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Palladium-Catalyzed Arylation of Ketones and Acetonitrile with *Ortho* Alkylation of Aryl Rings: De Novo Synthesis of Tetralines and Benzocycloheptenes

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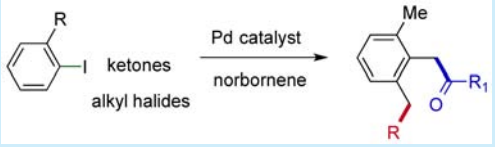
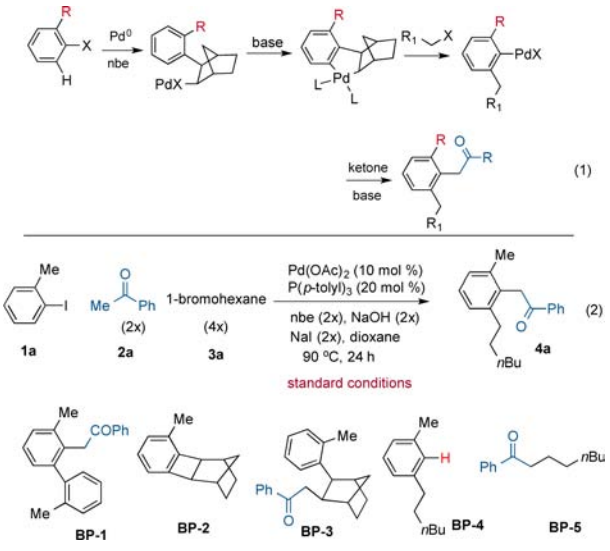
Supporting Information

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



The 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 (eq 1).



Oxidative addition of alkyl halides to the key palladacycle[2] was proposed, followed by *ortho* alkylation of the aryl rings. At the end, the *o*-alkylarylpalladium species is trapped by olefins[3] or other terminating reagents such as alkynes,[4] arylboronic acids,[5] cyanide,[6] imines,[7] *N*-tosylhydrazones,[8] and heterocycles.[9] Besides alkyl halides,[10] other electrophiles have been used recently to introduce aryl,[11] acyl,[12] and amino groups[13] at *ortho* positions. We envision that enolate anions generated in situ in the presence of bases can also intercept the downstream *o*-alkylarylpalladium species.[14] This kind of intermolecular *ortho*-alkylative arylation of ketones is yet to be realized. Certainly, many side reactions are foreseeable, such as premature couplings of upstream arylpalladium species, α-alkylation of ketones, and self-aldol condensation of ketones under basic conditions. In addition, Catellani-type reactions are 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 the first examples of three-component α-arylation of ketones accompanied by *ortho* alkylation of the aryl rings (eq 1). The products, α-aryl ketones having two different groups at the *ortho* postions of the aryl rings, are cumbersome to make via other methods. Previously, simple α-arylation reactions of ketones, including acetone,[16] were reported under Pd catalysis to couple *o*,*o*′-disubstituted aryl (pseudo)halides carrying two identical alkyl chains.[17] However, coupling of aryl halides carrying two different *o*-alkyl groups are rare because of the synthetic efforts to make the hindered aryl halides themselves.

We initially attempted a model reaction of 2-iodotoluene (**1a**), acetophenone (**2a**), and 1-bromohexane (**3a**). We detected significant amounts of byproducts from α-alkylation of the ketone **BP-5** and self-aldol condensation. Later, we were gratified to see that the use of NaOH in ethers such as dioxane, THF, and diglyme suppressed the side reactions. The reaction required triarylphosphines as supporting ligands, and several simple phosphines such as triphenylphosphine, tri-*m*-anisylphosphine, and tri-*p*-tolylphosphine formed efficient Pd catalysts, which delivered the desired product in about 60% yield (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 electron-withdrawing groups on the aryl rings of the ketone were tolerated. Moreover, the reactions of aliphatic ketones occurred selectively at the methyl groups.

The catalytic process was applied to other alkyl bromides and iodides (Figure 2a). In the reactions of alkyl iodides, no NaI

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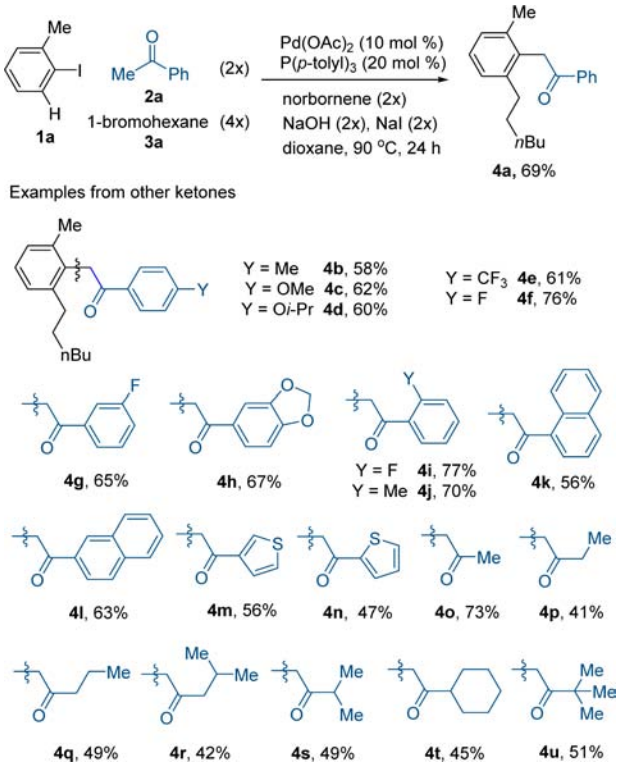


Figure 1. Examples of ketones in coupling of *o*-tolyl iodide.

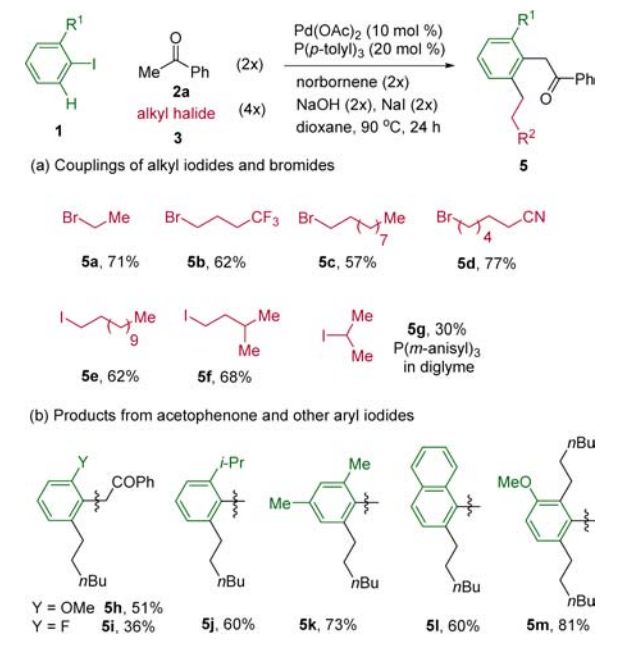
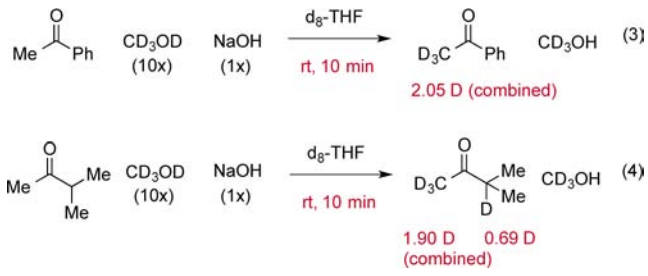


Figure 2. Scope of alkyl halides (a) and aryl iodides (b) in the couplings.

was needed. For couplings of isopropyl iodide, only 30% yield was obtained under slightly modified conditions using tri-*m*-anisylphosphine in diglyme. Other aryl iodides bearing *o*-methyl, *o*-isopropyl, and *o*-methoxy groups could also be used (Figure 2b). The reaction of *m*-anisyl iodide led to *o*,*o*′-dialkyl products.

We found that H/D exchange between acetophenone and methanol-d_4 occurred very rapidly 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 can be attributed to faster C−C reductive elimination at that site.

Furthermore, we successfully adopted the protocol for ketone couplings with 1-bromo-3-chloropropane, which formed 1,8-disubstituted tetralines (Figure 3a). Thus, the reaction

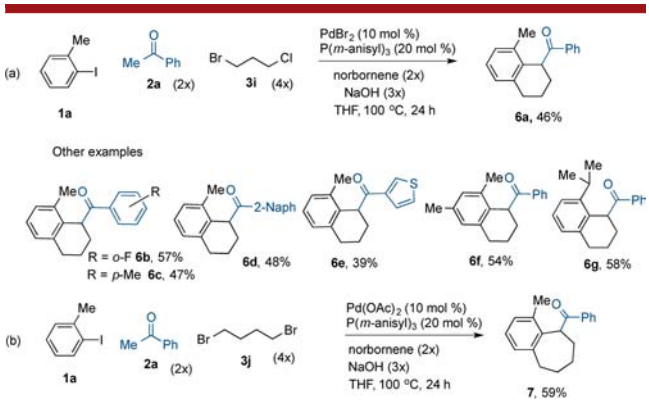


Figure 3. Synthesis of tetralines and benzocycloheptene using 1,ω-dihaloalkanes.

formed three 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 a 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 that 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] because of its special chair conformation[22] (Figure 3b). When 1-bromo-4-chlorobutane was used, the reaction produced noncyclized product **4** as the major product.

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 a 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% deuterium at each α-C−H bond. When 1,ω-dihaloalkanes were tested in the MeCN reaction, very little cyclization product was detected.

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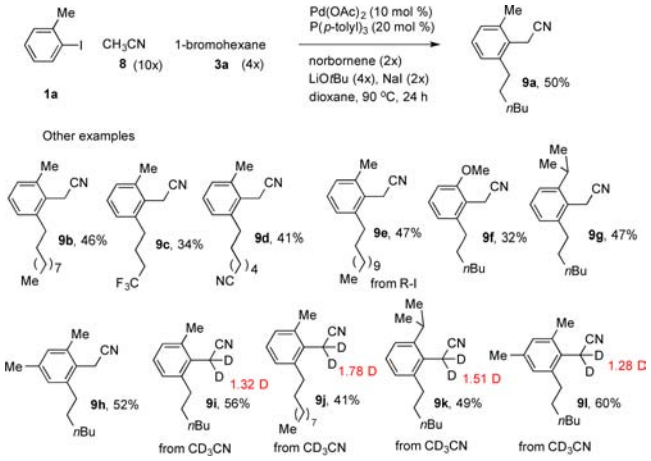

Figure 4. Couplings of acetonitrile.

In summary, we report for the first time the intermolecular α-arylation reaction of simple methyl ketones and acetonitrile that results in simultaneous *ortho* alkylation of aryl rings. Additionally, a one-pot synthesis of medicinally important tetralines and benzocycloheptenes was also achieved in the presence of 1,ω-dihaloalkanes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03130.

Procedures for couplings and characterization of isolated products (PDF)

NMR spectra of products as a proof of purity for isolated compounds (PDF)

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C.L. and J.C. contributed equally to the experiments in this work.

Notes

The authors declare no competing financial interest.

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