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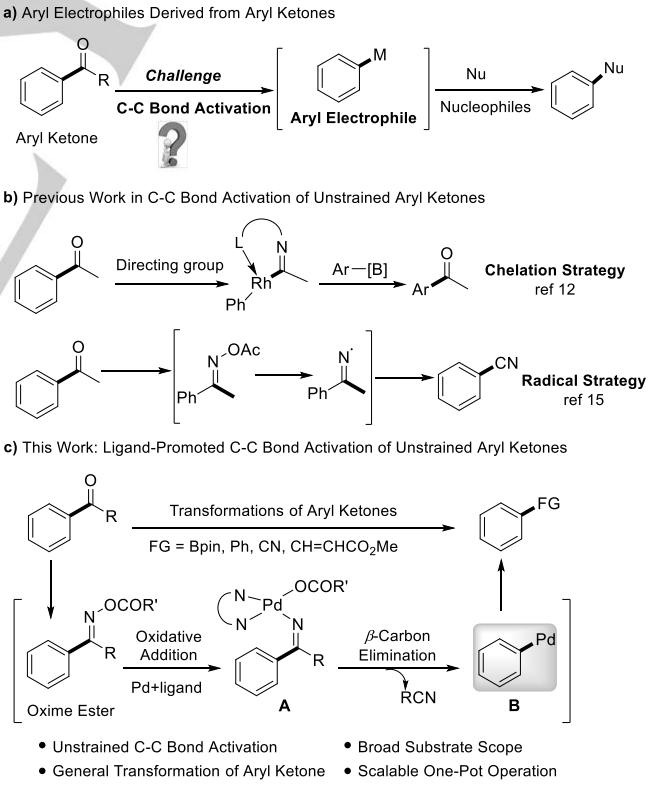
Transformations of Aryl Ketones via Ligand Promoted C–C Bond Activation

Hanyuan Li,[a],† Biao Ma,[a],† Qi-Sheng Liu,[a] Mei-Ling Wang,[b] Zhen-Yu Wang,[c] Hui Xu,[a] Ling-Jun Li,[a] Xing Wang,[a] Hui-Xiong Dai*[a]

Abstract: Coupling of aromatic electrophiles (aryl halides, aryl ethers, aryl acids, aryl nitriles etc.) with nucleophiles is core methodology for the synthesis of aryl compounds. Transformations of aryl ketones in analogous manner via carbon-carbon bond activation could greatly expand the tool-box of the synthesis of aryl compounds due to the abundance of aryl ketones. Exploratory study of this approach is typically based on carbon-carbon cleavage triggered by ring-strain release and chelation assistance, and the products are also limited to a specific structural motif. Here we report a ligand promoted *β*-carbon elimination strategy to activate the carbon-carbon bond, which allows for the establishment of a range of transformations of aryl ketones, leading to useful aryl borates, and also to biaryls, aryl nitriles, aryl alkenes. The use of a pyridine-oxazoline ligand is crucial for this catalytic transformation. A gram scale borylation reaction from aryl ketone via a simple one-pot operation was occurred successfully. The potential utility of this strategy was also demonstrated by the late-stage diversification of drug molecules Probenecid, Adapalene and Desoxyestrone, spice Tonalid as well as natural product Apocyin.

In recent years, transition-metal catalyzed cross-coupling reactions of electrophiles with nucleophiles are extremely powerful tools for generating carbon-carbon bonds and carbon-heteroatom bonds,[1] which have been widely employed in the synthesis of natural products and biologically active molecules, as well as in the industrial synthesis of pharmaceuticals, advanced materials and fine chemicals.[2] Besides the development of new catalysts for various coupling reactions, another important task is to extend the electrophile scopes, which would greatly increase the structural diversity of molecule library. Although, aryl halides (iodides, bromides and chlorides),[1,3] a series of oxygen-containing,[4] nitrogen-containing,[5] acid-containing,[6] and cyano-containing[7] aromatic compounds have been well established or extensively studied as electrophiles in the synthesis of aryl compounds; aryl ketones, a moiety widely found in pharmaceuticals and natural products,[8] however, are far less studied. This could be ascribed to the lack of effective methods to generate aryl electrophiles from aryl ketones. Currently, transition metal-catalyzed carbon-carbon bond activation is emerging as an innovative strategy for enabling novel transformations of organic molecules.[9] The formation of aromatic metal specie as an electrophile from an aryl ketone through transition metal-catalyzed C–C bond activation will open up a novel avenue for the transformation from aryl ketones to other functionalized aryl compounds (Scheme 1a). However, to break the C–C bond is very difficult due to the intrinsic inertness,[9b] which extremely restricts its application. So far, successful examples[9f] are limited to small rings[10] (three- and four-membered rings) or those substrates with directing groups[11] by utilizing the ring-strain release as a thermodynamic driving force or a directing group to enhance the activity. Recently, the Dong's group made a great breakthrough in the field of transformation of unstrained aryl ketone and realized a cross-coupling reaction between common ketones and arylboronic acid derivatives (Scheme 1b).[12] Due to the presence of directing group, acetyl was retained and a new aryl ketone was afforded via Ar-Ar exchange with boronic acids. Eventually, a general strategy to employ aryl ketones as aryl electrophiles in metal-catalyzed couplings remains largely undeveloped.



Scheme 1. Transformation strategies of aryl ketones. FG = functional group.

Oxime esters are a class of versatile building blocks that can be simply prepared from ketones and have been widely applied in transition metal-catalyzed organic synthesis.[13] Due to the

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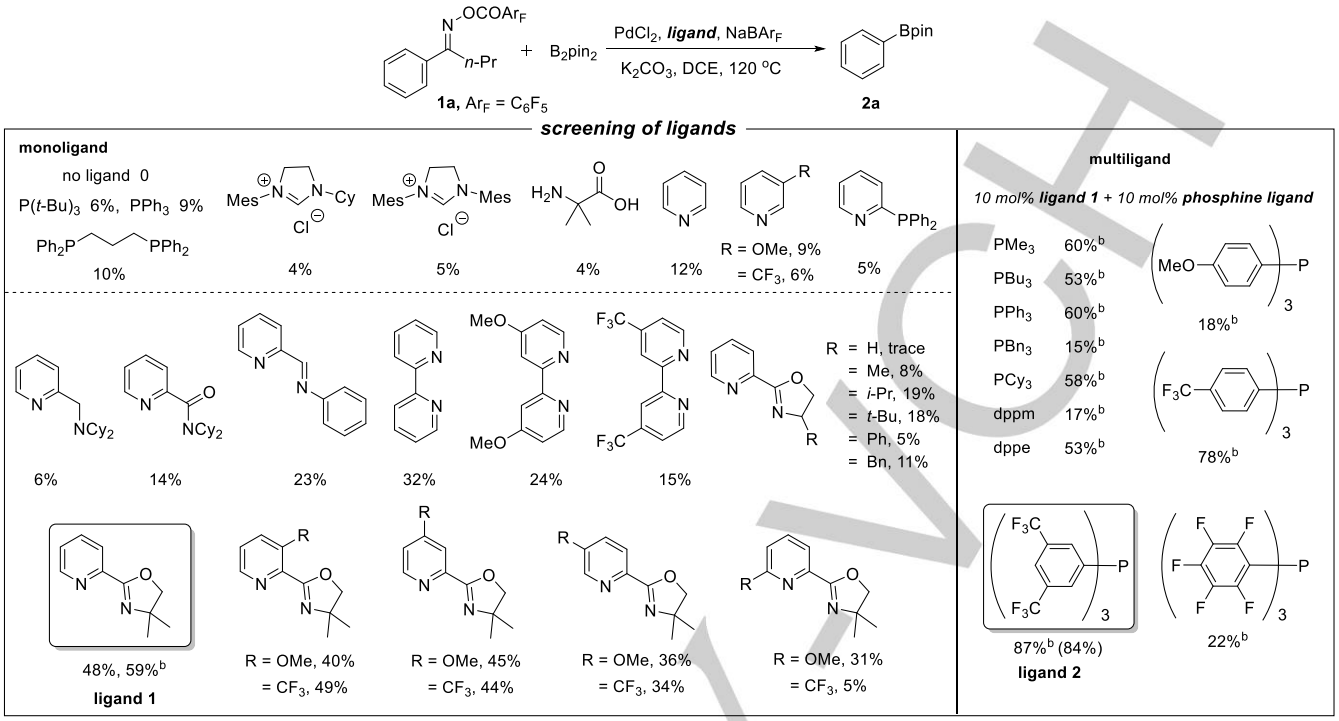
Table 1. Screening of ligands.[a]

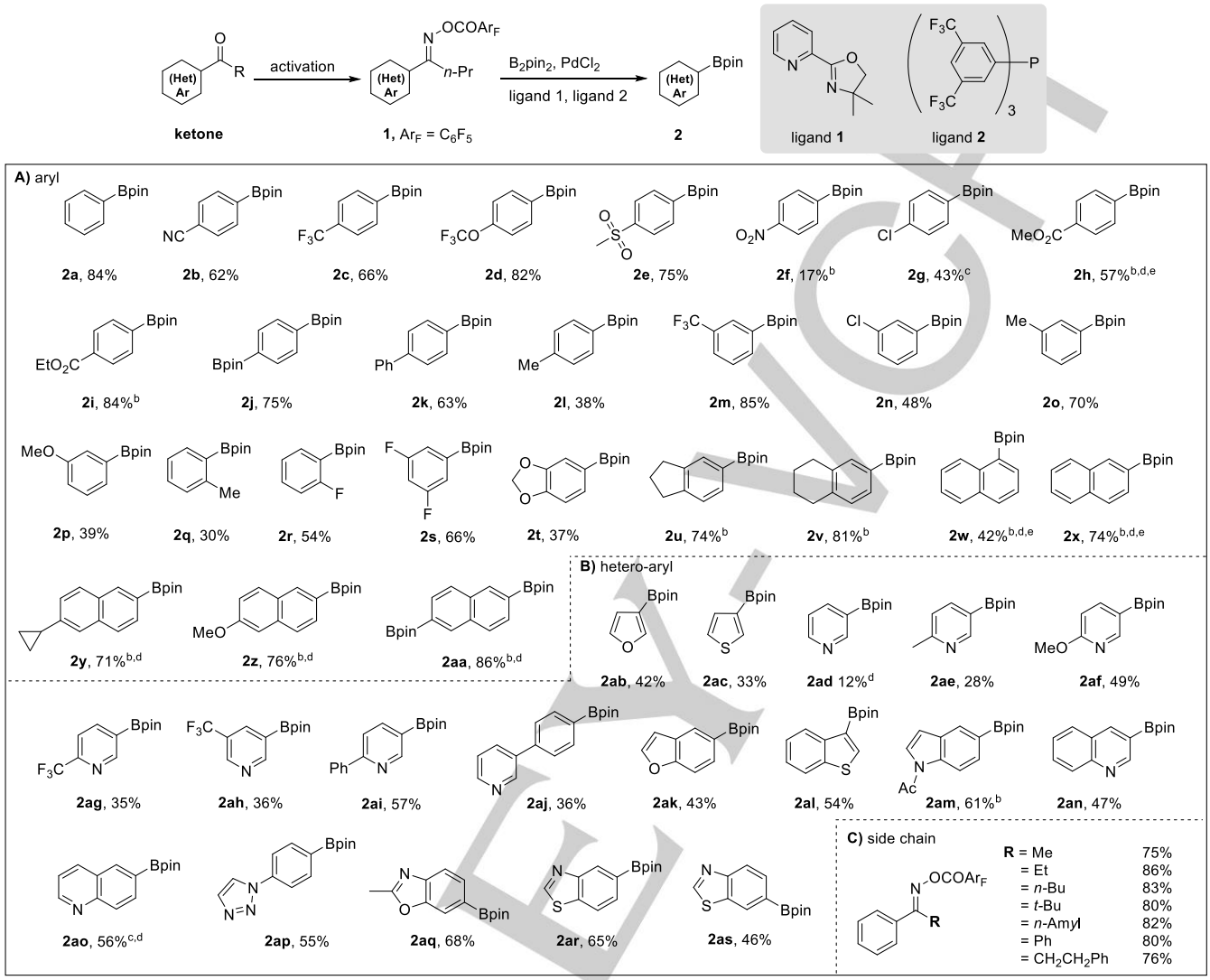


[a] Conditions: **1a** (0.1 mmol), B_2pin_2 (0.2 mmol), $PdCl_2$ (10 mol%), ligand (20 mol%), $NaBAr_F$ (20 mol%), K_2CO_3 (0.2 mmol), DCE (2.0 mL), N_2, 120 °C, 12 h. GC yields using dodecane as internal standard. [b] Performed with 2.0 equiv BHT. [c] Isolated yield in the parentheses.

weak N–O σ bond with an average energy of ~57 kcal mol^{-1}, oxime esters easily form a highly active imino radical catalyzed by metal or give imino-metal complexes through oxidative addition of a low-valent metal.[13,14] In 2018, an example of transformation of aryl ketones to aryl nitriles utilizing oxime ester substrates was reported by the Jiang's group,[15] in which alkyl group was removed through the C-C bond cleavage of radical pathway (Scheme 1b). In 2000, the Uemura's group presented a Pd(0)-catalytic transformation of cyclobutanone O-acyloximes to nitriles via *β*-carbon elimination from an alkyl palladium intermediate resulting from oxidative addition of the N–O bond of oxime to the Pd(0).[16] Notably, the ring-strain release acts as the driving force for *β*-carbon elimination. In contrast, unstrained substrates, such as aryl ketones, still remain a tremendous challenge. In view of the fact that developing a general approach to realize the cross coupling with unstrained aryl ketones as electrophiles could greatly expand the tool-box of the synthesis of aryl compounds. Here we report our effort and the development of a general method on the unstrained aryl ketones as electrophiles to realize the synthesis of aromatic compounds through C–C activation. In this catalytic cycle, the key arylpalladium(II) intermediate is formed through the ligand **1** promoted *β*-carbon elimination, which can be further converted to other aryl reagents, such as aryl borates, biaryls, aryl nitriles and aryl alkenes (Scheme 1c).

Aryl borates are important organic building blocks and are extensively applied in the construction of natural products, pharmaceuticals, and organic materials.[17] Therefore, we commenced our studies by investigating the borylation of aryl oxime esters derived from aryl ketones with B_2pin_2. First, a solution of **1a** and B_2pin_2 in DCE was heated in 120 °C in the presence of 10 mol% of $Pd_2(dba)_3$ and 2 equiv of K_2CO_3. The desired aryl borate product was not observed. To our surprise, aryl borate **2a** was found when the ligand bipyridine (bpy) was used albeit the low yield (3%). Using bpy as ligand, different catalysts and additives were screened, and a moderate yield (32%) was obtained when the 10 mol% of $PdCl_2$ and 20 mol% of $NaBAr_F$ (Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate)[18] were used. Given that the ligand played a crucial role in this reaction, we then sought to identify a more efficient ligand (Table 1). A series of ligands were found to be effective to this transformation including phosphines, carbenes, nitrogen-based and the amino acids ligands. However, bpy was still the optimal one. We turned to screen other bidentate ligands that have a similar molecular skeleton to bpy. A range of substituted bpys, pyridine-imines and pyridine-oxazolines were investigated, and the yield was increased to 48% when pyridine-oxazoline ligand **1** was used. During the mechanistic investigation (Scheme 2a), we found that the addition of radical inhibitor BHT (butylated hydroxytoluene) not only did not inhibit the reaction, but also increased the yield to 59%. Considering that this reaction involves two key processes: the formation of an aryl palladium intermediate and the borylation, we envisioned that a second ligand might promote the borylation step.[19] Based on this idea, we further screened the combination of ligand **1** and phosphine ligands which are beneficial to the borylation step.[20] Gratefully, when the phosphine ligands with an electron-withdrawing group were used, the yields increased dramatically. The best result was obtained using the combination of 10 mol% of ligand **1** and 10 mol% of ligand **2** and the desired product was obtained in

Table 2. Substrates scope.[a,f]

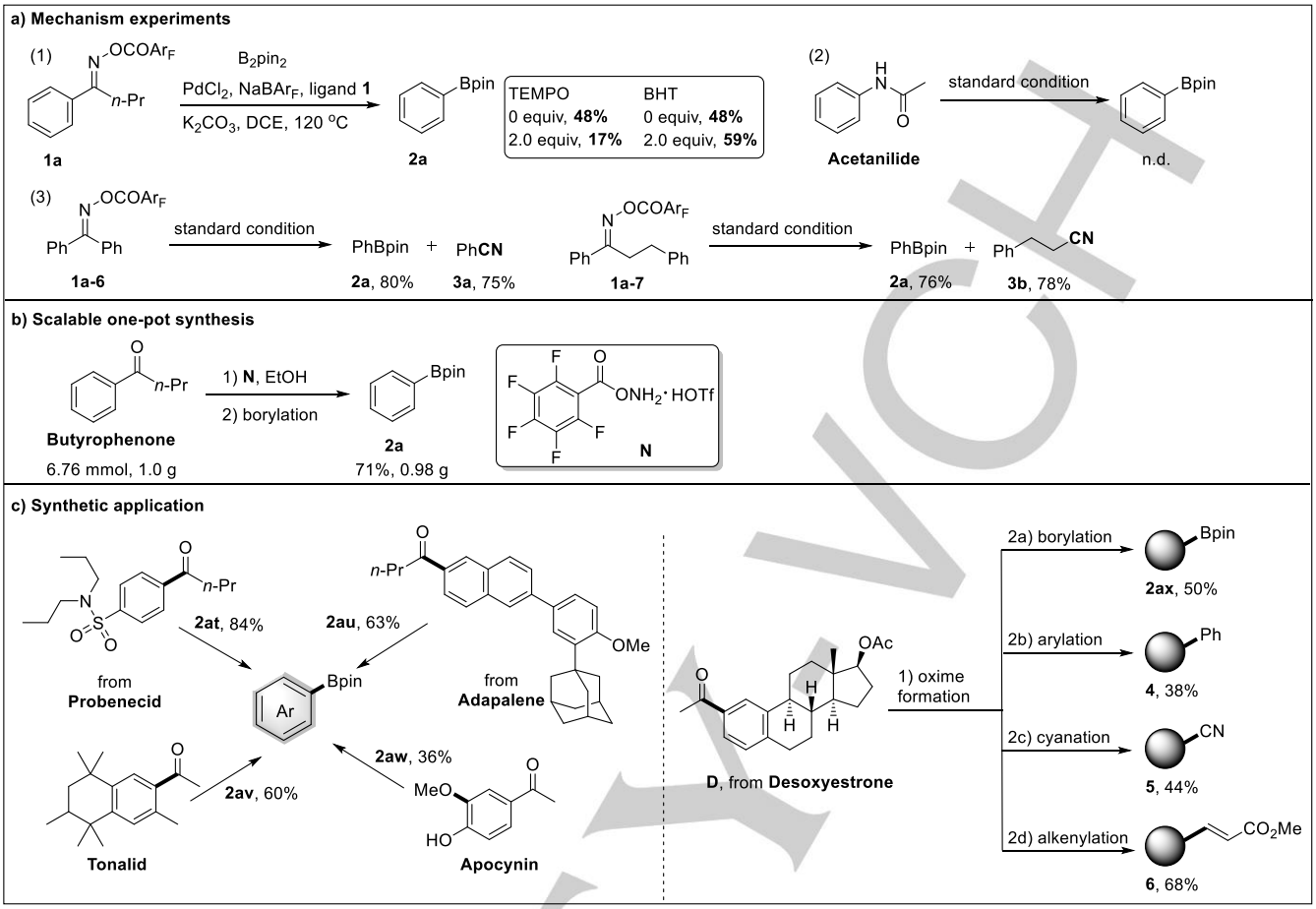


[a] Conditions: **1** (0.1 mmol), B_2pin_2 (0.2 mmol), $PdCl_2$ (10 mol%), ligand 1 (10 mol%), ligand 2 (10 mol%), $NaBAr_F$ (20 mol%), BHT (0.2 mmol), K_2CO_3 (0.2 mmol), DCE (2.0 mL), N_2, 120 °C, 12 h. [b] Me instead of *n*-Pr. [c] Performed using 15 mol% $PdCl_2$. [d] Performed solely with 20 mol% ligand 1. [e] Performed without BHT. [f] Isolated yields.

84% isolated yield.

To examine the generality of this transformation, a range of aryl substrates were subjected to the standard conditions (Table 2). We found that a variety of substituents on the aryl ring were well tolerated. Notably, the substrates bearing an electron withdrawing group such as CN, CF_3, CH_3SO_2, NO_2 and CO_2Me on the arene underwent the borylation reaction efficiently and the corresponding products were obtained in moderated to excellent yields. In addition, aryl substrates with disubstituted, bicycle and substituted naphthalenes could also be converted to the corresponding aryl borate in good to excellent yields (**2s**-**2aa**). Next, we examined the heteroaryl substrates and found that the reaction of furan, thiophene, pyridine and substituted pyridines proceeded smoothly to afford the desired products in moderated yields (**2ab**-**2aj**). Benzofuran, benzothiophene, indole, quinolines, triazole, benzoxazole and benzothiazoles substrates were also converted to the corresponding functionalized products **2ak**-**2as** in high yields. Furthermore, we investigated the compatibility of substituents on the other side of the aryl and found that both alkyl groups including methyl, ethyl, *n*-propyl, *n*-butyl, *t*-butyl, *n*-Amyl, CH_2CH_2Ph, and aryl group Ph were well tolerated.

In order to determinate whether the reaction proceeds via a radical intermediate or via an imino-palladium species formed by oxidative addition of Pd(0), radical quenchers 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO) and BHT were added into the reaction system. The addition of TEMPO led to a lower yield, which may be because TEMPO as oxidant competed with substrate oximes.[21] However, the addition of BHT led to a higher yield (Scheme 2a). These results imply that a radical should not be involved in the reaction. Under the standard conditions, the substrates **1a-6** and **1a-7** were smoothly converted to the corresponding aryl borates and the same amount of nitrile compounds (Scheme 2a). The potential path involving initial 1,2



Scheme 2. Mechanism experiments and further explorations. 2a) standard condition of borylation; 2b) $PhBF_3K$, $PdCl_2$, ligand, Ag_2CO_3, K_2CO_3, DCE, 110 °C, N_2; 2c) $Zn(CN)_2$, $PdCl_2$, ligand, $AgNTf_2$, K_2CO_3, DCE, 120 °C, N_2; 2d) methyl acrylate, $Pd(MeCN)_4(OTf)_2$, ligand, Ag_2CO_3, Na_2CO_3 DCE, 130 °C, N_2. See SI for detailed experiments.

compounds (Scheme 2a). The potential path involving initial 1,2 shift of the aryl group was also ruled out because the putative intermediate in this pathway, acetanilide, was ineffective under the standard conditions (Scheme 2a). Based on these results, a possible mechanism was proposed (Scheme 1c). First, oxidative addition of the N–O bond of the oxime ester to Pd(0) occurs to give an aryliminopalladium(II) intermediate **A**.[22] Subsequent *β*-carbon elimination promoted by ligand **1** affords arylpalladium species **B**. Finally, with the aid of ligand **2**, **B** was borylated to give the aryl boronic ester, and Pd(0) was regenerated. Furthermore, a gram-scale borylation reaction from aryl ketone via a one-pot operation could be performed to give the desired product in a satisfactory yield of 71% (Scheme 2b). To highlight the synthetic utility of this transformation, we applied this method to the late-stage diversification of complex molecules (Scheme 2c). Aryl ketones derived from drugs Probenecid **2at**, Adapalene **2au**, spice Tonalid **2av**, natural product Apocynin **2aw** were also suitable. Desoxyestrone[23] **D-1** can be easily acetylated to give intermediate **D** in 77% yield through Friedel–Crafts acetylation reaction. Compound **D** was then transformed into oxime ester **1ax** in 81% yield (see supporting information). Then the oxime **1ax** was subjected to standard conditions, and the borylated product **2ax** was formed in 50% yield. To further demonstrate the generality of this strategy, other transformations were also investigate. Through extensive screening and optimization, the oxime ester **1ax** can also be converted to biaryl **4**, aryl nitrile **5** and aryl alkene **6**.

In summary, we have developed an unstrained C–C bond activation strategy that allows aryl ketones to serve as aryl pseudohalides in cross-couplings. In this context, the formation of an aryl palladium species through *β*-carbon elimination promoted by pyridine-oxazoline ligand **1** is the key to success of this transformation. In addition, the key aryl palladium intermediate could be converted to a series of functionalized arenes, such as aryl borates, biaryls, aryl nitriles and aryl alkenes, indicating the generality and practicality of this strategy. The potential utility of these reactions were further demonstrated by the late-stage diversification of drug molecules Probenecid, Adapalene and Desoxyestrone, spice Tonalid as well as natural product Apocyin. Further efforts to understand the detailed mechanism of this transformation are ongoing. We also anticipate to apply this protocol to exploit other transformation of unstrained aryl, alkenyl and alkyl ketones.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: C–C bond activation • aryl ketone • borylation • Pd-catalyzed

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C–C bond Activation

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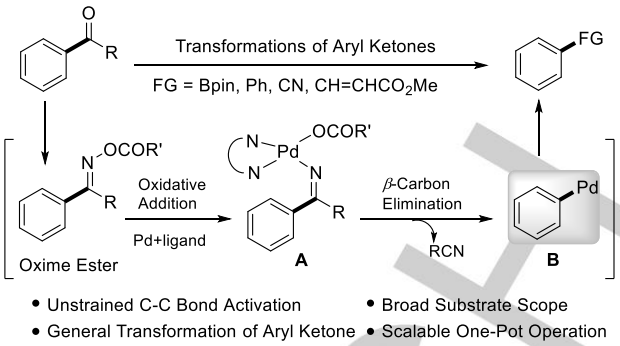

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