Palladium-Catalyzed Mono-α-Alkenylation of Ketones with Alkenyl Tosylates

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The transition metal-catalyzed a-arylations of ketones are powerful tools used by organic chemists for the construction of sp^3-sp^2 carbon-carbon bonds as well as biologically active ketone compounds.[1] In fact, *β,γ*-unsaturated ketone compounds also constitute important structural motifs in numerous bioactive and medicinally valuable compounds.[2] The research of transition metal-catalysed methods leading to these valuable compounds are of high interest and notably,[3] elegant nickel and palladium catalysts for the alkenylations of ketones with alkenyl halides were very recently disclosed by Helquist's group.[4] However, the utilization of other alkenyl electrophiles in this chemistry was lesser explored and further development was still desirable.[5]

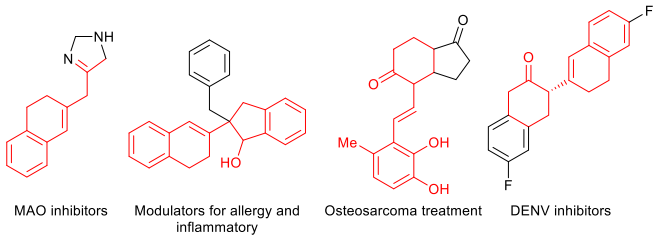
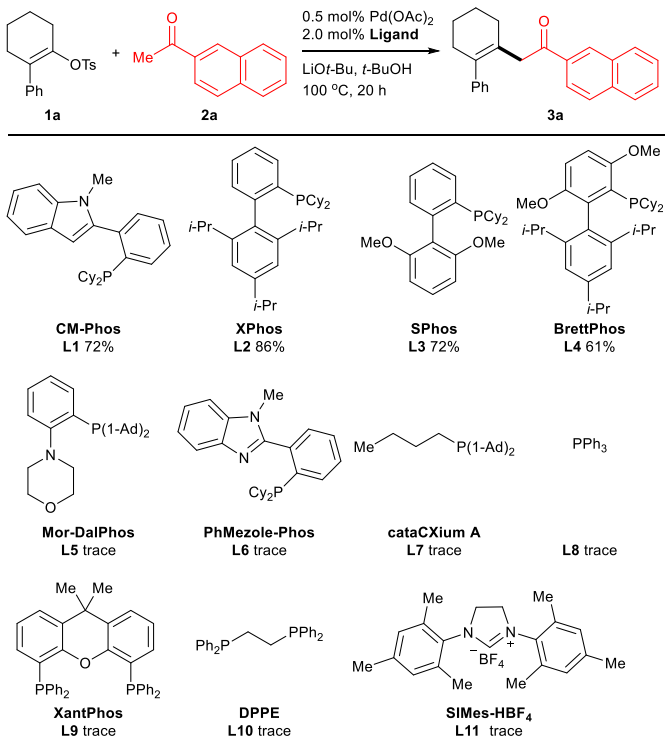


Figure 1 β,γ-Unsaturated carbonyl compounds and their potential medicinal applications.

Indeed, alkenyl sulfonates such as tosylates are desirable complements to alkenyl halides. Alkenyl tosylates can be prepared from a variety of commercially available carbonyl compounds which led to a number of substitution patterns not accessible with its halide counterparts,[6] while they are also more cost-effective when compared with alkenyl triflates in view of the sulfonating agents.[7] In terms of chemical stability, alkenyl triflates are subjected to hydrolytic decomposition upon prolonged storage.[8] For synthetic applications, alkenyl tosylates have a higher crystallinity to allow for simpler isolation and purifications.[9] However, the inherent stability of these non-activated alkenyl tosylates might lead to demanding oxidative additions with Pd(0) species. Moreover, the reaction was prone to several difficulties: First, subsequent alkenylations would occur due to the acidic α-protons of methyl ketones. Second, *β,γ*-unsaturated products might rearrange into *a,β*-conformation. Third, the demanding reductive elimination of the alkenyl-Pd-ketone enolate species need to be tackled by an effective ancillary ligand. With our previous experience in ketone functionalizations and cross-coupling with alkenyl tosylates,[10] we were intrigued to develop an efficient and general palladium catalyst to circumvent these problems. Herein, we report the general cross-coupling of ketone enolates with alkenyl tosylates, featuring ample substrate tolerance and low catalyst loadings (0.1-1.0 mol %). Our method allowed for the syntheses of mono-α-alkenyl ketones and acetones in good yields and with scalability.

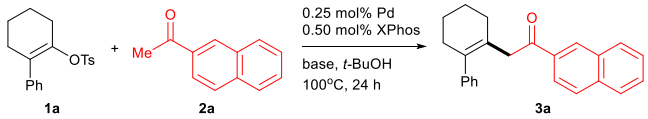
In the course of initial reaction development, a model reaction between an unprivileged sterically hindered alkenyl tosylate **1** and 2-acetonaphthone was sought to explore various reaction parameters such as ancillary ligands, solvent, bases and palladium sources (Scheme 1). At the outset of our investigation, the detosylation of alkenyl tosylates was observed and subsequently 1.5-fold of tosylates were used with relation to the ketones. We first evaluated the efficacy of a range of sterically and electronically diverse ligands. Among Buchwald's state-of-the-art biaryl phosphine ligands[9] (**L2-L4**), XPhos was found to efficiently promote the reaction and afforded the product in 86% yield. Our customized ligand CM-Phos[11] (**L1**) promoted the cross-coupling and led to a 72% product yield while PhMezole-Phos[12] (**L6**) only provided trace amount of product. *P*,*N*-type phosphine ligands showed inferior reactivity in this catalysis (**L5-L6**). An array of mono- and bidentate ancillary ligands were further surveyed (**L7-L11)**, including diadamantylalkyl phosphine cataCXium A, XantPhos and an *N*-heterocyclic carbene. However, trace amount of product was obtained for these entries. As suggested by these results, bidentate *P*,*P*- or *P*,*N*-ligands were ineffective in this reaction whereas monodentate phosphine ligands were superior in comparison. Although the upper ring of BrettPhos was more electron-rich than its analogue XPhos, it provided a lower product yield. This could presumably be due to that highly electron-rich phosphine ligands are not effective in the cross-couplings of ketone enolates, as previously reported in literature.[13] Control experiment with the absence of ligands showed no conversion of starting materials.



Scheme 1 Ancillary ligand screening. Reaction conditions: **1a** (0.3 mmol), LiO*t*-Bu (0.375 mmol), 2-acetonaphthone (0.25 mmol), *t*-BuOH (0.5 mL), $Pd(OAc)_2$ (0.5 mol%), **ligand** (2.0 mol %) at 100 °C for 20 h under N_2; calibrated GC yields were reported.

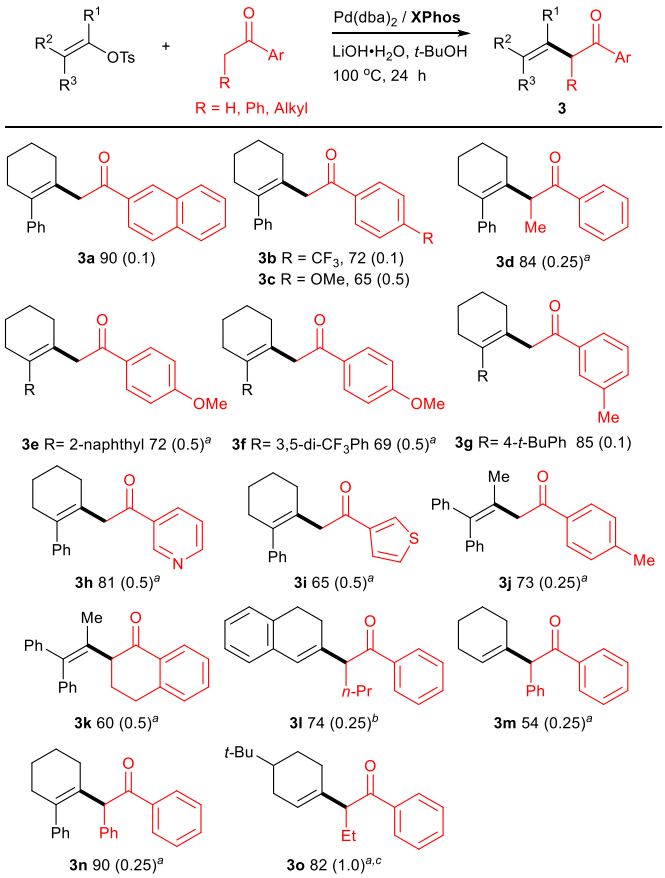
With a promising ligand in hand, we next studied a number of parameters for the optimal reaction conditions (Table 1). We found that strong bases containing lithium cation (Table 1, entries 1, 4-6) were leading bases in this reaction and provided 85-91% of product yields while their Na^+ and K^+ counterparts were ineffective (Table 1, entries 1 *vs.* 2-3). The use of weak bases such as Li_2CO_3 and K_3PO_4 led to inferior performances (Table 1, entries 7-8). Other reaction conditions were also investigated (see the Supporting Information, Table S1-S3), *t*-BuOH proved to be the available solvent for this system. Meanwhile, $Pd(dba)_2$ gave the best results among the Pd precursors and the best metal-to-ligand ratio was found to be 1:2 (Table S3).

Table 1 Reaction optimisation[a]



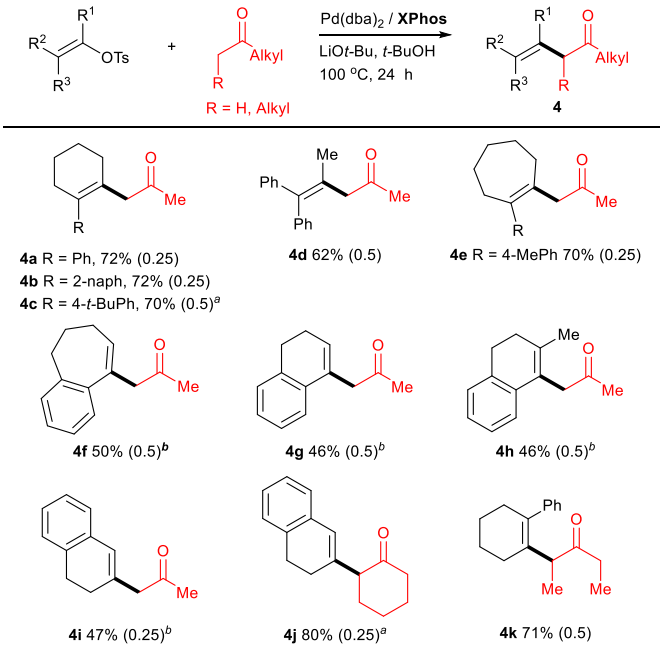
Entry	Pd source	Base	Yield (%)
1	$Pd(OAc)_2$	LiO*t*-Bu	91
2	$Pd(OAc)_2$	NaO*t*-Bu	40
3	$Pd(OAc)_2$	KO*t*-Bu	34
4	$Pd(OAc)_2$	$LiOH{\cdot}H_2O$	91
5	$Pd(OAc)_2$	LiOH	88
6	$Pd(OAc)_2$	LiHMDS	85
7	$Pd(OAc)_2$	K_3PO_4	38
8	$Pd(OAc)_2$	Li_2CO_3	n.d.
9	$Pd(dba)_2$	$LiOH{\cdot}H_2O$	94
10	$Pd(dba)_2$	$LiOH{\cdot}H_2O$	90[b]

[a] Reaction conditions: 1a (0.37 mmol), 2-acetonaphthone (0.25 mmol), base (0.37 mmol), *t*-BuOH (0.5 mL), Pd source (0.25 mol%), Pd:XPhos = 1:2 at 100 °C for 24 h under N_2; Calibrated GC yields were reported using dodecane as the internal standard. [b] $Pd(dba)_2$ (0.10 mol%).



Scheme 2 Catalytic mono-α-alkenylation of ketones. Reaction conditions: Alkenyl tosylates (0.75 mmol), $LiOH{\cdot}H_2O$ (0.75 mmol), ketone (0.5 mmol), *t*-BuOH (1.0 mL), $Pd(dba)_2$/**XPhos** = 1:2 at 100 °C for 24 h under N_2; isolated yields were reported. Catalyst loading was reported in parentheses as mol% of Pd with respect to ketone. Reaction times were not optimized for each substrate. [a] LiO*t*-Bu was used as base, [b] LiO*t*-Bu was used as base, 60 °C was used. [c] 80 °C was used.

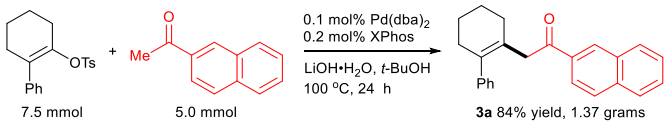
Having confirmed the optimal reaction condition, we next probed the substrate scope using the newly developed $Pd(dba)_2$/XPhos system. We examined a wide spectrum of fundamentally different substrates in terms of conjugation, electron-richness and steric profile (Scheme 2). Highly sterically hindered alkenyl tosylates, in which at most embedded a naphthyl group at the position, were able to couple with ketone enolates smoothly and gave good-to-excellent product yields (Scheme 2, **3a-3g**). Notably, heteroaryl methylketones, which were difficult substrates in ketone α-arylations, transformed to the corresponding products in moderate-to-good yields (Scheme 2, **3h-3i**).[14] Alkenyl tosylates derived from methyl ketones and α-tetralone were found to be applicable substrates in our system (Scheme 2, **3j-3l**). Cyclohexanone-derived substrates underwent the cross-coupling with ketone enolates efficiently (Scheme 2, **3m**). Additionally, 2-substituted acetophenone derivatives, which were congested at the sp^3-carbon, were also converted to desired products (Scheme 2, **3l-o**). Non-activated alkenyl tosylate[15] also reacted successfully in our system (Scheme 2, **3o**).



Scheme 3 Synthesis of small β,γ-unsaturated ketones by alkenylation of acetone and alkyl ketones. Reaction conditions: Alkenyl tosylates (0.25 mmol), base (0.375 mmol), ketone (2.5 mmol), *t*-BuOH (0.5 mL), $Pd(dba)_2$/**XPhos** = 1:2 at 100 °C for 24 h under N_2, isolated yields were reported. Catalyst loading was reported in parentheses as mol% of Pd with respect to ketone. Reaction times were not optimized for each substrate. [a] 60 °C was used. [b] Acetone (1 mL) was used as solvent, 60 °C was used.

Encouraged by the results and inspired by our previous works in acetone monoarylations,[10a, b] we were also intrigued to utilize acetone as a three-carbon feedstock for the syntheses of simple *β,γ*-unsaturated methylketone compounds (Scheme 3). Excessive alkyl ketones were used to dilute the viscous reaction mixture and counteract the facile aldol condensations. In general, 0.5 mol% of Pd catalyst allowed the cross-coupling of acetone enolates with a variety of alkenyl tosylates. Highly sterically congested enol tosylates (Scheme 3, **4a-4e**) were converted to the corresponding products in good yield, while entries **4f-4i** were afforded in moderate yields due to the presumable unstability of the products (Scheme 3, **4f-4i**). Cyclohexanone and 3-pentanone were successfully employed in the transformation and gave good yields (Scheme 3, **4j-4k**). It is worth to note that no by-products were obtained generally except that trace amount of diarylated ketone products were observed when **4f**, **4g** and **4i** were prepared.

In order to illustrate the synthetic utility of our system, we attempted to conduct our reaction in gram scale and successfully prepared 1.37 grams of **3a** (Scheme 4, 84% isolated yield) under standard reaction conditions.



Scheme 4 A Gram-scale reaction.

Conclusions

In summary, we have described the palladium-catalyzed selective mono-α-alkenylation of ketones using alkenyl tosylates. The combination of $Pd(dba)_2$ and XPhos as the catalytic system exhibited excellent chemo- and monoselectivity at a relatively low catalyst loading (0.1− 1.0 mol%). A series of tri- or tetra- substituted alkenyl tosylates were successfully reacted while extremely sterically hindered naphthyl substituted substrates were also tolerated. Problematic heteroaryl and aliphatic ketones were shown to be applicable substrates in our method. Application of the proposed catalyst for the syntheses of pharmaceutical motifs is now underway in our laboratory.

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