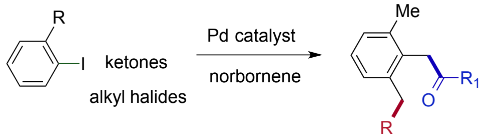
Palladium-Catalyzed Arylation of Ketones and Acetonitrile with ortho-Alkylation of Aryl Rings: de novo Synthesis of Tetralines and Benzocycloheptenes

Chuanhu Lei, Jiajia Cao and Jianrong (Steve) Zhou*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371

Supporting Information Placeholder

ABSTRACT: Palladium-catalyzed α-arylation reactions of ketones with simultaneous *ortho*-alkylaton offer 1,2,3-substituted arenes. The reactions of 1,ω-dihaloalkanes also allow facile construction of medicinally important tetralines.

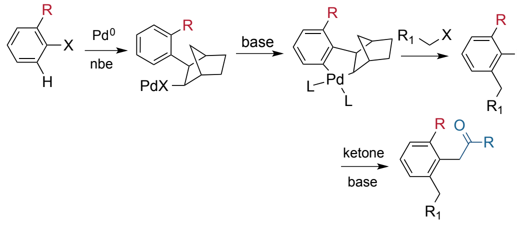


Catellani reaction allows facile functionalization of aryl halides at both *ipso* and *ortho* sites in one step.[1] A typical reaction pathway proceeds via a norbornene (nbe)-derived palladacycle, after *ortho*-CH activation of aryl rings (Scheme 1). Oxidative addition of alkyl halides on the palladacycle[2] was proposed to precede selective *ortho* alkylation of aryl rings. At the end of the catalytic cycle, *o*-alkyl arylpalladium species is trapped by olefin insertion.[3] Today, other carbon nucleophiles have been reported as *ipso* terminating reagents, such as alkynes,[4] arylboronic acids,[5] cyanide,[6] imines,[7] *N*-tosylhydrazones[8] and heterocycles.[9] In addition to alkyl halides as the *ortho* functionalizing electrophile,[10] other electrophiles emerged recently to introduce aryl,[11] acyl[12] and amino groups.[13]

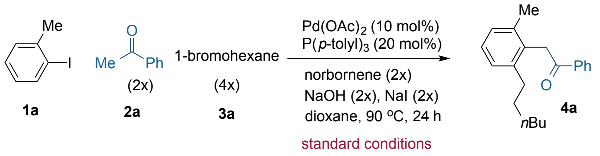
We envision that in situ generated ketone enolates anions can also intercept the late-stage *o*-alkyl arylpalladium species.[14] The intermolecular *ortho*-alkylative arylation of ketones was realized yet. Certainly, many side reactions are foreseeable such as premature couplings of upstream arylpalladium species, α-alkylation of ketones and self-aldol condensation of ketones. In addition, Catellani-type reactions were also known to have other byproducts, for example, from direct C-C ring closure of the palladacycles, multiple norbornene insertion and multiple aryl couplings.[15]

Herein, we disclose examples of 3-component α-arylation of ketones, which enables simultaneous *ortho*-alkylation (eq 1). The products, α-aryl ketones haveing two different *ortho* groups on aryl rings, are not easy to make via other reactions. Previously, Pd-catalyzed simple α–arylation reactions of ketones, including acetone,[16] were reported to couple *o,o'*-disubstituted aryl (pseudo)halides carrying two identical alkyl chains.[17] However, aryl halides carrying two different *ortho*-alkyl groups require multi-step synthesis.

We initially attempted a model reaction between 2-iodotoluene, 1-bromohexane and acetophenone and observed significant amounts of byproducts from α-alkylation of the ketone **BP-5** and self-aldol condensation. Later, we found that NaOH in ethereal solvents such as dioxane, THF and diglyme suppressed the side reactions. Simple triarylphosphines such as triphenylphosphine, tri-*m*-anisylphosphine and tri-*p*-tolylphosphine formed efficient Pd catalysts, which delivered about 60% yield of the desired product (eq 2), along with several byproducts. Very little byproduct **BP-5** was detected. The combination of palladium acetate and tri-*p*-tolylphosphine was successfully applied to the reactions of other aromatic ketones (Figure 1). Both electron-donating and withdrawing groups were tolerated on the aryl rings of ketones. Moreover, the reactions of aliphatic ketones occurred selectively at the methyl groups.



(1)



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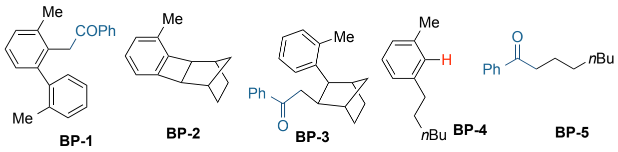


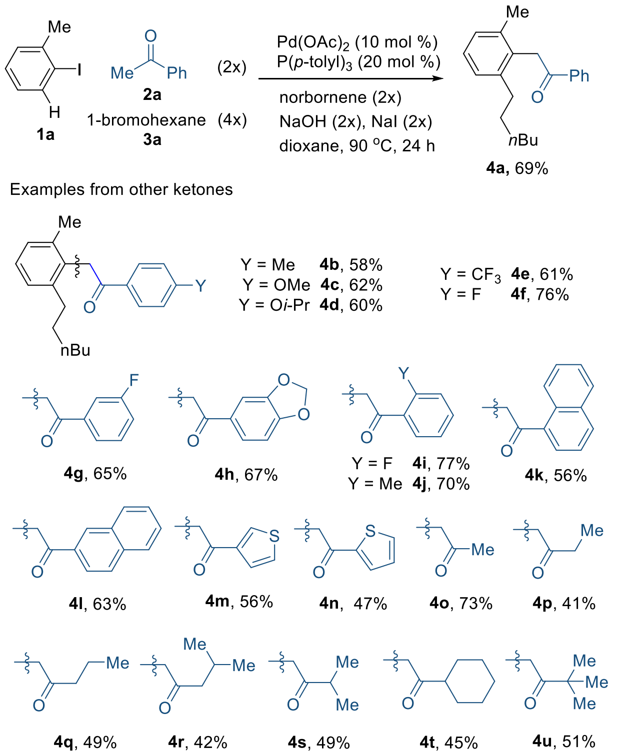


Figure 1. Examples of ketones in coupling of *o*-tolyl iodide.

The catalytic process was applied to other alkyl bromides and iodides (Figure 2a). In the reactions of alkyl iodides, no NaI was needed. For couplings of isopropyl iodide, only 30% yield was obtained under a slightly modificed condition using tri-*m*-anisylphosphine in diglyme. Other aryl iodides bearing *ortho* methyl, isopropyl and methoxy groups were also be (Figure 2b). The reaction of *m*-anisyl iodide led to *o,o'*-dialkyl products.

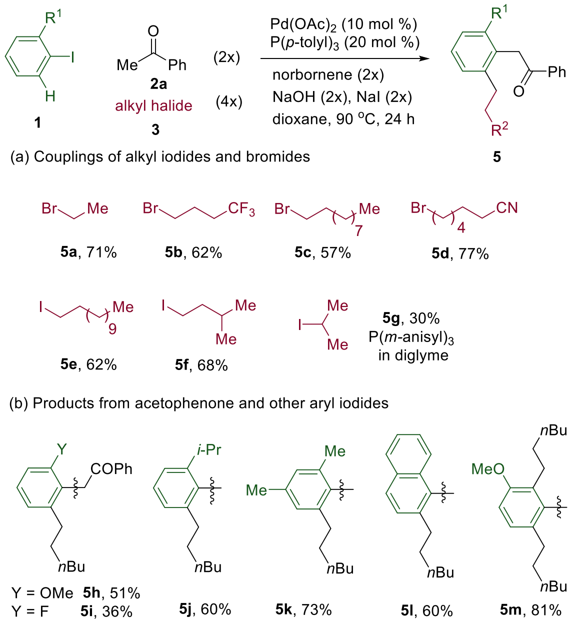
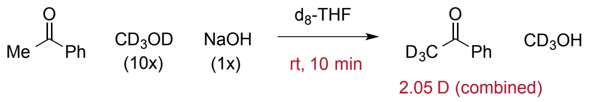


Figure 2. Scope of alkyl halides (a) and aryl iodides (b) in the couplings

We found that H/D exchange between acetophenone and methanol-d_4 occurred very fast at room temperature in the presence of NaOH (eq 3).[18] In H/D exchange of an aliphatic ketone, fast reversible deprotonation occurred at both α and α' positions (eq 4). Therefore, the regioselective coupling of aliphatic ketones at the less-hindered carbon on the ketones can be attributed to faster C-C reductive elimination on that site.



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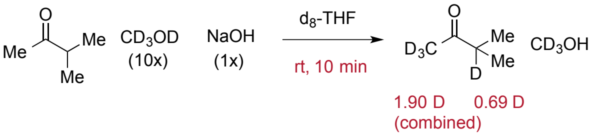

(4)

Furthermore, we successfully adopted the protocol for ketone couplings with 1-bromo-3-chloropropane that formed 1,8-disubstituted tetralines (Figure 3a). Thus, the reaction formed 3 new C-C bonds and a benzofused ring in one step. We found that NaI was detrimental to the productive pathway. In comparison, 1,3-dibromopropane gave low yield of the desired product **6a** (20%) and the main byproduct was **BP-2** (65%). We believe that the ring is formed at last via *intramolecular* alkylation of enolates, since the reaction conditions were optimized to suppress the *intermolecular* alkylation process. Tetraline is featured in mibefradil, a drug for the treatment of hypertension and chronic angina pectoris.[19] It is also present in podophyllotoxin, a lignin natural product, which is used as an antiviral agent. Its analogues are also promising anticancer agents.[20] Moreover, the reaction with 1,4-dibromobutane formed a benzocycloheptene, which is an important pharmacophore,[21] due to its special chair conformation[22] (Figure 3b). However, when 1-bromo-4-chlorobutane was used, the reaction produced noncyclized product **4** as the major product.

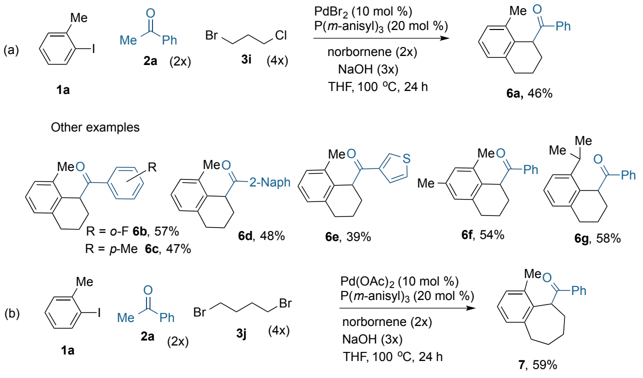

Figure 3. Synthesis of tetralines and benzocycloheptene using 1,ω-dihaloalkanes

The hindered α-aryl acetonitriles carrying two different *ortho* groups are not easy to prepare via traditional Pd-catalyzed arylation of alkyl nitriles.[23] The nitrile group is a versatile precursor to other groups such as alkylamines, aldehydes, ketones, esters, amides and tetrazoles.[24] We also realized similar *ortho*-alkylative arylation of acetonitrile, in the presence of LiO*t*-Bu (Figure 4). When acetonitrile-d_3 was used, the products retained ~65% of deuterium at each α C-H bond. When 1,ω-dihaloalkanes were tested in the MeCN reaction, very little cyclization product was detected.

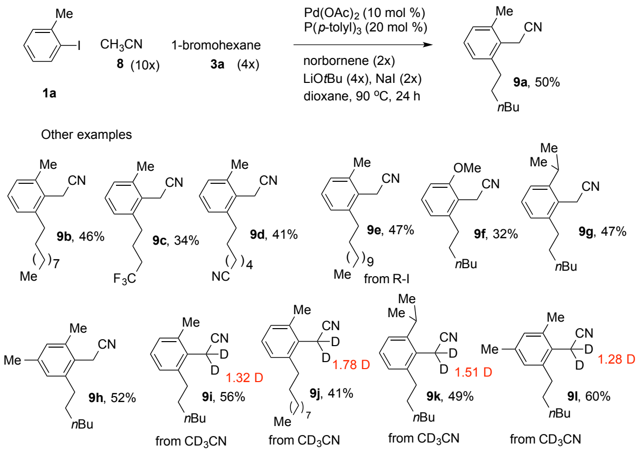

Figure 4. Couplings of acetonitrile

In summary, we report, for the first time, intermolecular couplings of aryl iodides, alkyl halides and ketones that resulted in simultaneous *ortho*-alkylation of aryl rings. The products are 1,2,3–trisubstituted arenes, which are difficult to synthesize from other methods. Similar double functionalization of aryl iodides was also realized with acetonitrile. Additionally we realized one-pot construction of medicinally important tetraline derivatives by using dihaloalkanes.

ASSOCIATED CONTENT

Supporting Information

Procedures for couplings, characterization of isolated products and NMR spectra of products as the proof of purity for isolated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

jrzhou@ntu.edu.sg

Author Contributions

CL and JC contributed equally to the experiments of this work.

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SYNOPSIS TOC