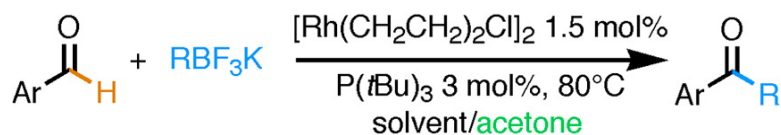Communication

Direct Access to Ketones from Aldehydes via Rhodium-Catalyzed Cross-Coupling Reaction with Potassium Trifluoro(organo)borates

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Direct Access to Ketones from Aldehydes via Rhodium-Catalyzed Cross-Coupling Reaction with Potassium Trifluoro(organo)borates

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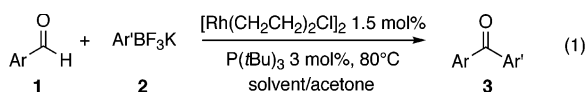
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Activation or functionalization of aldehyde carbon−hydrogen bonds by transition metal complexes has received increased interest because of its relevance to organic synthesis through conversion of aldehydes to ketones.[1] Hydroacylation,[1b,2] in which aldehydic hydrogen is activated by a transition-metal catalyst followed by addition to alkenes, is one of the most popular reactions involving such a transformation. Although intramolecular reactions have been extensively studied, intermolecular pathways are generally not favored because of decarbonylation processes. Several strategies have been developed to suppress decarbonylation,[3] one of the most efficient being the chelation of an auxiliary group (chelation-assisted hydroacylation).[4]

Another approach to access ketones from aldehydes, which would prevent decarbonylation, would consist of a Heck-type reaction with aldehydes (insertion and β-hydride elimination mechanism), a formal C−H activation process. Examples of such processes are rare and involve oxidative addition of iodoarene to low valent transition metal. Indeed, Miura et al.[5] reported a palladium-catalyzed coupling reaction of aryl iodides with salicylaldehydes. Ishiyama and Hartwig[6] described a rhodium-catalyzed Heck-type reaction of aryl halides with N-pyrazyl aldimines which allowed access to diaryl ketones upon hydrolysis. Cheng et al.[7] described a nickel-catalyzed coupling of aryl iodides with aromatic aldehydes affording directly diaryl ketones. However, a high temperature is generally needed under basic[6] or reductive conditions,[7] preventing the use of functionalized substrates. Furthermore, yields are generally moderate or limited with respect to substrate tolerance.[5]

We thought that the generation of catalytic organorhodium species via transmetalation instead of the previously reported oxidative addition pathway[5−7] would avoid the use of harsh conditions in such coupling. Several groups recently described the formation of diarylcarbinol from 1,2-addition of organometallic reagents to aldehydes,[8] but, to the best of our knowledge, no example of efficient direct formation of ketones using this strategy has been reported.[9,10] Recently, we discovered that potassium trifluoro(organo)borates[11] participated very efficiently in asymmetric rhodium-catalyzed 1,4-additions,[12] and we described an efficient access to α-amino acids via a tandem 1,4-additon/enantioselective protonation.[13]

We report here the first catalytic cross-coupling reaction of organometallic reagents with arylaldehydes to afford diaryl ketones via a Heck-type mechanism (eq 1).

$$\text{Ar} \overset{\text{O}}{\underset{\text{H}}{\bigparallel}} + \text{Ar'BF}_3\text{K} \xrightarrow[\substack{\text{P}(t\text{Bu})_3 \ 3 \ \text{mol\%}, \ 80°C \\ \text{solvent/acetone}}]{[\text{Rh}(\text{CH}_2\text{CH}_2)_2\text{Cl}]_2 \ 1.5 \ \text{mol\%}} \text{Ar} \overset{\text{O}}{\underset{}{\bigparallel}} \text{Ar'} \quad (1)$$

1   **2**   **3**

Indeed, reaction of **1a** with **2a** using [Rh(CH₂CH₂)₂Cl]₂ in conjunction with P(tBu)₃ ligand[14] as catalyst afforded a 95% GC yield of ketone **3a** at 80 °C, using a ternary mixture of toluene/acetone/water as solvent (conditions A), and only traces of carbinol were formed (Table, entry 1). This result was very surprising compared with the known 1,2-addition of organometallic reagents

Table 1. Rhodium-Catalyzed Formation of Diaryl Ketones from Aldehydes and Potassium Trifluoro(organo)borates[a]
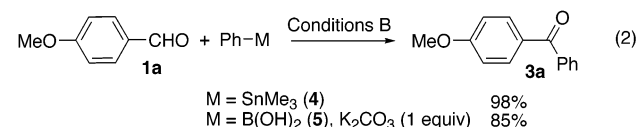
entry	Ar	Ar′	yield[b] (%)
1	4-MeOC₆H₄ **1a**	C₆H₅ **2a**	93 (A), 60 (B)
2	4-FC₆H₄ **1b**	**2a**	85 (B)
3	2-MeOC₆H₄ **1c**	**2a**	0 (A), 95 (B)
4	3-HOC₆H₄ **1d**	**2a**	83 (A), 72 (B)
5	4-HOC₆H₄ **1e**	**2a**	97 (B)
6	2-furyl **1f**	3-BrC₆H₄ **2b**	78 (B)
7	2-thienyl **1g**	3-CF₃C₆H₄ **2c**	83 (B)
8	4-HO-3-MeOC₆H₃ **1h**	2-MeC₆H₄ **2d**	94 (B)
9	**1f**	**2a**	73 (A), 91 (B)
10	**1e**	2,4,6-(Me)₃C₆H₂ **2e**	82 (B)

[a] Reactions conducted using 0.5 mmol of **1**, 2 equiv of **2** with 1.5 mol % of [Rh(CH₂CH₂)Cl]₂ and 3 mol % P(tBu)₃ at 80 °C in 2.5 mL of toluene/acetone/water 20:3:2 (conditions A) or 1,4-dioxane/acetone 4:1 (conditions B). [b] Isolated yields of ketone under conditions A or B.

to aldehydes, affording diarylcarbinols.[8] In fact, it appeared that the presence of acetone as cosolvent was crucial for the process, diarylcarbinols being obtained in quantitative yields in its absence. Under these conditions, a great variety of ketones were obtained from the reaction of aromatic aldehydes and potassium aryltrifluoroborates (Table 1 and eq 1).

Depending on the substrates, a mixture of dioxane/acetone as solvent (conditions B) sometimes afforded higher yields than the previous ternary mixture. Particularly, aldehyde **1c** (entry 3) failed to give any ketone under conditions A (carbinol being formed in quantitative yield), whereas under conditions B a quantitative yield of ketone was obtained. Good to excellent yields were generally achieved with many substitution patterns on the reaction partners. Particularly, acidic hydroxyl substituents on the aromatic ring were tolerated in this reaction, preventing tedious protection/deprotection sequences (entries 4, 5, 8, and 10). Heterocyclic aldehydes also underwent smooth coupling under these conditions (entries 6, 7, and 9). It is also noteworthy that this reaction allowed to access mono- (entries 3 and 8) and di-ortho-substituted benzophenones in high yields (entry 10). However, under these conditions, aliphatic aldehydes failed to react.

We were also pleased to find that, under conditions B, organostannanes and organoboronic acids participated equally well in the coupling reaction. Indeed, reaction of phenyltrimethylstannane (**4**) or phenylboronic acid (**5**) (in the presence of 1 equiv of K₂CO₃) with **1a** afforded the expected ketone in high yields (eq 2). It is important to note that, in the absence of added base, phenylboronic acid failed to afford ketones and carbinols were obtained.[8d]

$$\text{MeO}-\bigcirc-\text{CHO} + \text{Ph}-\text{M} \xrightarrow{\text{Conditions B}} \text{MeO}-\bigcirc-\overset{\text{O}}{\underset{}{\bigparallel}}-\text{Ph} \quad (2)$$

1a   **3a**

M = SnMe₃ (**4**)   98%
M = B(OH)₂ (**5**), K₂CO₃ (1 equiv)   85%

For the present reaction, two competitive mechanisms may be envisioned after the transmetalation step of the organometallic to

Scheme 1. Postulated Mechanism for the Formation of Ketones from Aldehydes and RBF$_3$K
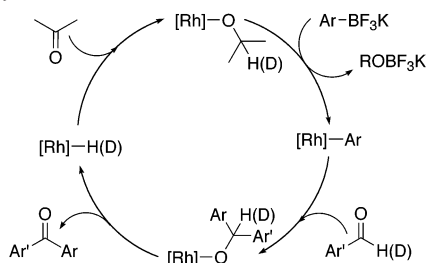
rhodium(I): the first one would involve C−H bond activation[1] followed by reductive elimination of ketone. The second pathway would imply insertion of the carbonyl bond into an arylrhodium(I) species, followed by β-hydrogen elimination to form a ketone (Heck-type mechanism). The first mechanism seems to be highly improbable not only from Hartwig's mechanistic studies of aldehydes insertion into arylrhodium(I)[15] but also because we never observed any traces of decarbonylation product, a commonly observed byproduct in reactions involving this C−H activation.[3] Even if aldehyde C−H activation may not be completely ruled out, we strongly favor a mechanism involving insertion/β-hydrogen elimination.

Whatever the initial steps of the mechanism are, a rhodium hydride species should be generated in the reaction. To understand the subsequent transformations of the putative rhodium hydride and the crucial role of acetone in this reaction, labeling studies were conducted (eq 3).
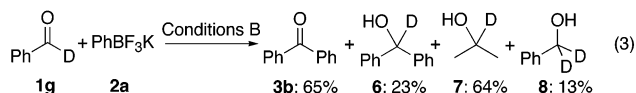
The reaction of benzaldehyde-d_1 (**1i**) with **2a** under conditions B afforded the expected benzophenone (**3b**) in 65% yield, together with 23% (determined by GC) of diphenylmethanol-d_1 (**6**). ^{2}H NMR spectra of the reaction mixture revealed the formation of 2-deuteriopropan-2-ol (**7**, $\delta = 3.64$ ppm, 64%), diphenylmethanol-d_1 (**6**, $\delta = 5.53$ ppm, 23%), and 1,1-dideuteriophenylmethanol (**8**, $\delta = 4.35$ ppm, 13%) as the sole observable deuterated compounds. From these results it appeared that equal amounts of benzophenone and propan-2-ol-d_2 were formed during the reaction, indicating that formation of benzophenone is linked to the reduction of acetone. Formation of 1,1-dideuteriophenylmethanol may originate from insertion of rhodium hydride into the starting benzaldehyde.

The overall mechanism is believed to involve a transmetalation of the organometallic reagent to rhodium(I) complex, followed by insertion of the aldehyde into the arylrhodium(I) (Scheme 1). β-Hydride elimination from the generated alkoxorhodium(I) complex[15] would release diaryl ketone and a rhodium(I) hydride species. The latter reacts with acetone to afford an alkoxorhodium(I) complex, which is suited for transmetalation with the boron reagent. Transmetalation of organoboron compounds to alkoxo or hydroxo complexes of palladium,[16] rhodium,[17] or ruthenium[18] have been described, allowing the regeneration of arylmetal species. It is not clear at present why the starting aldehyde does not react (or to a minor extent) with rhodium hydride in the same way as acetone does.

We have thus described for the first time the cross-coupling reaction of organometallic reagents with aldehydes to access ketones directly under mild conditions. Deuterium labeling studies suggest that this efficient reaction occurs via a Heck-type mechanism followed by unusual hydrogen transfer thanks to inexpensive acetone playing the part of hydride acceptor.

Supporting Information Available: Experimental procedures and description of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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