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# Palladium-catalyzed arylation of vinylic acetates. Phosphine ligand influenced regioselectivity

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ABSTRACT

A palladium-catalyzed coupling reaction of aryl bromides with vinylic acetates in the presence of tributyltin methoxide has been described. The α-arylation aldehyde product and the aryl ketone were obtained in the presence of P(*t*-Bu)$_3$ and P(*o*-Tol)$_3$, respectively.



During the last decade, the palladium-catalyzed α-arylation of carbonyl derivatives has become a versatile tool for advanced organic synthesis. The importance of this C–C bond construction method is evident from the huge number of publications that appeared recently.[1] Due to reactivity issues and despite considerable progress made in this field, the α-arylation of aldehydes remains less explored.

In 2002, Miura and co-workers disclosed the first Pd-catalyzed α-arylation of aldehydes with aryl bromides.[2] The reaction was carried out using palladium diacetate as catalyst with the bulky P(*t*-Bu)$_3$ as phosphine ligand and cesium carbonate as base. Although the dioxane was used as a solvent to limit the formation of aldol by-products, the yields were generally modest. Based on these pioneering findings, the groups of Buchwald[3] and later Hartwig[4] developed an efficient and general protocol for the α-arylation of aldehydes with aryl bromides and chlorides in dioxane in the presence of cesium carbonate using Pd(OAc)$_2$/racemic BINAP or [{Pd(allyl)Cl}$_2$]/dppf or Q-phos as catalytic system. Despite better yields and increasing the scope of aldehydes, these protocols suffer from some limitations (the coupling between aldehydes and electron-rich aryl bromides and aryl chlorides still remains difficult). In 2008, Buchwald and co-workers proposed an improved protocol for this palladium-catalyzed reaction.[5] Using Pd(OAc)$_2$/xantphos or SPhos in wet dioxane (24 ppm $H_2O$) in the presence of $Cs_2CO_3$, good to excellent yields were obtained for various aldehydes with electron-rich aryl bromides. More recently, according to these previous studies they described an asymmetric intramolecular version of this reaction with phosphanyloxazoline-based ligands.[6] The high yields and enantioselectivities reach this protocol attractive for applications in total synthesis. In the same time, Xiao and co-workers reported a palladium-catalyzed direct acylation of aryl bromides with aldehydes.[7] While in the presence of palladium and ligand the reaction of aryl halides and aldehydes lead to the α-arylation as shown by Buchwald and Hartwig, the addition of pyrrolidine and 4 Å MS in the reaction mixture gives the aryl ketone via the formation in situ of an enamine followed by a Heck-type reaction.

In 2007, relying on palladium-catalyzed α-phenylation of ketones via tin enolates described by Migita and co-workers,[8] we investigated the α-arylation of aldehydes. Surprisingly, no expected product was observed but only acylation of the aromatic group was achieved affording unexpected aryl ketones.[9] We found that 5 mol % of PdCl$_2$[P(*o*-Tol)$_3$]$_2$ in DMSO at 100 °C in the presence of 2 equiv of vinylic acetate and 2 equiv of $Bu_3SnOMe$ are the best reaction conditions to obtain a complete conversion of aryl bromides (Scheme 1).

In this study, various phosphine ligands were tested and we noticed the formation of the product of α-arylation of aldehydes using the tri-*tert*-butylphosphine. Intrigued by this observation,

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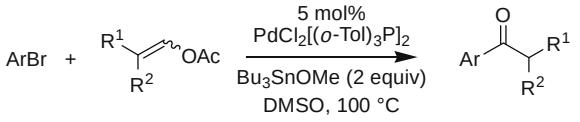



**Scheme 1.** Pd-catalyzed acylation of arylbromides.

we set out to examine the influence of the phosphine on the regioselectivity of this palladium-catalyzed reaction. We compared the coupling reaction of 2-methyl-1-propen-1-yl acetate **2** with various aryl bromides **1** using either tri-*tert*-butylphosphine (method A) or tri(*o*-tolyl)phosphine (method B). The results are shown in Table 1.

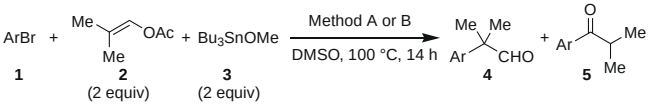
As can be seen the reaction afforded low to good yields of coupling products. The formation of the aldehyde **4** or the aryl ketone **5** appears to be both dependent on the aryl bromide and the phosphine. As previously reported,[9] in the presence of tri(*o*-tolyl)phosphine (Method B), the aryl ketone **5** was obtained as the major product (ratio **5**:**4** >90/10 except with 4-nitro-bromobenzene, entry 24). Using the tri-*tert*-butylphosphine (method A), a complete inversion of selectivity was observed in most cases (ratio **4**:**5** >80/20, entries 1, 3, 5, 9 and 13). For the 4-nitro-bromobenzene, the conversion and the yield are too low to conclude (entry 23). On the other hand it is noteworthy that the regioselectivity of the coupling reaction in the presence of the tri-*tert*-butylphosphine is very sensitive to the steric hindrance. A slight decrease of the selectivity of the formation of aldehyde **4** was observed with α-bromonaphthalene, *o*-methoxy-bromobenzene, and *o*-methyl-bromobenzene (entries 5, 9, and 17). In the case of more sterically hindered aromatic derivatives as 2-bromo-*N*,*N*-dimethylaniline and *o*,*o*′-dimethyl-bromobenzene the aryl ketones **5** were achieved in high selectivities (ratio **5**:**4** >97/3).

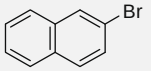
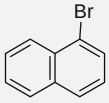
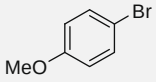
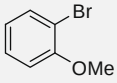
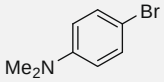
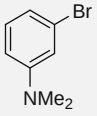
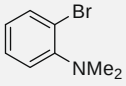
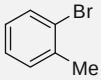
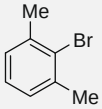
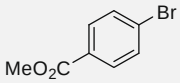
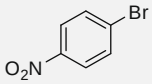
Aware of the influence of ligand on the outcome of the reaction, the tricyclohexylphosphine was also used instead of P(*t*-Bu)$_3$. Unfortunately, as Miura and coll. noticed in the α-arylation of aldehydes with aryl bromides,[2a] we did not observe any coupling reaction between the β-bromonaphthalene and **2**.

Based on our previous work,[9] two concurrent mechanisms can be considered. In the presence of tri(*o*-tolyl)phosphine (cycle B) the aryl ketone **5** was produced via the addition of the aryl group to a ketene whereas in the presence of tri-*tert*-butylphosphine (cycle A) the aldehyde **4** was obtained as the major product following the classical catalytic cycle of α-arylation of aldehydes (Scheme 2). Hartwig and Roy reported that reductive elimination of aryl halide is made easy by the addition of tri-*tert*-butylphosphine to a dimeric tri(*o*-tolyl)phosphine arylpalladium (II) halide complexe.[10] Consequently, the difference of reactivity in our reaction would be due to a faster reductive elimination with P(*t*-Bu)$_3$ than with P(*o*-Tol)$_3$ after the formation of the intermediate **A**. Moreover, the bulkiest phosphine[11] P(*o*-Tol)$_3$ helps the β-*H*-elimination to give the palladium-ketene intermediate **B**. This is also consistent with the preferential formation of the aryl ketone **5** when sterically hindered *ortho*-substituted aryl bromides are used.

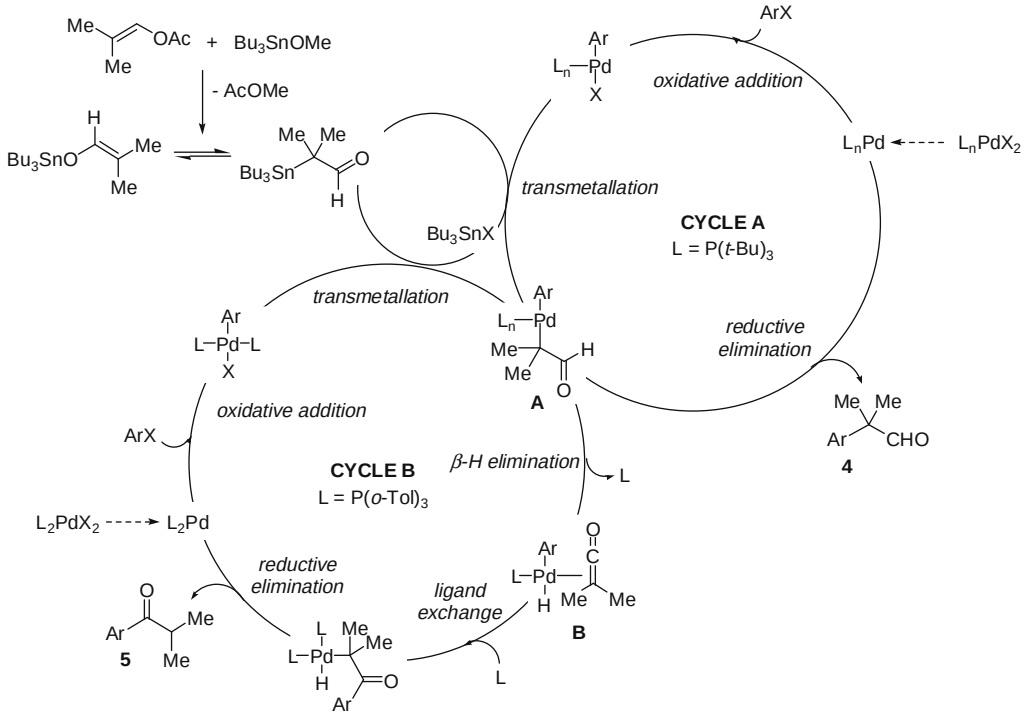
Having established that the tri-*tert*-butylphosphine leads to the α-arylation product, we turned our attention to the reactivity of aryl bromides in the presence of vinyl acetate and monosubstituted vinylic acetates. Reaction of β-bromonaphthalene with vinyl acetate under the method A reaction conditions (Scheme 3) afforded a complex mixture from which the α,β-unsaturated aldehyde **6** was isolated in 28% yield (in the presence of P(*o*-Tol)$_3$, method B,[9] the corresponding aryl ketone was isolated in 41% yield). The aldehyde **6** was probably formed through a palladium-catalyzed coupling reaction followed by enolization of the aldehyde-aldolization–crotonization cascade reactions. The use of 3-phenyl-1-propen-1-yl acetate instead of vinyl acetate also provided a

**Table 1**
Palladium-catalyzed arylation of 2-methyl-1-propen-1-yl acetate **2**

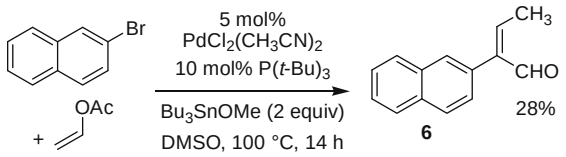



| Entry | Aryl bromide **1** | Method[a] | Ratio **4**/**5**[b] | Yield[c] (%) |
|---|---|---|---|---|
| 1 |  | A | 95/5 | 68 |
| 2 | | B | 5/95 | 57 |
| 3 |  | A | 97/3 | 75 |
| 4 | | B | 3/97 | 75[d] |
| 5 |  | A | 80/20 | 70 |
| 6 | | B | 3/97 | 76[d] |
| 7 |  | A | 70/30 | 36 |
| 8 | | B | 3/97 | 75 [d] |
| 9 |  | A | 92/8 | 60 |
| 10 | | B | 3/97 | 51 |
| 11 |  | A | 55/45 | 48 |
| 12 | | B | 3/97 | 42 |
| 13 |  | A | 97/3 | 78 |
| 14 | | B | 10/90 | 69 |
| 15 |  | A | 3/97 | 79 |
| 16 | | B | 3/97 | 75 |
| 17 |  | A | 65/35 | 64 |
| 18 | | B | 3/97 | 41 |
| 19 |  | A | 3/97 | 57 |
| 20 | | B | 3/97 | 43 |
| 21 |  | A | Inextricable mixture | |
| 22 | | B | 3/97 | 62 |
| 23 |  | A | 97/3 | 21 |
| 24 | | B | 45/55 | 39 |

[a] Method A: 5 mol % $PdCl_2(CH_3CN)_2$, 10 mol % P(*t*-Bu)$_3$. Method B: 5 mol % $PdCl_2[P(o\text{-}Tol)_3]_2$.
[b] Ratio determined by $^1$H NMR from the crude mixture.
[c] Isolated yield (average of two runs).
[d] See Ref. 9.




**Scheme 2.** Working catalytic cycle.




**Scheme 3.** Pd-catalyzed reaction with vinyl acetate.

complex mixture from which no aldehyde could be isolated (72% yield of aryl ketone with method B).[9]

Miura and co-workers[2a] reported that the formation of aldol products was overcome by the use of dioxane instead of the DMF. Relying on these observations, we decided to check our reaction in dioxane. Whatever the phosphine and palladium source used, no reaction occurred in these reaction conditions.

In summary, we have shown that a change of ligand can lead to a dramatic inversion of the regioselectivity in the palladium-catalyzed addition of aryl bromides to vinylic acetate. However, the reaction conditions described here in the presence of tri-*tert*-butylphosphine are not satisfactory. At this stage of work, the scope of the reaction remains limited to disubstituted vinylic acetates. Further investigations of the reaction conditions, as well as mechanistic studies are currently underway and will be reported in due course.

## Acknowledgments

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.048.

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11. Tolman's cone angle: P(*o*-Tol)$_3$ = 194°; P(*t*-Bu)$_3$ = 182°; P(Cy)$_3$ = 170°.