isophorone was slower than the H8-isophorone (kH8-IP/kD8-IP=1.7), but smaller than 2 (Scheme 3b). 3-Phenyl-1*H*-inden-1-one, which is a non-enolizable enones, gave trace yield of product. The result indicates that the α-arylation reaction should not undergo the C–H activation pathway (Scheme 3c). The α-arylation reaction was performed using D5-isophorone. The deuterium (85% D) was observed at 3-methyl position of product **4d**, which may support the α-arylation reaction involving the isomerization process (Scheme 3d).



Scheme 3. Mechanistic investigation.

On the basis of the mechanistic experiments, the catalytic cycle producing **3** and **4** is proposed as shown in Scheme 4. Palladium(0) species **A** undergoes an oxidative addition reaction with ArCl to give arylpalladium species **B** which then undergoes transmetallation with deprotonated isophorone to generate complex **C**. In the case of arylpalladium species **C** bearing the less electron-donating phosphine ligand which (i.e. –PPh_2), arylpalladium species **C** undergoes a smooth Csp^2–Csp^3 reductive elimination to give the γ-arylated product **3**. In the case of arylpalladium species **C** bearing strong electron-donating ancillary phosphine ligand (i.e., –P*t*-Bu_2), complex **C** does not favor the occurrence of a more demanding Csp^2–Csp^3 reductive elimination,[13a, 15] and undergoes the σ–π–σ isomerization[9] to enter the favorable α-arylation cycle. Complex **D** further isomerize to give complex **E** which undergoes a more facile Csp^2–Csp^2 reductive elimination[15] to give α-arylated product **4**. It should be noted that the electron-rich but extremely bulky ligand may obstruct the isomerization to give a more steric congested complex **D,** but it may promote the reductive elimination of complex **C** to give γ-arylated product **3**.



Scheme 4. The proposed mechanism of α- and γ-arylation of isophorone.

We then first optimized the reaction conditions for the γ-arylation reaction (see the Supporting Information, Table S1) and explored the substrate scope (Table 2). In general, γ-arylation of isophorone proceeded smoothly under 0.05-1 mol% Pd catalyst loading. Electron-neutral (4-H, 4-Me, 4-*t*-Bu, 3-Me, and 3,5-diMe) and -rich (4-OMe, 3-OMe, 3-OEt, 3,5-diOMe, and 1,2-methylenedioxy) aryl chlorides were converted to the corresponding products in good-to-excellent yields (Table 2, compounds **3a**, **3b**, **3c**, **3d**, **3e**, **3f**, **3g**, **3h**, **3i**, and **3j**). Sterically hindered substrates were also applicable in our system (Table 2, compounds **3l**, **3m**, and **3q**). Highly sterically congested aryl chlorides were converted to the corresponding products with excellent yield (Table 2, compounds **3n**, **3o**, **3p**, and **3r**). Electron-deficient aryl chlorides, which were previously reported as challenging substrates, were smoothly transformed to the desired products in high yields under low catalyst loading (Table 2, compounds **3s**, **3t**, **3u**, and **3v**). Common functional groups such as nitrile, ketone, ester, and amide were well-tolerated under these reaction conditions (Table 2, compounds **3w**, **3x**, **3y**, **3z**, **3aa**, and **3ac**). Dialkyation could be done when 4,4'-dichlorobenzophenone was used (Table 2, compound **3ab**). Apart from a variety of aryl chlorides, heteroaryl chlorides were also examined. Under our developed catalyst system, pyridyl, quinolinyl, thienyl, and benzothiazolyl chlorides were coupled with isophorone efficiently (Table 2, compounds **3ad**, **3ae**, **3af**, **3ag**, **3ah**, **3ai**, **3aj**, **3ak**, **3am**, and **3an**). Dialkylation could be done when 2,6-dichloropyridine was used (Table 2, compound **3al**).

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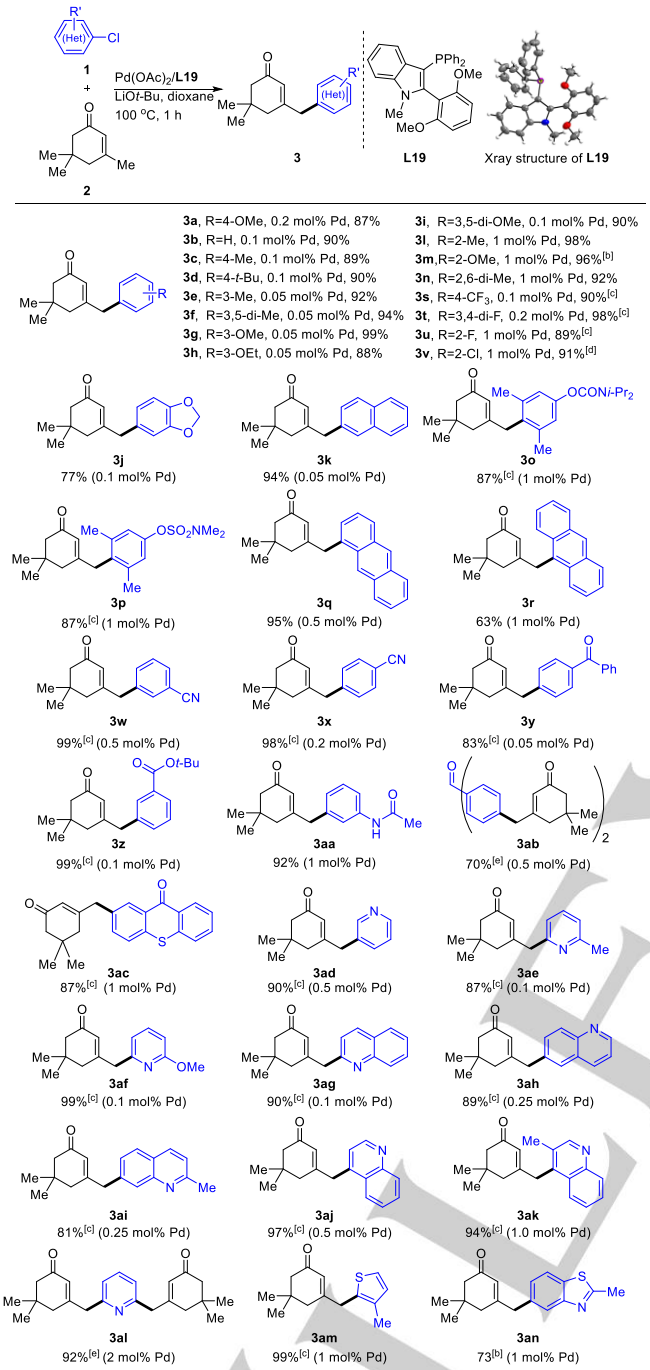
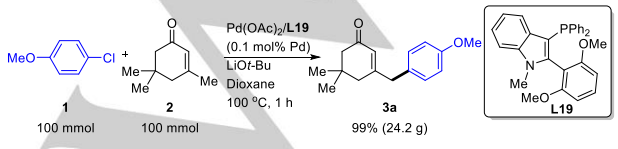
Table 2. Palladium-catalyzed γ-arylation of isophorone with (hetero)aryl chlorides[a]



[a] Reaction conditions: ArCl (1.0 mmol), isophorone (1.0 mmol), $Pd(OAc)_2$: **L19** = 1:2, LiO*t*-Bu (5.0 mmol) and dioxane (3.0 mL) were stirred at 100 °C for 1 h under N_2. Isolated yields. [b] The reaction was stirred for 2 h. [c] LiO*t*-Bu (2.5 mmol) was used. [d] 1,2-Dichlorobenzene (1.5 mmol) was used. [e] Isophorone (2.0 mmol) and LiO*t*-Bu (5.0 mmol) were used.

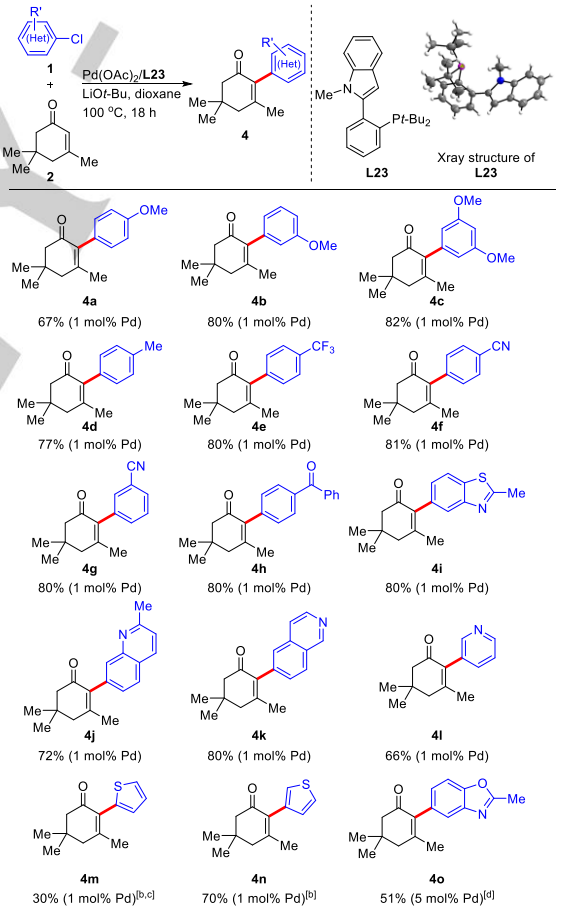


Scheme 5. Large scale experiment of γ-arylation of isophorone.

To test the feasibility of scaling up the current reaction conditions, a large-scale γ-arylation of isophorone was conducted (Scheme 5). 4-Chloroanisole and isophorone were directly scaled up 100 times to give the coupling product without any diminishing of the yield.

Having the optimal reaction conditions (see the Supporting Information, Table S2), we next examined the substrate scope of our newly developed catalyst system in α-arylation of isophorone (Table 3). Electron-rich (4-OMe, 3-OMe, and 3,5-diOMe), -neutral (4-Me), and -poor (4-CF_3) aryl chlorides were converted to the corresponding products in good-to-excellent yields (Table 3, compounds **4a**, **4b**, **4c**, **4d**, and **4e**). The aryl chlorides bearing an array of common functional groups, such as nitrile and ketone, were compatible and afforded excellent product yields (Table 3, compounds **4f**, **4g**, and **4h**). A variety of heterocyclics such as benzothiazole, quinoline, isoquinoline, pyridine, thiophene, and benzoxazole were also feasible substrates (Table 3, compounds **4i**, **4j**, **4k**, **4l**, **4m**, **4n**, and **4o**).

Table 3. Palladium-catalyzed α-arylation of isophorone with (hetero)aryl chlorides[a]



[a] Reaction conditions: ArCl (1.0 mmol), isophorone (2.0 mmol), $Pd(OAc)_2$: **L23** = 1:2, LiO*t*-Bu (1.5 mmol) and dioxane (3.0 mL) were stirred at 100 °C for 18 h under N_2. Isolated yields. [b] $Pd(dba)_2$ was used and the mixture was stirred at 110 °C. [c] Isophorone (5.0 mmol) was used. [d] ArCl (0.2 mmol), isophorone (0.4 mmol), $Pd(OAc)_2$: **L23** = 1:2, LiO*t*-Bu (0.3 mmol) and dioxane (0.6 mL) were stirred at 100 °C for 18 h under N_2.

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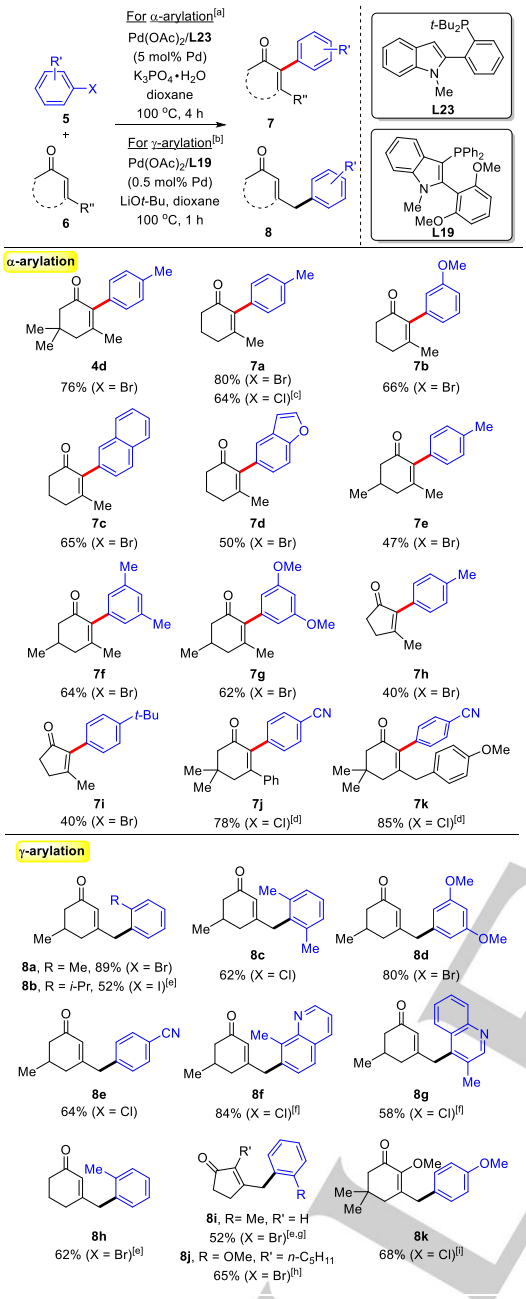
Table 4. Palladium-catalyzed α- and γ-arylation of α,β-unsaturated ketones with aryl halides



[a] Reaction conditions: ArBr/Cl (0.2 mmol), α,β-unsaturated ketones (0.4 mmol), $Pd(OAc)_2$ (5 mol% Pd), **L23** (10 mol%), $K_3PO_4·H_2O$ (1.0 mmol) and dioxane (0.6 mL) were stirred at 100 °C for 4 h under N_2. Isolated yields. [b] ArBr/Cl (0.2 mmol), α,β-unsaturated ketones (0.3 mmol), $Pd(OAc)_2$ (0.5 mol% Pd), **L19** (1 mol%), LiO*t*-Bu (0.5 mmol) and dioxane (0.6 mL) were stirred at 100 °C for 1 h under N_2. Isolated yields. [c] 18 h was conducted. [d] ArCl (1.0 mmol), α,β-unsaturated ketones (1.0 mmol), $Pd(OAc)_2$ (1 mol% Pd), **L23** (2 mol%), LiO*t*-Bu (2.5 mmol) and dioxane (3.0 mL) were stirred at 100 °C for 16 h under N_2. [e] α,β-unsaturated ketones (0.4 mmol) was used. [f] 90 °C was conducted. [g] $Pd(OAc)_2$ (4 mol% Pd), **L19** (8 mol%) were used. [h] 2 h was conducted. [i] ArCl (1.0 mmol), α,β-unsaturated ketones (1.0 mmol), $Pd(OAc)_2$ (1 mol% Pd), **L19** (2 mol%), LiO*t*-Bu (5 mmol) and dioxane (3.0 mL) were stirred at 100 °C for 2 h under N_2.

We then investigated other α,β-unsaturated ketones as the cross-coupling partners (Table 4). For α-arylation, using the catalyst system comprising of $Pd(OAc)_2$/**L23**, when a weaker base K_3PO_4 • H_2O was applied, 3-methyl-2-cyclohexenone, 3,5-dimethyl-2-cyclohexenone and 3-methyl-2-cyclopentenone were found to be applicable substrates (Table 4, compounds **7a**–**7i**). Good-to-excellent α-arylated product yields were obtained. Heteroaryl bromide was also a feasible substrate and afforded the corresponding product in moderate yield (Table 4, compound **7d**). However, poor conversions were observed for heteroaryl chlorides, such as 5-chloro-2-methylbenzothiazole, 7-chloroquinaldine, and 2-chloroquinoline. For γ-arylation, aryl halides also coupled with α,β-unsaturated ketones smoothly and afforded the corresponding products in good yield (Table 4, compounds **8a**–**8k**) in the presence of $Pd(OAc)_2$/**L19**. Products generated from the electron-rich aryl halides may be less subjected to the undesired further condensation reactions under the strongly basic condition and offered a better yield. Heteroaryl halides were coupled with normal α,β-unsaturated ketones smoothly and afforded the corresponding products in good yields (Table 4, compounds **8f** and **8g**). Aryl iodide was also found to be an applicable substrate (Table 4, compound **8b**).

In summary, the first ligand-controlled, site-selective α- and γ-arylation of α,β-unsaturated ketones with (hetero)aryl halides was established. The site selectivity of the reaction is switchable via simply changing the phosphine ligands to access either α-arylated or γ-arylated products in good-to-excellent yields with low catalyst loading and good functional group compatibility.

Acknowledgements

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Keywords: Palladium • Ligand • Arylation • α,β-Unsaturated Ketones • Site-selectivity

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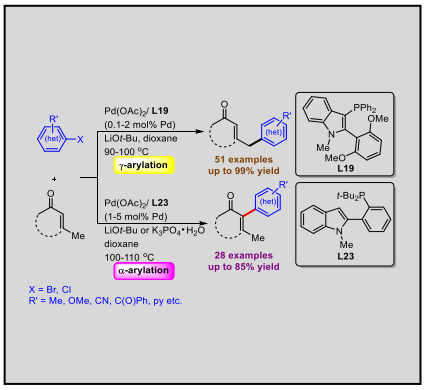

The first palladium-catalyzed site-selective γ- and α-arylation of α,β-unsaturated ketones with a wide range of (hetero)aryl halides is described. The site selectivity of the reaction between γ- and α-position is switched simply by changing the ligands. $Pd(OAc)_2$/**L19** favors γ-arylation, while $Pd(OAc)_2$ with newly developed **L23** favors α-arylation.