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Palladium-catalyzed α-arylation of ketones on solid support: scope and limitations

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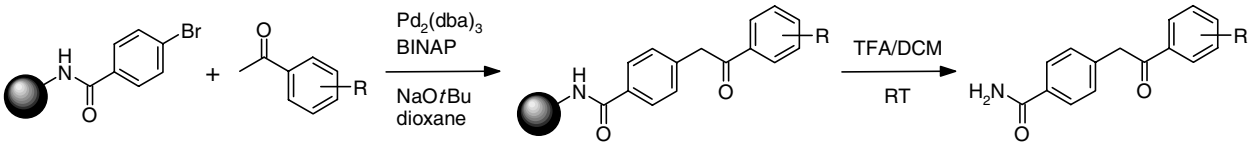
Abstract—The palladium-catalyzed α-arylation of ketones on solid support is described. Using modified Buchwald–Hartwig reaction conditions, the coupling of immobilized 4-bromobenzamide with various aromatic, heteroaromatic, and aliphatic ketones was investigated. Subsequent cleavage from the resin provided the desired α-aryl ketones almost in moderate to high yields and good to excellent purities. The scope and limitations of this protocol will be discussed.

The solid-phase synthesis of low-molecular-weight compounds along with high-throughput screening has evolved into a powerful tool for the discovery of new pharmaceutical lead structures. One major focus in this area is on the expansion of the solid-phase synthesis toolbox that allows for the further exploration of the pharmaceutical diversity space.[1] In the course of our ongoing efforts directed toward the solid-phase synthesis of general-purpose screening libraries, we were interested in exploiting the palladium-catalyzed α-arylation of ketones for library preparation. The resulting α-arylated ketones may serve as valuable key intermediates in the synthesis of a wide range of drug-like molecules including medicinally important heterocycles.[2] Almost concurrent, Buchwald and Hartwig independently reported efficient procedures for the palladium-catalyzed α-arylation of ketones with tailor-made catalyst/ligand systems in a versatile manner.[3,4] This methodology has been proven as reliable, robust, and useful for a wide range of substrates.[5–9]

However, to the best of our knowledge, the palladium-catalyzed α-arylation of ketones on solid support remains unexplored. Herein, we describe the successful adaptation of the solution-phase procedures onto the requirements of a solid-phase synthesis (Scheme 1). Initially, the coupling reaction on solid support was investigated using acetophenone and immobilized 4-bromobenzamide, prepared from polystyrene Rink amide resin and 4-bromo-benzoic acid chloride. High conversions were obtained, when the standard protocol of the Buchwald– Hartwig α-arylation[3,4] was modified for solid-phase synthesis toward a higher load of reagents. Finally, we ended up using 15 equiv of ketone, 20 mol % of $Pd_2(dba)_3$ in combination with 80 mol % 2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl (BINAP) as the catalyst and significant excess (18 equiv) of sodium *tert*-butylate as base in 1,4-dioxane as the preferable set of reagents. Subsequent cleavage from the Rink amide resin was carried out with trifluoroacetic acid in methylene chloride (v/v = 1:1) yielding the desired



Scheme 1.

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coupling product in fair yield[10] and excellent purity.[11] Having the optimized protocol in hands,[12] the scope and limitations of the reaction were investigated using aliphatic as well as aromatic ketones (Tables 1–3).

When acetophenone or its alkyl-substituted analogues are subjected to the above mentioned reaction conditions, the yields are found in a moderate range (35–70%), whereas the purity of the single compounds is good to excellent (85–>95%; Table 1, entries 1–3). Alkoxy-substituted acetophenones display a similar outcome in terms of purities (>95%) and yields (62–66%; Table 1, entries 4 and 5). Instead, dimethylamino-substituted acetophenones under these reaction conditions were found to yield certain byproducts diminishing especially the purity into the 55–70% range (Table 1, entries 6 and 7).[2]

When 4-acetylbenzonitrile and 4-hydroxyacetophenone were used as substrates, only traces of the intended products were detected (Table 1, entries 8 and 9). To our surprise, propiophenones did not react at all, although they were described as good substrates under

Table 1. Aromatic substrates for Buchwald–Hartwig coupling

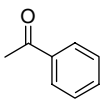
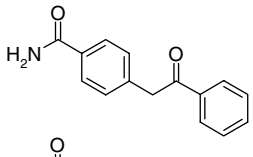
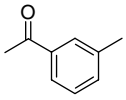
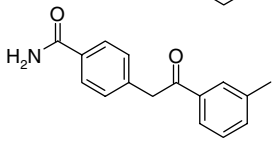
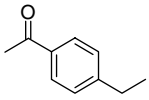
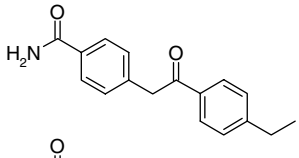
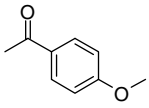
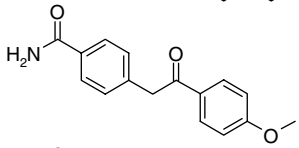
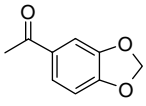
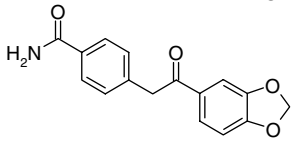
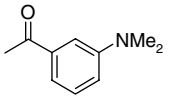
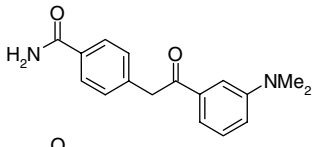
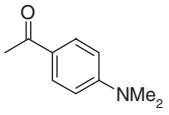
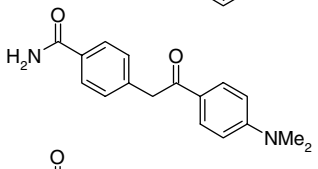
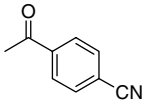
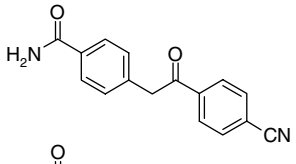
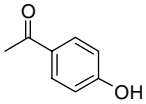
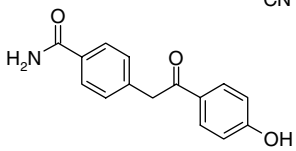
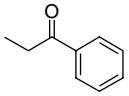
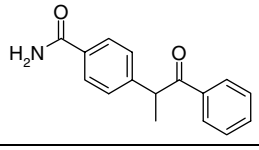
Entry	Substrate	Product	Yield[10] (%)	Purity[11] (%)
1			56	>95
2			35	>95
3			69	85–90
4			66	>95
5			62	>95
6			77	55–60
7			62	65–70
8			Trace	20–30
9			Trace	15–20
10			0	N/A

Table 2. Aliphatic substrates for Buchwald–Hartwig coupling

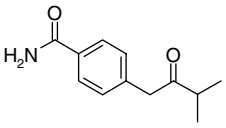
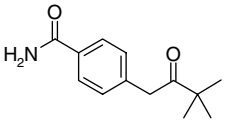
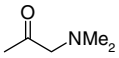
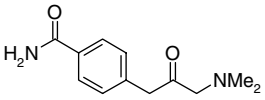
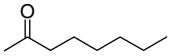
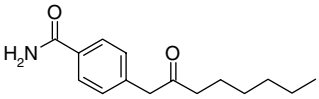
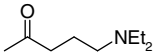
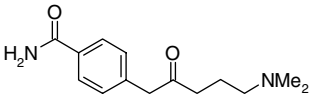
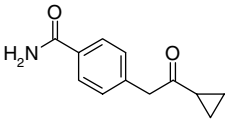
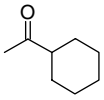
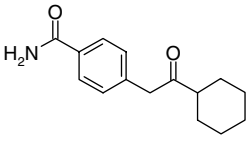
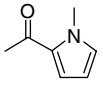
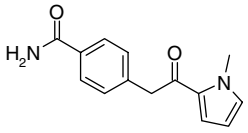
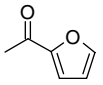
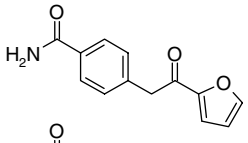
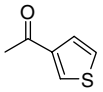
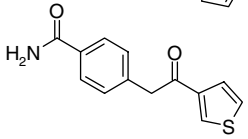
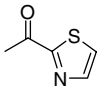
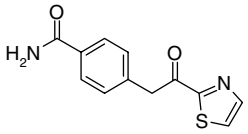
Entry	Substrate	Product	Yield[10] (%)	Purity[11] (%)
11			82	90–95
12			99	90–95
13			77	>95
14			70	85–90
15			78	85–95
16			93	85–90
17			69	85–90

Table 3. Heteroaromatic substrates for Buchwald–Hartwig coupling

Entry	Substrate	Product	Yield[10] (%)	Purity[11] (%)
18			61	90–95
19			91	30–35
20			96	25–30
21			97	30–35

comparable solution-phase conditions (Table 1, entry 10).[3]

The reaction of methyl-alkyl ketones with resin-bound 4-bromo-benzamide was characterized by high yields

and high purities in general (Table 2). Nevertheless, except for pinacolin (Table 2, entry 12), small amounts of dialkylation products were observed in all cases (1–10%). In contrast to the aromatic series, dialkylamino-substituted ketones nicely form the desired products in moderate yields (77–78%) and good to excellent purities (Table 2, entries 13 and 15).

The reaction of heteroaromatic ketones with resin-bound 4-bromo-benzamide was characterized by highly variable yields as well as purities (Table 3). This is exemplified when comparing the reactivity of 2-acetyl-1-methylpyrrole with 2-acetyl-furan (Table 3, entries 18 and 19). In the pyrrole case, the yield is in a moderate range (61%), whereas the purity is excellent (90–95%). In the furan case, the yield is high (91%), but the purity is low (30–35%). In this and other examples (Table 3, entries 20 and 21), several side products such as ring-opened fragments were observed and partly identified by LC/MS. Variations in the established catalytic protocol unfortunately did not alter these findings. So, as a consequence, heteroaromatic substrates may be α-arylated by this methodology, but will require a subsequent purification of the crude material.

Additionally, we have investigated the use of cyclic ketones as substrates for this arylation reaction. With some rare exceptions (cyclohexanone or cycloheptanone), the intended products were observed as traces out of a very complex mixture. Similarly, 1,3-diketo compounds are not suitable for the use under the described reaction conditions.

In summary, the palladium-catalyzed α-arylation of ketones was successfully adapted to solid support using modified Buchwald–Hartwig reaction conditions. In the case of aromatic as well as aliphatic methyl ketones, the desired α-arylated ketones were obtained almost in moderate to high yields and good to excellent purities. However, heteroaromatic ketones and alicylic ketones may be sensitive to side reactions (bis-arylation, fragmentation, heteroaromatic ring opening/decomposition) and must be carefully re-examined. The overall methodology is robust and opens a versatile diversity platform for multiple purposes, for example, in subsequent heterocyclic chemistry.

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10. Yields refer to the crude products and were calculated on the basis of the initial loading of the resin.
11. Purities and product identities were determined by LC/MS analysis using a Hewlett-Packard HP 1100 liquid chromatography system equipped with diode array detector coupled to a Micromass ZMD-400 spectrometer. The compound purity was monitored based on the UV absorbency at 214 nm. The presence of all desired compounds was confirmed by their molecular mass, except entry 10.
12. Representative experimental procedure: Rink amide AM resin (10 g, 7.0 mmol, loading of 0.70 mmol/g, 1% cross-linking, 100–200 mesh) was Fmoc deprotected with 20% piperidine/DMF (100 mL) at room temperature for 1 h, filtered, and washed successively with DMF, CH_2Cl_2, THF as well as CH_2Cl_2. The resin was charged with diisopropylamie (6.3 mL, 36.0 mmol) in THF (25 mL) as well as 4-bromo-benzoic acid chloride (4.75 g, 21.6 mmol) in THF (75 mL), and the mixture was shaken at room temperature for 18 h. The resin was filtered and washed in the same way as described above. Last trace of solvent was removed in vacuo overnight to provide the derivatized resin with a theoretical loading capacity of 0.72 mmol/g based on 100% conversion. Under an atmosphere of argon the 4-bromo-benzoic acid Rink amide resin (70 mg, 50 μM, loading: 0.72 mmol/g) was suspended in a solution of acetophenone (91 mg, 75 μM) in anhydrous 1,4-dioxane (1 mL). A solution of $Pd_2(dba)_3$ (9 mg, 10 μM), 2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl (25 mg, 40 μmol, BINAP) and NaO^tBu (87 mg, 900 μmol) in anhydrous 1,4-dioxane (0.5 mL) was added and the reaction mixture was heated at 70 °C for 20 h. After filtration, the resin was washed with methanol, THF, DMF, THF, and CH_2Cl_2. Finally, after drying, the product was released from the resin by treatment with TFA in CH_2Cl_2 (v/v = 1:1) for 1 h. Filtration and evaporation yielded 6.7 mg (28 μmol, 56% of theory) 4-(2-oxo-2-phenylethyl)-benzamide. LC/MS: 1.87 min, >95% (214 nm), *m/z* 239 [M+H$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.47 (s, 2H); 7.31 (s, br, 1H), 7.33 (d, $J = 8.1$, 2H), 7.55 (t, $J = 7.6$, 2H), 7.66 (t, $J = 7.3$, 1H), 7.81 (d, $J = 8.1$, 2H), 7.91 (br s, 1H), 8.05 (d, $J = 7.6$, 2H). HRMS calcd for $C_{17}H_{17}N_2O_2$ [M+ACN+H$^+$]: 281.1285; found 281.1297.