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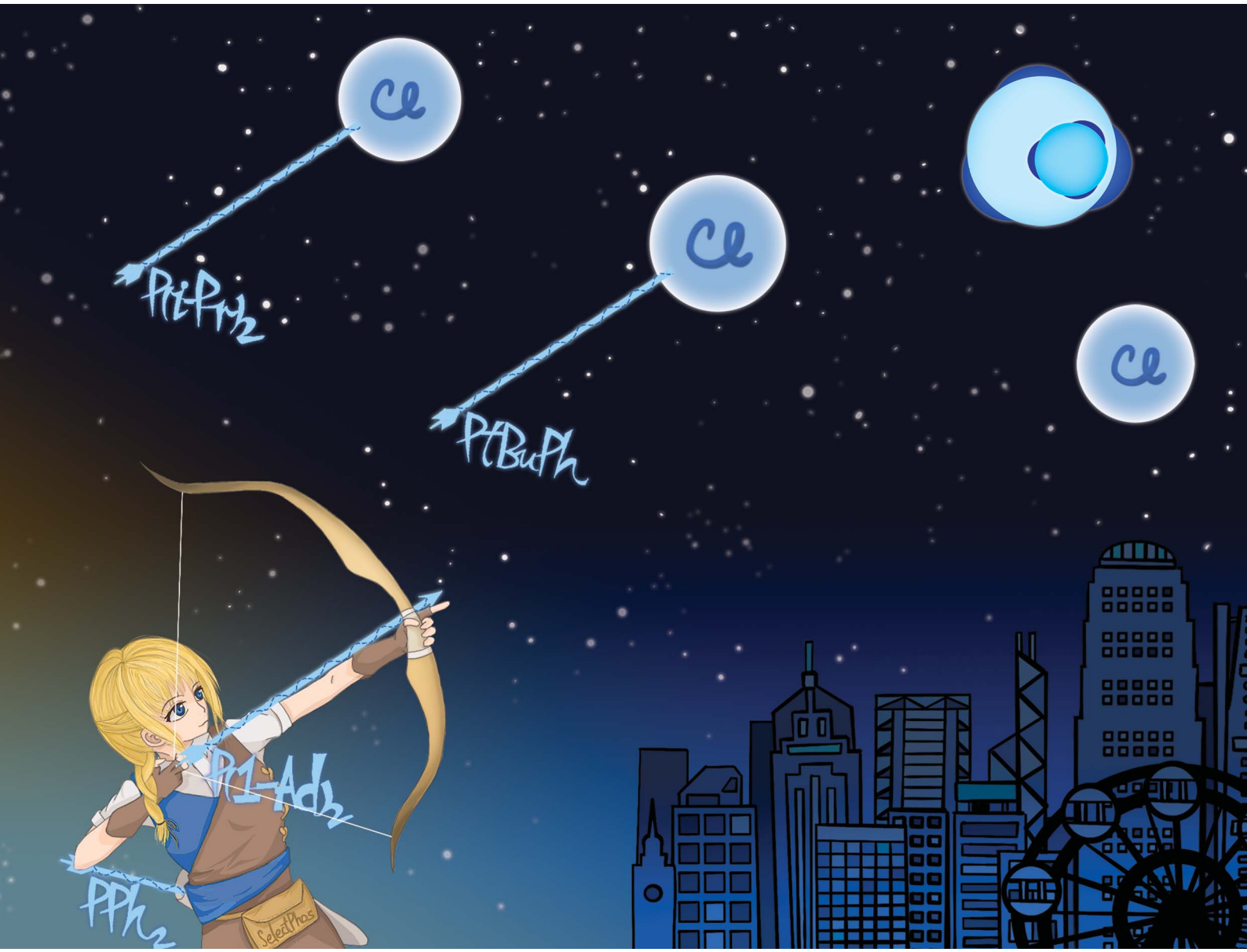

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EDGE ARTICLE

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Palladium-catalyzed chemoselective direct α-arylation of carbonyl compounds with chloroaryl triflates at the C–Cl site†

Zicong Chen,[a] Changxue Gu,[a] On Ying Yuen[a] and Chau Ming So *[ab]

This study described palladium-catalyzed chemoselective direct α-arylation of carbonyl compounds with chloroaryl triflates in the Ar–Cl bond. The Pd/SelectPhos system showed excellent chemoselectivity toward the Ar–Cl bond in the presence of the Ar–OTf bond with a broad substrate scope and excellent product yields. The electronic and steric hindrance offered by the $-PR_2$ group of the ligand with the C2-alkyl group was found to be the key factor affecting the reactivity and chemoselectivity of the α-arylation reaction. The chemodivergent approach was also successfully employed in the synthesis of flurbiprofen and its derivatives (*e.g.*, –OMe and –F).

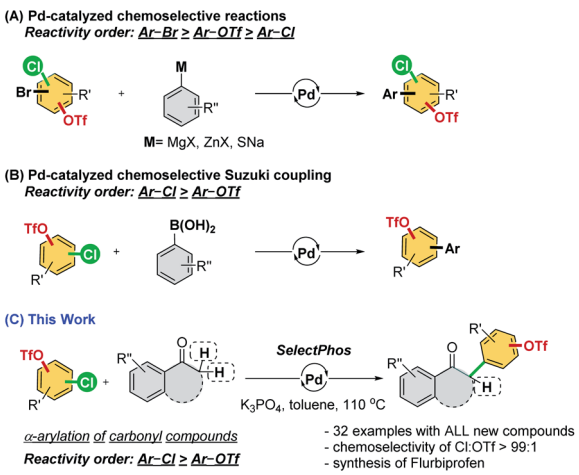
Introduction

Palladium-catalyzed cross-coupling reactions are versatile tools in organic synthesis for constructing new bonds between two motifs.[1] The functionalization of aryl (pseudo)halides provides practical synthetic routes for academia and industry for new chemical entities.[2] However, in previous studies of cross-coupling reactions, substrates frequently bear only a single electrophile.[1] Despite the fact that substrates bearing two or more reactive electrophilic sites could introduce a huge challenge to both reactivity and chemoselectivity,[3] many natural products and materials with multiple electrophilic sites exist. The success in controlling chemoselectivity sequences allows iterative or sequential cross-couplings[4] for the construction of more complicated molecules with optimal pathways and steps.

Aryl halides and triflates are the most widely used electrophiles, and they have a generally accepted reactivity order of I > Br ≈ OTf > Cl.[5] However, the reactivity order is sometimes substrate dependent and affected by the reaction conditions, which has resulted in a considerable challenge in the practical usage of these reactions. Therefore, much effort has been devoted to understanding the effects of catalysts and developing a substrate-independent chemoselective reaction following the conventional reactivity order (Scheme 1A).[6]

As ligands are an indispensable factor in cross-coupling reactions, developing appropriate ligands that can directly manipulate the reactivity sequence (*i.e.*, –Cl > –OTf) is an incredibly attractive strategy and would significantly broaden the choice of synthetic routes in actual applications.[7] However, only a few reports demonstrating Suzuki coupling and a single example of the Stille reaction have demonstrated the possibility of inverting the conventional reactivity order in cross-coupling reactions, which is still highly difficult to achieve (Scheme 1B).[7]

α-Arylated carbonyl motifs are commonly found in natural products and pharmaceutically active molecules.[8] The palladium-catalyzed α-arylation of ketones was initiated by Miura,[9] Buchwald,[10] and Hartwig,[11] which constituted a milestone in this field of research.[12] We envision that the palladium-



Scheme 1 Palladium-catalyzed chemoselective reaction of aryl (pseudo)halides.

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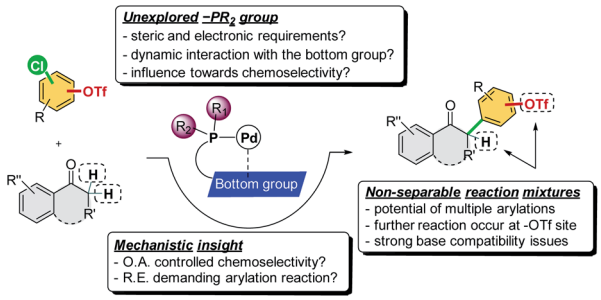


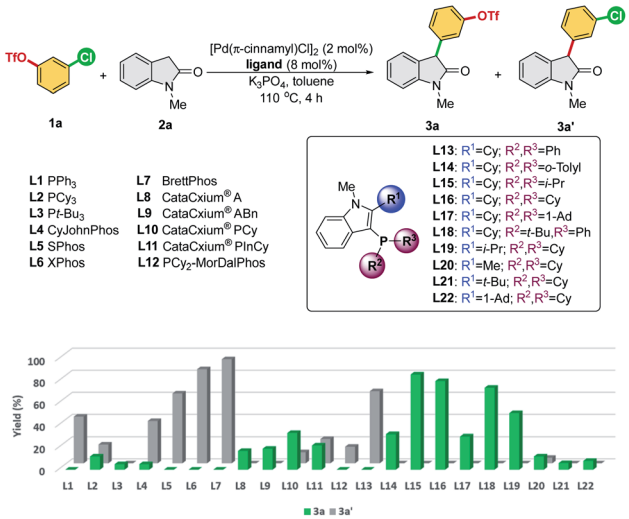
Scheme 2 Challenges of the chemoselective direct α-arylation reaction.

catalyzed chemoselective α-arylation of carbonyl compounds with multi-(pseudo)halogenated electrophiles could offer a robust and attractive methodology for synthesizing a new series of these important compounds. Herein, we attempt to develop an α-arylation reaction of carbonyl compounds through the chemoselective cross-coupling of chloroaryl triflates (Scheme 1C).

To achieve this reaction, several issues must be tackled (Scheme 2). First, the oxidative addition step is considered critical in determining the chemoselectivity of cross-coupling reactions, which has been proposed to be affected by the ligation state of the metal center in previous studies.[7d,13] However, the reductive elimination step was also reported to be the rate-determining step in direct α-arylation reactions, which are affected by the electron nature of the ligand's –PR_2 group.[14] In fact, the fundamental phosphine ligands, such as PCy_3 and P*t*-Bu_3, have been commonly employed in the study of the oxidative addition step to account for –Cl/–OTf chemoselectivity.[7] As such, the factors of ligand design with mechanistic insights for handling a chemoselective reaction involving the potential reductive elimination-demanding step remain unexplored. Second, the catalytic system must offer excellent chemoselectivity toward the Ar–Cl bond and leave the Ar–OTf bond intact to prevent the occurrence of multiple arylation reactions from generating non-separable reaction mixtures. Third, the catalytic system should be promoted using a mild base to prevent triflate hydrolysis. To the best of our knowledge, there have been no studies on the transition metal-catalyzed chemoselective C–Cl (over C–OTf) direct α-arylation of carbonyl compounds using chloroaryl triflates.

Results and discussion

We commenced our study by initially examining the ligand effect using oxindoles, which correspond to a class of privileged structural motifs in natural products and pharmaceutical agents.[15] The cross-coupling of 3-chlorophenyl triflate **1a** and 1-methylindolin-2-one **2a** was selected as the reaction model to probe the feasibility of the commercially available and sophisticated ligands for chemoselective coupling reactions (Scheme 3). PCy_3 (**L2**) and P*t*-Bu_3 (**L3**) reportedly provide good chemoselectivity for the Ar–OTf of the former and Ar–Cl bond of the latter in the Suzuki coupling of 4-chlorophenyl triflate.[7a]



Scheme 3 Ligand screening of chemoselectivity in α-arylation of *N*-methyl oxindole. Reaction conditions: **1a** (0.20 mmol), **2a** (0.20 mmol), K_3PO_4 (0.40 mmol), toluene (1.0 mL), and under N_2. The yield was calibrated by GC-FID using dodecane as the internal standard.

However, in this context, PCy_3 (**L2**) yielded a mixture of **3a**/**3a**′, and P*t*-Bu_3 (**L3**) was not effective toward this reaction. PPh_3 (**L1**) along with Buchwald-type biphenyl ligands (**L4–L7**), which have Pd-arene π-coordination with its *ortho*-aryl group and act as the bis-coordinated ligand, prefers to react with the Ar–OTf bond and follows the conventional reactivity order of Ar–OTf > Ar–Cl to yield **3a**′. The CataCxium series (**L8–L11**) showed activity toward the Ar–Cl bond. However, this series of ligands suffers from low activity (**L8–L9**) and the formation of the reaction mixture of **3a**/**3a**′ (**L10–L11**). P,N-type ligand **L12**, which acts as a bis-coordinated ligand, has also shown chemoselectivity toward the Ar–OTf bond.

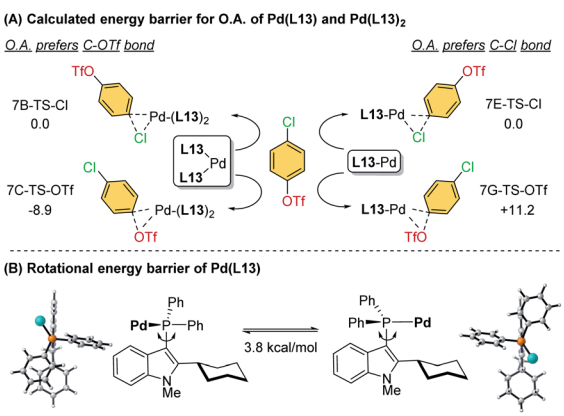
Recently, we developed a novel phosphine ligand, SelectPhos (**L15**), with a C2-cyclohexyl-substituted indole skeleton, which was found to be active toward the chemoselective Suzuki–Miyaura coupling reaction.[7f] The preagostic interaction and the steric hindrance offered by the C2-alkyl group enabled the inversion of the conventional selectivity order of Ar–Cl > Ar–OTf. Thus, we investigated the feasibility of alkyl-indole-based phosphines (**L13–L22**)[16] in the chemoselective α-arylation reaction. We found that **L15** (SelectPhos) and **L16** (CySelectPhos) inverted the chemoselectivity (–Cl over –OTf), affording the desired product with excellent yields through the Ar–Cl bond cleavage. The structure of the C2-alkyl group has a critical influence on the reaction. Either replacing the cyclohexyl group with the smaller –Me (**L20**) or more steric hindered the tertiary alkyl group of –*t*-Bu (**L21**) or –Ad (**L22**), but lacking methine hydrogen significantly lowered the chemoselectivity and reactivity of the catalyst.[17] To further probe the importance of the C2-secondary alkyl group, a ligand with the C2-i-Pr group (**L19**) was newly synthesized. The Pd/**L19** system afforded a slightly lower yield of **3a** in the α-arylation reaction with unchanged chemoselectivity at the Ar–Cl bond.

In addition to the C2-alkyl groups, extra attention was paid to evaluating the effects of dynamic interactions between –PR_2

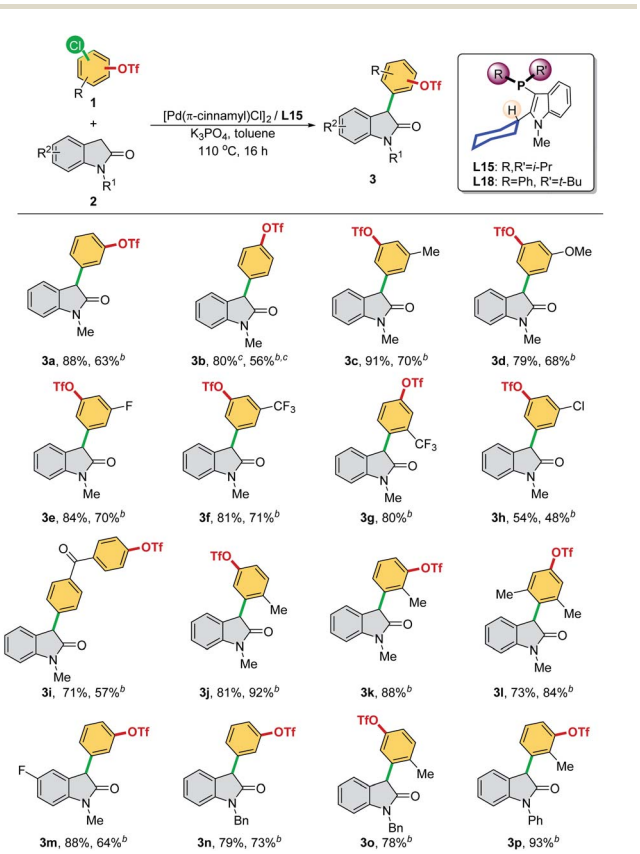
modules and the C2-alkyl group of alkyl-indole-based phosphines (**L13–L18**), which has been unexplored to date. The $-PR_2$ was found to be critical and able to alternate the rate-determining steps of the α-arylation reaction when only a single electrophile was involved.[18] In general, the $-PR_2$ moiety with an alkyl group, such as –i-Pr (**L15**), –Cy (**L16**), –Ad (**L17**), and –*t*-Bu (**L18**), demonstrated chemoselectivity toward the Ar–Cl bond. Surprisingly, palladium with the ligand bearing the $-PPh_2$ group (**L13**) could chemoselectively react with the Ar–OTf bond to yield product **3a′**. We suspected that **L13** with a relatively small $-PPh_2$ might be able to bis-ligate the palladium center to form $Pd(L)_2$ species. Thus, we further synthesized **L14** with a larger $-P(o\text{-tolyl})_2$ group, which demonstrated a preference toward the Ar–Cl bond and yielded the product **3a** selectively.[19]

To further investigate the ligand effects on the chemoselectivity of the $-PR_2$ moiety, we performed a density functional theory (DFT) study of the oxidative addition process for the bis-ligated $Pd(\mathbf{L13})_2$ to evaluate the effects of the $-PPh_2$ on the chemoselectivity (Scheme 4). The calculations were performed at the SMD(toluene) B3PW91-D3(BJ)/6-31G*//B3PW91-D3(BJ)/Def2-TZVP level of theory (see ESI for details†). The calculated results indicated that $Pd(\mathbf{L13})_2$ favored the oxidative addition of C–OTf (**7C-TS-OTf**) over C–Cl (**7B-TS-Cl**) by 8.9 kcal mol^{-1}, which also agrees with the previous finding that the bis-coordinated palladium complex preferred the C–OTf bond activation (Scheme 4A).[7d] To examine whether chemoselectivity may be governed by the electron-deficient property of $-PPh_2$ to react with the C–Cl bond, a simulation of the oxidative addition of 4-chlorophenyl triflate using Pd-**L13** was attempted (Scheme 4A), and the result shows that mono-ligated Pd-**L13** favored the oxidative addition of C–Cl (**7E-TS-Cl**) over C–OTf (**7G-TS-OTf**) by 11.2 kcal mol^{-1}. Furthermore, the rotational energy barrier study of Pd/**L13** and Pd/**L15** *via* the constrained-relaxation scan was performed (see ESI, Fig. S6† for details). The calculated energy barrier for the $-PPh_2$ group (**L13**) rotation along the indole skeleton was about 3.8 kcal mol^{-1} (Scheme 4B), which should be at least 8.1 kcal mol^{-1} lower than the rotational energy barrier of the $-Pi\text{-}Pr_2$ group (**L15**). The low rotational energy barrier of the $-PPh_2$ group might be a possible reason for the facial bis-ligation to form the $Pd(L)_2$ species and the C–OTf selectivity. These results indicate that in addition to the effects of the C2-substituted group of the ligand core, the steric effect offered by the $-PR_2$ group is also an important factor in chemoselectivity.

We then optimized the reaction conditions using SelectPhos (**L15**) for the direct α-arylation reaction (see ESI, Table S2† for details). The replacement of palladium sources had no effect on the chemoselective outcome (Table S2,† entries 1–3), and neither did the ligand ratio (Table S2,† entry 10). Milder bases were found to be inferior to this reaction, while the triflate group was decomposed by the strong base (Table S2,† entries 5–6). Toluene was found to be the best of the solvents tested (Table S2,† entries 3 and 7–8). Based on the chemoselective Ar–Cl bond (over Ar–OTf bond) functionalization enabled by the Pd/**L15** system, we explored both electrophiles and nucleophiles (Scheme 5). The Pd/**L15** system demonstrated high efficiency in the cross-coupling of substituted chloroaryl triflates, including electron-rich/deficient substitutions (–OMe, –Me, –F, $-CF_3$, and –Cl) in *meta*/*para*-positions (**3c–3f**, **3h**, **3i**). Substrates with the ketone carbonyl were also compatible under these conditions



Scheme 4 (A) Calculated energy barrier for the oxidative addition step of Pd(**L13**) and $Pd(\mathbf{L13})_2$ and (B) rotational energy barrier of Pd(**L13**).



Scheme 5 Palladium-catalyzed α-arylation of oxindoles through chemoselective C–Cl bond cleavage[a] ([a]Reaction conditions: **1** (0.20 mmol), **2** (0.20 mmol), $[Pd(\pi\text{-cinnamyl})Cl]_2$ (2 mol%), **L15** (8 mol%), Pd : L = 1 : 2, K_3PO_4 (0.40 mmol), toluene (1.0 mL), 110 °C, and 16 h. Isolated yields were reported. The chemoselectivity ratio between Ar–Cl and Ar–OTf was >99/1. [b]**L18** was used. [c]Reaction conditions: 80 °C and 14 h).

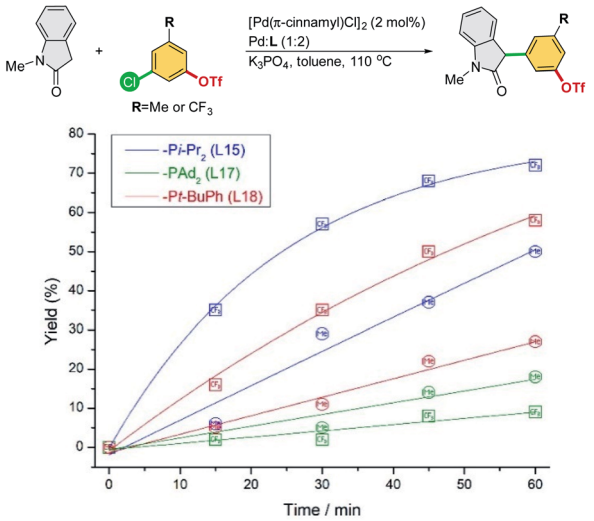
(**3i**). When a fluoro group was substituted at the C5 position of the oxindole, a good product yield was obtained (**3m**). Other N-substituted oxindoles, such as *N*-benzyl (**3n**, **3o**) and *N*-phenyl (**3p**), were also feasible substrates and afforded the corresponding products in a good yield. Although **L18** generally showed inferior results compared to **L15**, interestingly, Pd/**L18** was found to be more effective in the reaction of sterically hindered substrates (**3g**, **3k**, and **3l**) and complementary to **L15** in expanding the substrate scope.

We attempted buried volume and steric map analyses to understand the steric properties of the **L15** and **L18** in the catalysis reaction (Fig. 1).[20] In addition to the $\%V_{bur}$ of **L15** with –Pi-Pr_2 larger than that of **L18** with –P*t*-BuPh, as well as the large steric contributions of the cyclohexyl group of both ligands at the SE quadrant, the steric map showed that the steric impact of the two isopropyl P-substituents of **L15** was evenly spread over the SW, NW, and NE quadrants, while the steric impact of –P*t*-BuPh **L18** was biased toward the NE quadrants (Ph, NW and *t*-Bu, NE), which might facilitate the coordination of hindered substrates to yield the products.[21]

A series of experiments were conducted to further investigate the origin of the ligand effects on reactivity and chemoselectivity. 3-Chloro-5-(trifluoromethyl)phenyl triflate and 3-chloro-5-methylphenyl triflate were selected to probe the electronic effect with respect to the initial rate of α-arylation (Scheme 6).

Electron-deficient 3-chloro-5-(trifluoromethyl)phenyl triflate proceeded faster than electron-rich 3-chloro-5-methylphenyl triflate, suggesting that oxidative addition could be the rate-limiting step for both Pd/**L15** and Pd/**L18** systems. The faster reaction rate of Pd/**L15** may be attributed to its dialkyl phosphine group (–Pi-Pr_2), which should be more electron-rich than the aryl-alkyl phosphine group (–P*t*-BuPh) of the Pd/**L18** system. Interestingly, the Pd/**L17** system with the most electron-rich –PAd_2 group showed the slowest reaction rate compared to the Pd/**L15** and Pd/**L18** systems. Moreover, electron-deficient 3-chloro-5-(trifluoromethyl)phenyl triflate, which is more prone to oxidative addition, proceeded at a slower rate than electron-rich 3-chloro-5-methylphenyl triflate with the Pd/**L17** system. Among the Pd/**L15**, Pd/**L17**, and Pd/**L18** systems tested, the reactions undergo the C–Cl pathway chemoselectively.

A set of individual and competition experiments were further conducted for Pd/**L15**, Pd/**L17**, and Pd/**L18** systems (Scheme 7). For Pd/**L15** and Pd/**L18** systems, both the individual experiments (Scheme 7A) and competition experiments (Scheme 7B) showed that the electron-poor 3-chloro-5-(trifluoromethyl) phenyl triflate **2f** offered the corresponding product in a higher yield than the electron-rich 3-chloro-5-methylphenyl triflate **2c**. These results suggested that the oxidative addition step could be the rate-limiting step for both Pd/**L15** and Pd/**L18** systems.



Scheme 6 Reaction rate study of electronically different chloroaryl triflates in the cross-coupling of *N*-methyl-oxindole.

However, for the Pd/**L17** system, the results of the individual experiments (Scheme 7A) showed that the electron-rich 3-chloro-5-methylphenyl triflate **2c** gives the corresponding product in a higher yield than the electron-poor 3-chloro-5-(trifluoromethyl)phenyl triflate **2f**. In contrast, the competition experiments of Pd/**L17** (Scheme 7B) showed that the electron-poor 3-chloro-5-(trifluoromethyl)phenyl triflate **2f** offered the corresponding product in a higher yield than the electron-rich 3-chloro-5-methylphenyl triflate **2c**. The results of the competition reaction may be due to a more rapid oxidative addition of the electron-poor 3-chloro-5-(trifluoromethyl) phenyl triflate **2f** followed by a slow reductive elimination step, thus inhibiting the catalyst from reacting with electron-rich 3-chloro-5-methylphenyl triflate **2c**. These experimental results suggest

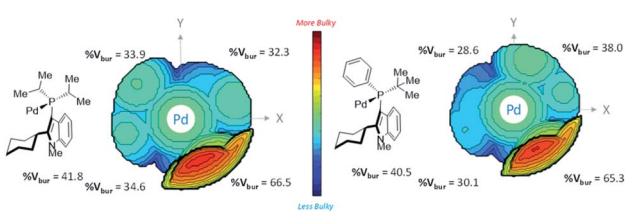
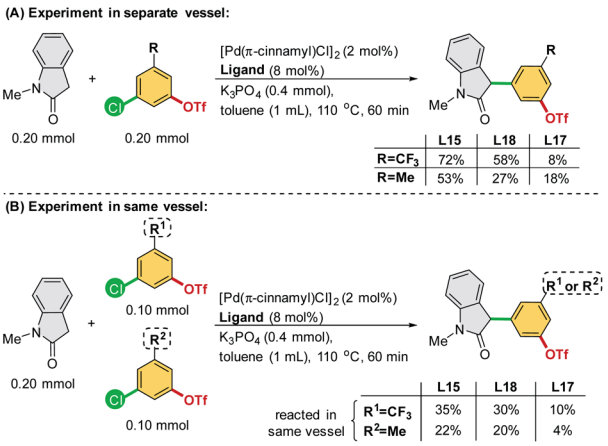


Fig. 1 $\%V_{bur}$ *vs.* steric map representation of Pd-**L15** and Pd-**L18**.



Scheme 7 Individual and competition experiments of different chloroaryl triflates.

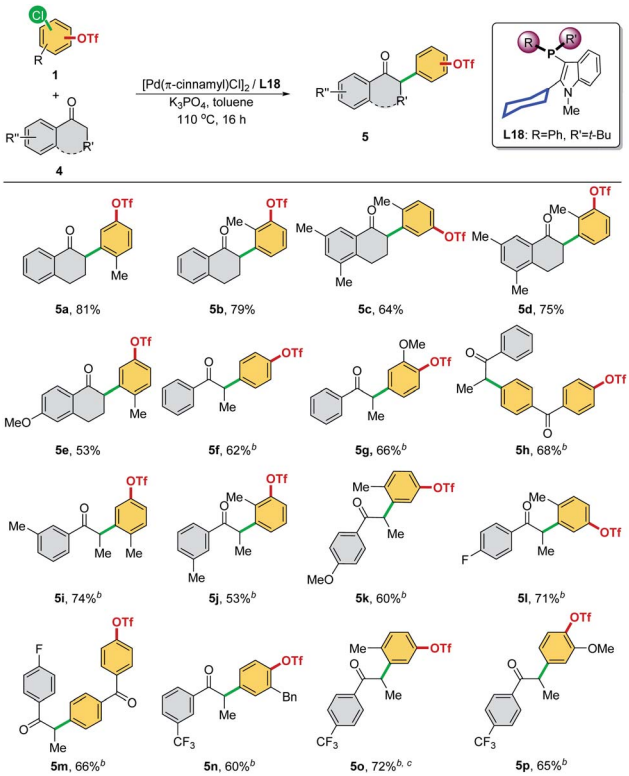
that reductive elimination is likely to be the rate-limiting step in the catalytic cycle involving the Pd/**L17** system.[14,22]

The experimental results (Schemes 6 and 7) of Pd/**L15** and Pd/**L18** systems suggested that the oxidative addition step could be the rate-limiting step in the α-arylation reaction, accompanied by the previous DFT study results[7f] of Pd/**L15** which prefers oxidative addition of the C–Cl bond over the C–OTf bond, which should account for the chemoselective formation of the C–Cl reacted product.

For the Pd/**L17** system, chemoselectivity of the Pd/**L17** system remained unchanged (Ar–Cl > Ar–OTf), even if the oxidative addition of Ar–Cl was not the rate-limiting step. To have a better insight into the reasons of the Pd/**L17** system why the C–OTf pathway is not preferable, a series of DFT calculations were conducted (Fig. 2).

The monoligated Pd-**L17** reacted with 4-chlorophenyl triflate, and oxindole was used for the study. In the reaction of the C–Cl pathway, aligned with the kinetic study, the calculated results suggested that the energy barrier of the reductive elimination step (**8F-TS**, 13.2 kcal mol^{-1}) was higher than the oxidative addition of C–Cl (**8C-TS**, 9.6 kcal mol^{-1}). In the reaction of the C–OTf pathway, the oxidative addition of the C–OTf (**8I-TS**, 13.9 kcal mol^{-1}) showed a higher energy barrier than the reductive elimination step (**8L-TS**, 12.6 kcal mol^{-1}). The higher energy barrier of the oxidative addition step of C–OTf (**8I-TS**, 13.9 kcal mol^{-1}) than the C–Cl (**8C-TS**, 9.6 kcal mol^{-1}) may disfavor the C–OTf pathway of the reaction, which might account for the preference of chemoselectivity toward the C–Cl bond in the Pd/**L17** system.

We then investigated other ketones as cross-coupling partners in the chemoselective α-arylation reaction (Scheme 8). The –Cl site was selectively reacted, regardless of whether the C–Cl and C–OTf bonds were positioned *meta* (**5a–5e**, **5i–5l**, and **5o**) or *para* (**5f**, **5g**, **5n**, and **5p**) to each other and whether functional groups were present (**5h** and **5m**). α-Tetralone with different substitutions were applicable coupling partners, affording the desired α-arylated products with exclusive chemoselectivity (**5a–5e**). A diversity of aryl ethyl ketones was examined as substrates (**5f–5p**). Electron-neutral (–H, and 3-Me), rich (4-OMe), and poor (4-F, 3-CF_3, and 4-CF_3) aryl ethyl ketones were α-arylated smoothly in good product yields with excellent chemoselectivity



Scheme 8 Palladium-catalyzed α-arylation of ketones through chemoselective C–Cl bond cleavage[a] ([a]Reaction conditions: **1** (0.20 mmol), **4** (0.20 mmol), [Pd(π-cinnamyl)Cl]$_2$ (2 mol%), **L18** (8 mol%), Pd : L = 1 : 2, K_3PO_4 (0.40 mmol), toluene (1.0 mL), 110 °C, and 16 h. Isolated yields were reported. The chemoselectivity ratio between Ar–Cl and Ar–OTf was >99/1. [b]K_3PO_4 (0.50 mmol) was used. [c]The chemoselectivity ratio between Ar–Cl and Ar–OTf was >25/1).

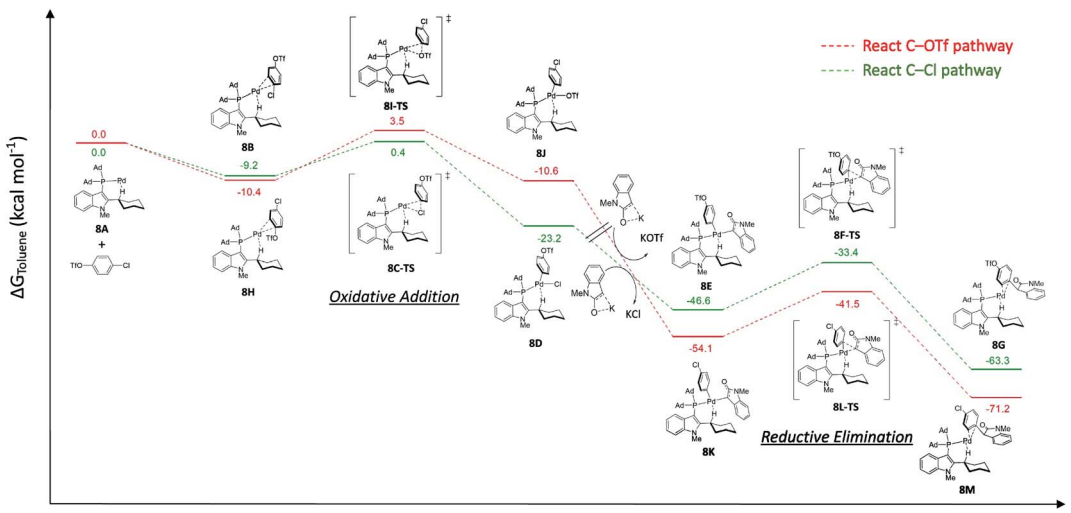
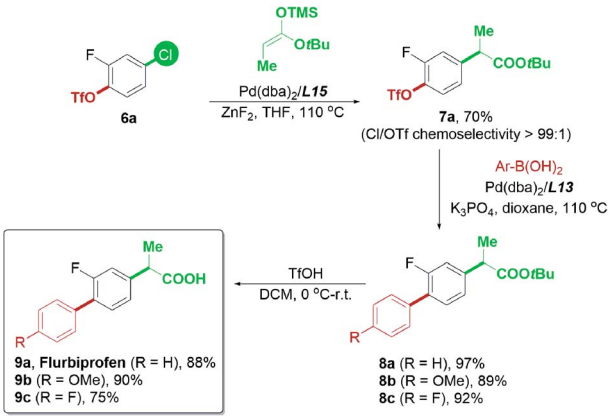


Fig. 2 Free energy profiles calculated for the chemoselective Pd-**L17** cross-coupling reaction of 4-chlorophenyl triflate with 1-methyloxindole.



Scheme 9 Synthesis of flurbiprofen using the chemoselective strategy.

at the –Cl site. It is worth noting that all of the products (Schemes 5 and 8, **3a–3p** and **5a–5p**) synthesized with this chemoselective reaction were new compounds, which offered a convenient pathway to access the new class of synthetically valuable molecules.[23]

Based on the successful attempt to functionalize ketones, we are encouraged to expand the scope of nucleophiles further and apply this chemoselective cross-coupling system to synthesize new pharmaceutical substances.[24] Flurbiprofen is a commercial nonsteroidal anti-inflammatory drug, and the optimization of its synthetic methods has been widely studied.[10d,25] Flurbiprofen has two functional groups attached to the fluorobenzene linker; thus, it was considered an appropriate final product for examining the practicability of our palladium-catalyzed chemoselective system (Scheme 9). In view of the α-arylation of esters, reactions generally required strong bases such as NaHMDS,[11c] LiHMDS,[26] and $LiNCy_2$ [27] in previous reports, which may not be tolerated by the triflate electrophile. To minimize the potential hydrolysis of aryl triflates with a strong base and further enhance the potential usage of carbonyl derivatives in the chemoselective reaction, we attempted to use the ester enolate[28] as a convenient alternative to *tert*-butyl propionate. The mild reaction conditions required for trimethylsilyl enolates in Pd-catalyzed transformations[28b] offered a good advantage for our current study.

Using the ester enolate of *tert*-butyl propionate, 4-chloro-2-fluorophenyl triflate **6a** was successfully converted into the key intermediate **7a** *via* Pd/**L15**-catalyzed chemoselective Ar–Cl bond cleavage, paving the way for subsequent transformations. Subsequent Suzuki–Miyaura coupling enabled by the Pd/**L13** system could afford **8a–8c** efficiently. Upon acidic hydrolysis, flurbiprofen **9a** and its derivatives **9b–9c** were prepared with a satisfactory yield (Scheme 9). Thus, the practicability of this chemoselective transformation has proven to be promising and is worthy of further exploration.

Conclusions

In summary, for the first time, we developed a chemoselective palladium-catalyzed α-arylation reaction. The α-arylation reactions of carbonyl compounds, including oxindoles, ketones, and enol ester, were achieved to access a new class of carbonyl compounds that covers a wide range of chloroaryl triflates with an inversion of the common reactivity order of C–Cl > C–OTf. Furthermore, this strategy was successfully applied to synthesize flurbiprofen. We anticipate that this method will provide new insights into the optimal pathways for synthesizing complex molecules.

Data availability

NMR and HRMS spectra and characterization data of the compounds and crystallographic data of **L17**, and experimental and computational details are provided in the ESI.†

Author contributions

The manuscript was written through the contributions of all authors. All authors have given approval regarding the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

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17 There is a preagostic interaction between the methine hydrogen on the cyclohexyl group and Pd center, which may play a role in stabilizing and affecting the activity of the unsaturated Pd complex during oxidative addition. The steric effect induced by the C2-cyclohexyl group may prevent the formation of the L_2Pd species. For details, see ref. 7*f*. For the references describing the role and the importance of C–H…M interactions, see: (*a*) H.-J. Cao, Q. Zhao, Q.-F. Zhang, J. Li, E. J. M. Hamilton, J. Zhang, L.-S. Wang and X. Chen, *Dalton Trans.*, 2016, **45**, 10194–10199; (*b*) H. Darmandeh, J. Löffler, N. V. Tzouras, B. Dereli, T. Scherpf, K.-S. Feichtner, S. V. Broeck, K. V. Hecke, M. Saab, C. S. J. Cazin, L. Cavallo, S. P. Nolan and V. H. Gessner, *Angew. Chem., Int. Ed.*, 2021, **60**, 21014–21024.

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20 The percent buried volumes of **L15** and **L18** were calculated using SambVca (Salerno molecular buried volume calculation) 2.1 software.

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23 We have examined some of the heteroaryl chloride/triflates such as 5-chloropyridin-2-yl triflate, 6-chloropyridin-2-yl

triflate, 5-chloropyridin-3-yl triflate. However, the reaction of heteroaryl substrates was not successful, which suffered from the severe decomposition of the starting material, and/or formation of a very low yield of product with the triflate group hydrolyzed to a hydroxyl group. Further study is needed to address this issue.

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