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Sterically Hindered Benzophenones via Rhodium-Catalyzed Oxidative Arylation of Aldehydes

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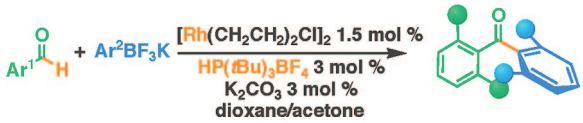

Efficient cross-coupling, allowing a straightforward access to congested benzophenones, between aromatic aldehydes and potassium aryltrifluoroborates, is described in the presence of a rhodium/tri-*tert*-butylphosphane catalyst system and acetone as cosolvent. The use of the stable phosphonium salts of tri-*tert*-butylphosphane prevented the use of highly oxidizable tri-*tert*-butylphosphane and allowed a careful control of the stoichiometry with the rhodium.

Benzophenone frameworks are encountered in organic materials[1] as well as in numerous natural products,[2] one of the most representative of biologically active compounds being balanol,[3] a PKC inhibitor. The Friedel−Crafts acylation[4] and the reaction of carboxylic acid derivatives, for example, nitriles, Weinreb amides, anhydrides, or acid chlorides with lithium, magnesium, or aluminum reagents to give the corresponding ketones,[5] are important C−C bond-forming reactions commonly used in organic synthesis. Another general approach consists of the condensation of an organometallic reagent (lithium, magnesium) to aldehydes followed by oxidation.[6] However, these reactions, conducted under either highly basic and nucleophilic or acidic conditions, are incompatible with most functional groups, and the construction of elaborated benzophenones generally involves further functionalization steps that are time-consuming and generally low yielding.[1−6]

Alternatively, the transition-metal-catalyzed reaction of acyl chlorides or anhydrides with organometallic reagents (mainly organoboronic acids) has emerged as a promising tool to construct benzophenone frameworks under milder conditions.[7] Another elegant approach, starting from aldehydes, consists of a transition-metal-catalyzed hydroacylation reaction[8] or Heck-type reaction with aryl halides[9] or organoboranes.[10,11] Preparation of hindered benzophenones under mild conditions would be highly desirable but is still a challenge in organic synthesis.

However, all these reactions, and particularly the highly desirable mild transition-metal-catalyzed reactions, are limited to reagents that are sterically unencumbered. The majority of biologically active benzophenones are sterically congested substrates[2,6] (at least di-*ortho*-substituted) and are still, and more efficiently, prepared by the addition of aryllithium or arylmagnesium to aldehydes followed by oxidation.[12]

We report here a solution to this longstanding limitation: a direct access to highly congested benzophenones under very mild conditions. We recently described a straightforward access

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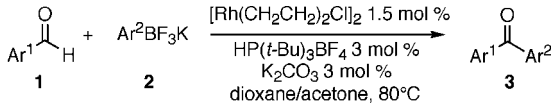
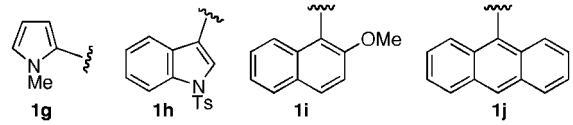
SCHEME 1. Rhodium-Catalyzed Formation of Congested Benzophenones



Ar^1 = 4-MeOC$_6$H$_4$ (**1a**), 2-thienyl (**1b**), 2-furyl (**1c**), 4-HO-3-MeOC$_6$H$_3$ (**1d**), 2,4,6-(Me)$_3$C$_6$H$_2$ (**1e**), 2,4,6-(MeO)$_3$C$_6$H$_2$ (**1f**)



Ar^2 = 2-MeC$_6$H$_4$ (**2a**), 2-MeOC$_6$H$_4$ (**2b**), 2,6-(Me)$_2$C$_6$H$_3$ (**2c**), 3-MeOC$_6$H$_4$ (**2d**), 1-naphthyl (**2e**), 2-naphthyl (**2f**)

to benzophenones via the rhodium-catalyzed coupling of organoboron reagents, and particularly potassium organotrifluoroborates,[13,14] with aldehydes using inexpensive acetone as hydride acceptor.[10a] However, the presence of *ortho*-substituents on both reaction partners generally prevented the formation of benzophenones, low yields, or absence of reactivity being observed, as well as reproducibility problems. Moreover, the use of unstable P(*t*-Bu)$_3$ as a ligand, which is readily oxidized, prevented a careful control of the stoichiometry of the ligand compared to rhodium. We wondered if the use of stable, easily handled, and commercially available phosphonium salt HP(*t*-Bu)$_3$BF$_4$[15] would provide a solution to previous limitations.

Several bases, used in catalytic amount, were evaluated to release the free phosphane ligand in the rhodium-catalyzed reaction of potassium 2-methylphenyltrifluoroborate (**2a**) with 4-methoxybenzaldehyde (**1a**) (Scheme 1). Potassium carbonate and diisopropylethylamine were found to be suitable (Table 1, entries 1 and 2), affording nearly quantitative yield of *ortho*-substituted benzophenone **3aa** in a dioxane/acetone mixture at 80 °C and in less than 1 h. Because of its low cost and ease of handling, potassium carbonate was selected to liberate the ligand from its salt.

Indeed, using 1 equiv of P(*t*-Bu)$_3$ as its phosphonium salt compared to rhodium, high yields of mono- and di-*ortho*-substituted benzophenones were achieved in the reaction of various potassium aryltrifluoroborates and aldehydes (Scheme 1, Table 1, entries 1−10). Heterocyclic aldehydes, such as thiophene (**1b**), furan (**1d**), pyrrole (**1g**), or indole (**1h**) derivatives, underwent clean reaction with different *ortho*-substituted trifluoroborate salts, affording straightforward access to heterocyclic benzophenones (entries 4 and 5 and 7 and 8) whose preparation, using conventional reactions, is not obvious. In the same way, acidic phenol functional groups were tolerated (entry 6). For certain substrates, an increase of the reaction temperature to 100 °C, as well as an increase of the amount of P(*t*-Bu)$_3$ compared to rhodium, allowed a significant increase in the yields (entries 9 and 10).

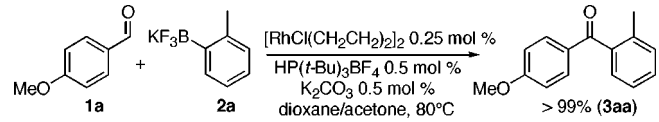
We wondered if these conditions would be amenable for the construction of highly congested benzophenones. We were

TABLE 1. Rhodium-Catalyzed Formation of Congested Benzophenones from Aldehydes[a]

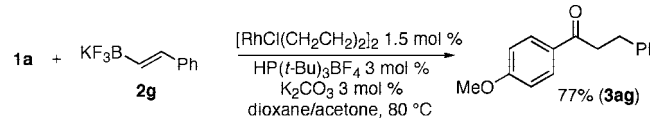
entry	Ar^1CHO	Ar^2BF_3K	yield[b]
1	**1a**	**2a**	97%[c] (**3aa**)
2	**1a**	**2a**	98% (**3aa**)
3	**1a**	**2b**	87% (**3ab**)
4	**1b**	**2a**	94% (**3ba**)
5	**1c**	**2a**	69% (**3ca**)
6	**1d**	**2a**	79% (**3da**)
7	**1h**	**2d**	77% (**3hd**)
8	**1g**	**2c**	48% (**3gc**)
9	**1i**	**2f**	52%[d] (**3if**)
10	**1i**	**2f**	70%[d,e] (**3if**)
11	**1e**	**2a**	76% (**3ea**)
12	**1j**	**2e**	90% (**3je**)
13	**1i**	**2a**	62% (**3ia**)
14	**1j**	**2a**	76% (**3ja**)
15	**1i**	**2e**	45%[d] (**3ie**)
16	**1i**	**2c**	31%[d,f] (**3ic**)
17	**1e**	**2c**	59% (**3ec**)
18	**1j**	**2c**	65% (**3jc**)

[a] Reactions conducted using 0.5 mmol of **1**, 2 equiv of **2** with 1.5 mol % of [Rh(CH$_2$CH$_2$)$_2$Cl]$_2$, 3 mol % of HP(*t*-Bu)$_3$BF$_4$, and 3 mol % of K_2CO_3 at 80 °C in 2.5 mL of 1,4-dioxane/acetone 4:1. [b] Isolated yield of ketone. [c] Using 3 mol % of *i*-Pr$_2$NEt in place of K_2CO_3. [d] Reaction conducted at 100 °C. [e] Using 6 mol % of HP(*t*-Bu)$_3$BF$_4$ and 6 mol % of K_2CO_3. [f] Formation of 46% of (2,6-dimethylphenyl)(2-methoxynaphthalen-1-yl)methanol.

SCHEME 2. Low Catalytic Loading in the Rhodium-Catalyzed Formation of Benzophenones



SCHEME 3. Rhodium-Catalyzed Addition of Potassium Alkenyltrifluoroborates



pleased to find that tri- and even tetra-*ortho*-substituted benzophenones were readily accessed in moderate to good yields using this reaction (entries 11−18). For example, reaction of **1j**, a di-*ortho*-substituted aldehyde, with **2e** afforded the tri-*ortho*-substituted ketone **3je** in 90% yield, and on reaction with **2c**, tetra-*ortho*-substituted benzophenone **3jc** was obtained in 65% yield (entries 12 and 18). Slightly lower yields were observed in the formation of some sterically hindered tetra-*ortho*-substituted benzophenones because of competitive formation of carbinol with those congested substrates (entry 16). However, yields ranging from 31 to 65% (entries 16−18) were achieved for the direct preparation of tetra-*ortho*-substituted benzophenones from aldehydes using this one-step reaction.

Indeed, it appeared that the only competitive methods to this reaction are the condensation of aryllithium or arylmagnesium to acyl chlorides or aldehydes followed by oxidation, reactions occurring under highly basic conditions that are incompatible with hydroxyl, carbonyl, cyano, and other labile functional groups. It is also important to note that all the reactions were complete within less than 1 h in the presence of 3 mol % of catalyst. However, reactions conducted on aliphatic aldehydes failed to give any detectable traces of ketone: only carbinols were obtained in moderate yield.

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To demonstrate further the synthetic usefulness of this procedure, a reaction was conducted using lower catalyst loading. Indeed, reaction of aldehyde **1a** and potassium aryltrifluoroborate **2a** in the presence of 0.25 mol % of rhodium dimer catalyst afforded the expected benzophenone **3aa** in quantitative yield (Scheme 2).

Contrary to the reaction with potassium aryltrifluoroborates, the reaction of aldehydes with alkenyltrifluoroborates did not yield the expected α,β-unsaturated ketone, but a saturated product. Indeed, reaction of **1a** with potassium styryltrifluoroborate (**2g**) under optimized conditions afforded ketone **3ag** in 77% yield (Scheme 3) because the generated intermediate enone is a better hydride acceptor than acetone.[10a,b]

We have described for the first time a straightforward access to congested benzophenone frameworks starting from readily available aryl aldehydes and potassium aryltrifluoroborates. This reaction, occurring under neutral conditions, allowed the direct formation of di-, tri-, and even tetra-*ortho*-substituted benzophenones under operationally simple conditions, thanks to the use of stable phosphonium salt of P(*t*-Bu)$_3$. This reaction, operationally simple and providing efficient alternative for the construction of benzophenones, would be useful in organic synthesis.

Experimental Section

General Procedure for the Synthesis of Benzophenones: Preparation of (2-Methoxy-1-naphthyl)-(2-naphthyl)methanone (3if), entry 9. In a septum-capped vial, [Rh(C_2H_4)$_2$Cl]$_2$ (2.9 mg, 1.5 mol %), HP(*t*-Bu)$_3$BF$_4$ (4.4 mg, 3.0 mol %), K_2CO_3 (2.1 mg, 3.0 mol %), and potassium 2-naphthyltrifluoroborate **2f** (234 mg, 1.0 mmol, 2.0 equiv) were introduced successively, placed under argon atmosphere, and dissolved in 1 mL of freshly degazed 1,4-dioxane. After 15 min, aldehyde **1i** (93 mg, 0.5 mmol) in solution in 0.5 mL of anhydrous degazed acetone and 1 mL of dioxane were added, and the reaction mixture was heated at the indicated temperature. After the reaction was complete, solvents were removed under reduced pressure and the crude product purified by chromatography on silica gel to afford 81 mg of a light yellow solid (52% yield): R_f (Ch/AcOEt, 90:10) = 0.41; flash chromatography eluent cyclohexane/AcOEt 98:2; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (3H, s), 7.33−7.42 (3H, m), 7.45−7.52 (1H, m), 7.55−7.65 (2H, m), 7.80 (1H, d, ^3J = 8.1 Hz), 7.85−7.95 (3H, m), 8.01 (1H, d, ^3J = 9.0 Hz), 8.12 (1H, dd, ^3J = 8.4 Hz, ^4J = 1.7 Hz), 8.24 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.6, 113.2, 123.1, 124.2, 124.6, 126.6, 127.5, 127.8, 128.2, 128.5, 128.6, 128.9, 129.8, 131.3, 131.9, 132.3, 132.7, 135.5, 136.0, 154.2, 197.7; EI-MS *m*/*z* = 312 [M]$^+$ (100%); HRMS (EI) calcd for $C_{22}H_{16}O_2$ 312.1150, found 312.1146.

Acknowledgment. This work was supported by the Centre National de la Recherche Scientifique (CNRS).

Supporting Information Available: Experimental procedures and description and NMR spectra of compounds **3aa**−**3jc**. This material is available free of charge via the Internet at http://pubs.acs.org.

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