
# Palladium-Catalyzed Selective α-Arylation of ortho-Bromoacetophenones

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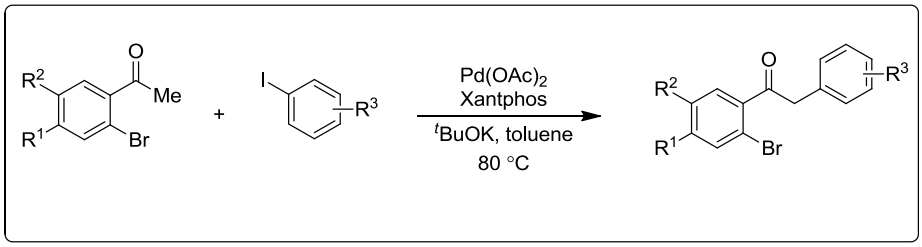
**GRAPHICAL ABSTRACT**




**Abstract:**

Synthesis of 1-(2-bromophenyl)-2-phenylethanones via an intermolecular Pd-catalyzed α-arylation of 1-(2-bromophenyl)ethanones, is presented. The method relies on a selective C–H activation (α-arylation) of relatively more reactive external iodo-arenes as coupling partners without affecting the bromo-substituent. Moreover, the scope and generality of the method has been well studied by employing the reaction on iodo-arenes bearing electron withdrawing, simple and electron donating groups on the aromatic ring.

**Keywords:** Pd-catalysis; α-arylation; 1-(2-bromophenyl)ethanones; iodo-arenes; C–H activation

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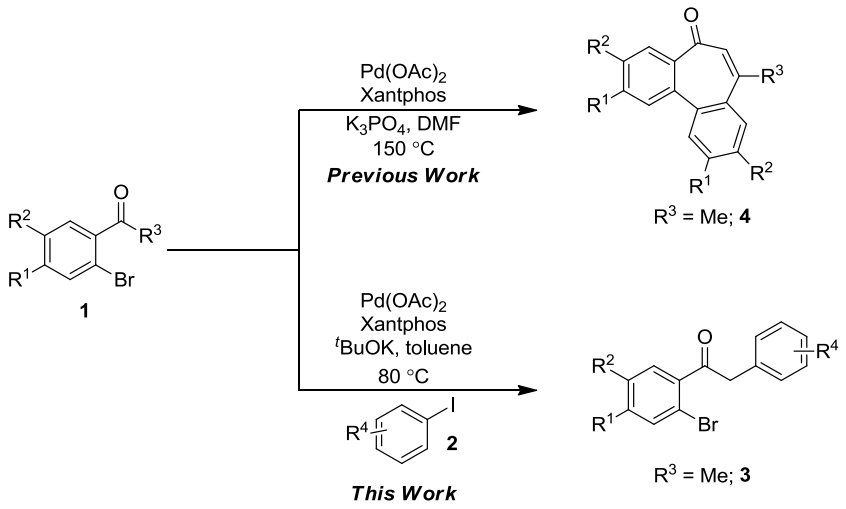
## INTRODUCTION:

Synthetic organic chemistry has always faced the challenge of developing sustainable methods. In this regard, efficient construction of C–C bonds has been achieved by transition-metal catalysis. Among them, palladium has gained recognization as one of the most used metals for a wide spectrum of reactions. Namely, Heck,[1] Stille,[2] Suzuki,[3] Sonogashira[4] and Buchwald-Hartwig[5] coupling transformations are some of the renowned reactions. Even very recently, reactions of C–H activation via organo-palladium intermediate species have been versatile in this field.[6,7]

The α-arylation is one of the C–H activation of $sp^3$ carbon present next to the carbonyl functionality, which involves C-C bond formation, by the reaction of aryl halide and the carbonylcompond having α-hydrogens. Classical arylation of ketones follow the nucleophilic aromatic substitution reaction of a stabilized enolate on the aryl halide. This method requires stoichiometric amount of arylating reagent and

is hard to deal and various synthetic methods have to be followed to make different alkylating reagents for the α-arylation of ketones. Due to these main concerns chemists felt to develop new methods for the α-arylation of ketones and have come up with a new transition metal catalyzed α-arylation of ketones. In this regard Buchwald and Hartwig contributed a core part and developed various unusual and active palladium catalytic systems, by means of synthesizing diverse sterically hindered alkyl and electron-rich phosphine ligands for the selective α-arylation[8] of ketones. As per few reports, α-arylations play a key step in synthesis of various intermediates present in natural and unnatural products.[9]

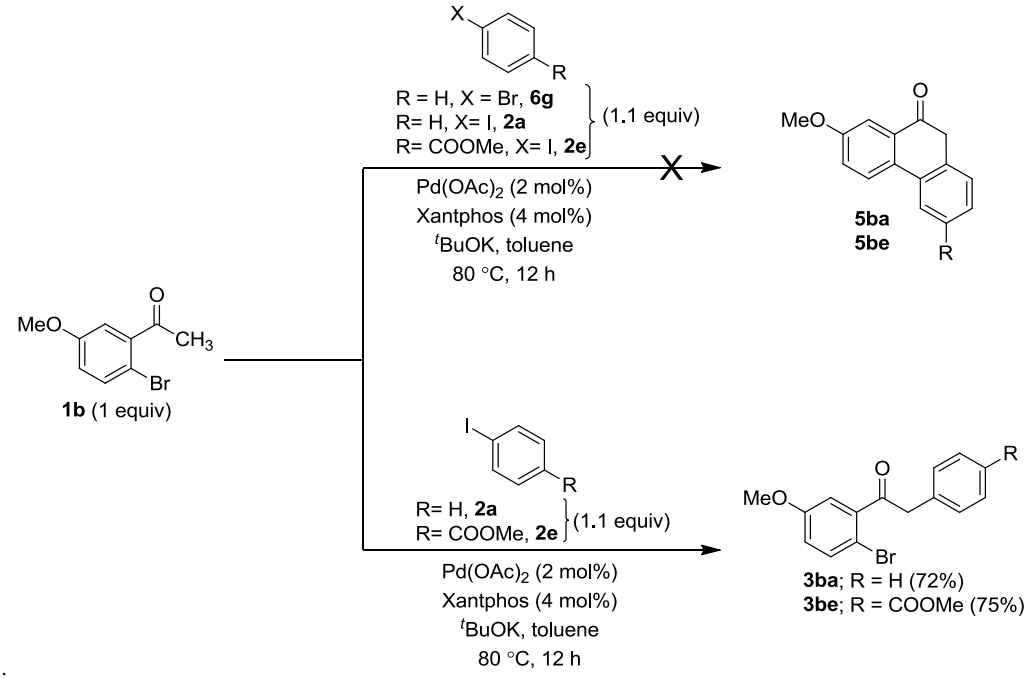
In an extension to our ongoing research passion on transition-metal catalysis,[10] particularly in domino one-pot,[10f,g] domino sequential one-pot[10d,e] processes,we recently reported a novel domino Pd-catalysis for the synthesis of novel 7-Methyl-5*H*-dibenzo[a,c][7]annulen-5-ones,[10g] Herein, we present selective α-arylation of 1-(2-bromophenyl)ethanones using external iodo-arenes without affecting the bromo-substituent of 1-(2-bromophenyl)ethanones (Scheme 1).




Scheme 1. Comparison of the alkyl group directing Pd-catalysis.

## RESULTS AND DISCUSSION

When Pd-catalysis of **1b** was explored with the external halobenzenes (**2a**, **2e** & **6g**) as the coupling partners, it did not deliver the expected fused cyclic system (**5ba** & **5be**) via bi-aryl formation followed by intramolecular Buchwald-Hartwig coupling, rather, impeded just after α-arylation stage and gave the ketones (**3ba** & **3be**). It is worth mentioning that the selective α-arylation was found successful only in case of more reactive external iodo-arenes (**2a** & **2e**) than the corresponding bromo counterparts (Scheme 2).[10g]

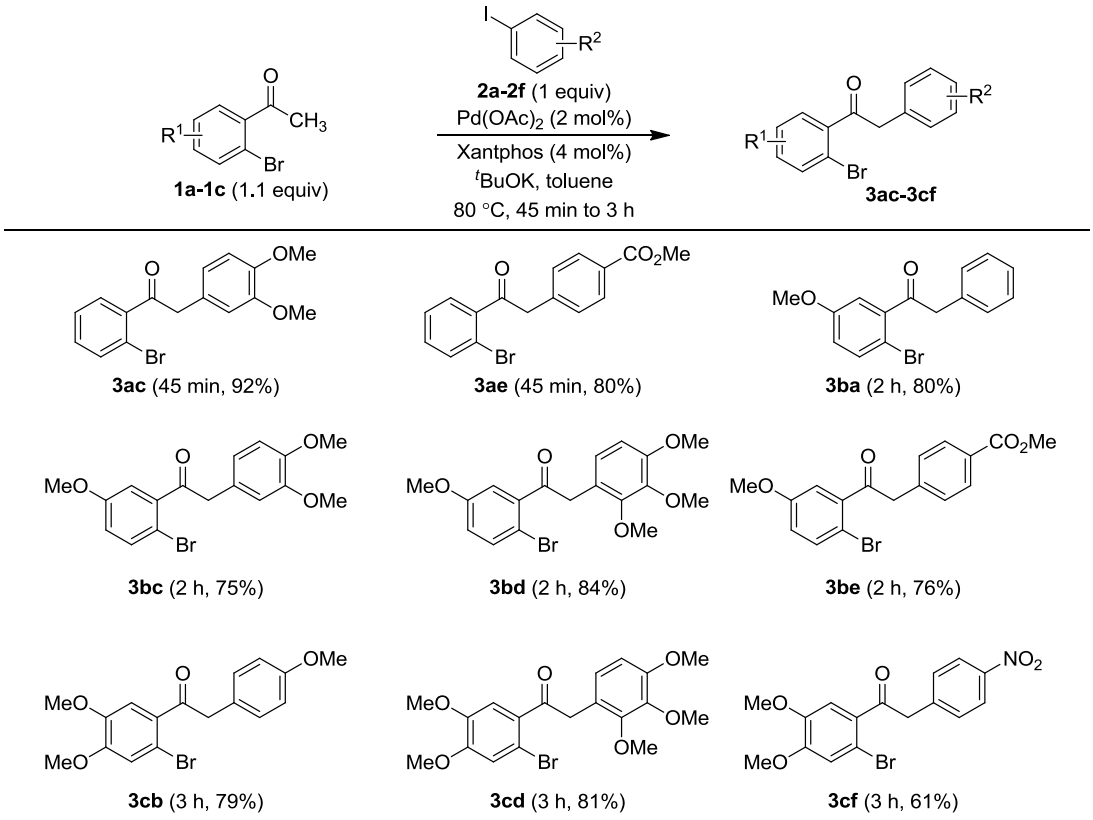



Scheme 2. Reported α- arylation of 2-bromoacetophenone **2b**.

The α-arylations[9] have been established by the research groups of Buchwald and Hartwig. Recently, the Willis et al reported α-arylation even by using 1-bromo-2-iodobenzenes as coupling partners.[11] Unlike the Willis et al report, the present work describes α-arylation wherein the bromo-substituent is part of the acetophenone **1** (Scheme 2). The study began with the preparation of 2-bromoacetophenones **1b** using the standard reaction conditions (methylmagnesiumiodide addition to 2-bromobenzaldehydes and oxidation of the resulted secondary alcohol to the corresponding ketone).[10f, 10g] However, after several attempts, we realized that reported reaction conditions[10g] for longer reaction time was not so general and applicable for other systems. In most of the cases, it was observed the formation of bi-α-arylation products along with the

small amount of other by-products as well. This can be justified because of the fact that the little excess of iodo-arenes (**2a** & **2e**) other than 2-bromoacetophenone **1b** would always tend to participate for second α-arylation. Therefore, various attempts were made to identify the suitable reaction conditions. Gratifyingly, it was recognized that the conditions[8a] reported by Buchwald et al were found suitable to our systems (i.e. with 1 equivalent of iodo-arene and 1.1 equivalents of 2-bromoacetophenone). Moreover, these optimized conditions were found broadly applicable to various iodo-arenes containing electron withdrawing, simple, and electron donating substituents on the aromatic ring. Comparatively, the reaction was completed in shorter reaction time (i.e. typically 45 min to 3 h) than that reported previously[10g] and furnished clean α-arylation products **3ac-3cf** in very good yields as shown in Table 1.

Table 1. Pd-catalyzed α-arylation of 2-bromoacetophenones **1a–1c** with iodo-arenes **2a–2f**.[a,b,c]




[a] All reactions are carried out on 0.5 mmol scale of iodo-arenes in 4 mL of toluene (0.12 M).
[b] Yields in the parentheses are isolated yields of chromatographically pure products.
[c] For compounds **3ac**-**3cf** the first letter refers to the 2-bromoacetophenes **1a**-**1c** whereas the second letter indicates the aromatic ring coming from iodo-arenes **2a**-**2f**.

## CONCLUSION

In summary, we have developed a Pd-catalysis selective α-arylation of 1-(2-bromophenyl)ethanones, for the synthesis of 1-(2-bromophenyl)-2-phenylethanones. The relatively more reactive external iodo-arenes than bromo-arenes are identified as suitable coupling partners.

## EXPERIMENTAL SECTION

**1-(2-bromophenyl)-2-(3,4-dimethoxyphenyl)ethanone (3ac)**: **General Procedure-1** followed with aryliodide **2c** (132.0 mg, 0.50 mmol), *ortho*-bromoacetophenone **1a** (109.4 mg, 0.55 mmol), $Pd(OAc)_2$ (2.2 mg, 2 mol%), xantphos (11.6 mg, 4 mol%), $^t$BuOK (72.9 mg, 0.65 mmol) and dry toluene (4 mL) at 80 °C for 45 min. Silica gel column chromatography (20 g, petroleum ether/ethyl acetate, 85:15 to 80:20) furnished the title compound **3ac** (155 mg, 92%) as yellow solid, recrystallized the solid with dichloromethane/hexane, m. p. 74–76 °C. [TLC control (petroleum ether/ethyl acetate 90:10), $R_f$(**1a**)=0.55, $R_f$(**2c**)=0.45 and $R_f$(**3ac**)=0.20, UV detection]. IR (MIR-ATR, 4000–600 $cm^{-1}$): $\nu_{max}$=2956, 2923, 2852, 1697, 1587, 1512, 1463, 1422, 1259, 1154, 1140, 1025, 791, 757, 678 $cm^{-1}$. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$=7.57 (d, 1H, *J*=7.8 Hz, Ar-H), 7.35–7.15 (m, 3H, Ar-H), 6.78 (d, 1H, *J*=8.7 Hz, Ar-H), 6.76 (dd, 1H, *J*=8.7 and 1.9 Hz, Ar-H), 6.74 (d, 1H. *J*=1.9 Hz, Ar-H), 4.15 (s, 2H, $ArCOCH_2$), 3.83 (s, 3H, $ArOCH_3$), 3.82 (s, 3H, $ArOCH_3$) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): 201.8 (s, Ar-C=O), 148.9 (s, Ar-C), 148.1 (s, Ar-C), 141.4 (s, Ar-C), 133.5 (d, Ar-CH), 131.4 (d, Ar-CH), 128.6 (d, Ar-CH), 127.2 (d, Ar-CH), 125.8 (s, Ar-C), 121.9 (d, Ar-CH), 118.6 (s, Ar-C), 112.7 (d, Ar-CH), 111.2 (d, Ar-CH), 55.8 (q, 2C, 2 × $ArOCH_3$), 49.0 (t, Ar-CO*C*$H_2$) ppm. HR-MS (ESI+) m/z calculated for $[C_{16}H_{16}{}^{79}BrO_3]^+$=$[M+H]^+$: 335.0277; found 335.0294, $[C_{16}H_{16}{}^{81}BrO_3]^+$=$[M+H]^+$: 337.0259; found 337.0274.

## SUPPLEMENTARY MATERIAL

Copies of $^1$H and $^{13}$C NMR spectra related to this article can be found online at.


## ACKNOWLEDGMENTS

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