Carbinol derivatives *via* rhodium-catalyzed addition of potassium trifluoro(organo)borates to aldehydes†
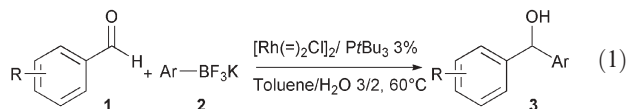
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Reaction of potassium aryltrifluoroborates with aldehydes, in the presence of a rhodium catalyst, afforded carbinol derivatives in high yields under mild aqueous conditions; this efficient reaction proved to be general, allowing the production of highly hindered diarylmethanols and aliphatic aldehydes were also reactive under these conditions.

Rhodium-catalyzed asymmetric 1,4-additions of organometallic reagents to Michael acceptors have recently emerged as a powerful tool for carbon–carbon bond formation.[1,2] In that field, we showed that potassium trifluoro(organo)borates[3] were highly suitable partners and developed very efficient conditions for asymmetric 1,4-additions to unsaturated substrates.[4,5] Moreover, we also described unusual reactivity of Baylis–Hillman adducts in such reactions[6] and an efficient reaction to access directly chiral amino acids *via* tandem 1,4-addition/enantioselective protonation.[7]

On the other hand, rhodium-catalyzed additions of organometallic reagents to aldehydes have been developed to a lesser extent, whereas diarylmethanols are important intermediates for the synthesis of biologically active compounds.[8] Even if the addition of strong organometallics (RLi, RMgX) to aldehydes constitutes one of the most versatile methods to generate secondary alcohols, limitations as to their use arise from their high reactivity as nucleophile or base, which often gives rise to undesired side reactions in the synthesis of multifunctional compounds. The addition of organozinc reagents to aldehydes in racemic and asymmetric versions is now well documented,[9] but examples of aryl transfer are often limited to the introduction of a phenyl group.[10,11] Indeed, the rhodium-catalyzed addition of arylstannanes,[12] arylsilanes[13] and arylboronic acids[14] to aldehydes has emerged as a promising alternative. Moreover, they afford the opportunity to conduct reactions under aqueous conditions. However, despite the various conditions described for rhodium-catalyzed addition to aldehydes, few of them have a general character and examples of efficient addition to aliphatic aldehydes or involving hindered substrates are scarce or have not been described. Moreover, most of them are generally limited to activated aryl aldehydes bearing electron-withdrawing substituents. Thus, there is still a need for efficient conditions to be developed for the addition of organometallic reagents to electron rich or hindered aromatic aldehydes and to aliphatic ones.

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We thought that the highly useful potassium trifluoro(organo)-borates[3] would be appropriate organometallic partners in this reaction.[15] Batey *et al.* were the first to demonstrate the feasibility of this approach and described the addition of these organometallics to aryl aldehydes but the reaction was limited to electron deficient substrates.[5] In this communication we want to report efficient and general access to carbinol derivatives *via* rhodium-catalyzed addition to aldehydes thanks to the use of potassium trifluoro(organo)borates, highly stable and easily prepared organoboron derivatives (Eqn. (1)).

$$R\text{—}\underset{1}{\begin{array}{c}\end{array}}\text{—}\overset{O}{\underset{H}{\parallel}} + Ar\text{—}BF_3K \xrightarrow[\text{Toluene/H}_2\text{O 3/2, 60°C}]{[\text{Rh(=)}_2\text{Cl}]_2/ P t\text{Bu}_3\ 3\%} R\text{—}\underset{3}{\begin{array}{c}\end{array}}\text{—}\overset{OH}{\underset{Ar}{|}} \quad (1)$$

Optimization of the reaction conditions was conducted using potassium phenyltrifluoroborate (**2a**) and 4-tolualdehyde or 4-anisaldehyde (**1a**) as coupling partners. The rhodium precursor already used by Miyaura[14a] and Batey,[5] [Rh(acac)(CO)$_2$], showed poor activity (maximal conversion: 20%) on these unactivated aldehydes whatever the ligand and the solvent tested, except at higher temperature (100 °C, 50% conversion using dppf). Moreover, association of dppf with other rhodium precursors ([Rh(acac)(CH$_2$CH$_2$)$_2$], [Rh(cod)Cl]$_2$, [Rh(cod)$_2$]PF$_6$ or [Rh(CH$_2$CH$_2$)$_2$Cl]$_2$) did not improve these results under standard conditions (DME/H$_2$O, 80 °C). Among the tested ligands,[16] it appeared that the reaction was strongly favored with electron rich ligands as described for the addition of organoboronic acids. Indeed tri-*tert*-butylphosphane and *N*-heterocyclic carbenes, respectively introduced by Miyaura[14b] and Fürstner,[14c] appeared to be the best adapted ligands in this reaction, but the use of *N*-heterocyclic carbenes required harsher reaction conditions. After optimization of the rhodium precursor, ligand, solvent and temperature, the best system turned out to be the association of the dimer [Rh(CH$_2$CH$_2$)$_2$Cl]$_2$ and tri-*tert*-butylphosphane in a 3/2 mixture of toluene/H$_2$O at 60 °C. Indeed, under these aqueous conditions, potassium trifluoro(phenyl)borate (**2a**) added quantitatively to 4-methoxybenzaldehyde (**1a**) in less than 1 hour (Table 1, entry 1).

With optimal conditions in hand, the addition of different potassium trifluoro(organo)borates on various aldehydes was examined to explore the scope of the reaction (Table 1). Electron deficient aldehydes such as 4-nitrobenzaldehyde (**1b**) or 4-trifluoromethylbenzaldehyde (**1c**) underwent addition very efficiently (entries 2 and 3, 96% yield). Halide-substituted aryl aldehydes (entries 4–6) were also revealed to be compatible with this reaction, affording carbinols in high yields, particularly bromide-substituted aldehyde did not undergo oxidative addition.

Table 1   Rh-catalyzed 1,2-addition of RBF$_3$K to aryl aldehydes^a

$$Ar{-}CHO \; (1) \; + \; Ar'{-}BF_3K \; (2) \xrightarrow[\text{Toluene/H}_2\text{O 3/2, 60 °C}]{[\text{Rh}(=)_2\text{Cl}]_2/\, P t\text{Bu}_3\; 3\%} Ar{-}\underset{\text{OH}}{\overset{}{\text{CH}}}{-}Ar' \; (3)$$

Entry	ArCHO	ArBF$_3$K	Yield^b
1	4-MeOC$_6$H$_4$ **1a**	Ph **2a**	97
2	4-NO$_2$C$_6$H$_4$ **1b**	**2a**	96
3	4-CF$_3$C$_6$H$_4$ **1c**	4-MeOC$_6$H$_4$ **2b**	96
4	4-ClC$_6$H$_4$ **1d**	**2a**	81
5	4-BrC$_6$H$_4$ **1e**	**2a**	94
6	4-FC$_6$H$_4$ **1f**	4-ClC$_6$H$_4$ **2c**	95
7	2-MeOC$_6$H$_4$ **1g**	**2a**	99
8	4-HOC$_6$H$_4$ **1h**	**2a**	94
9	3-HOC$_6$H$_4$ **1i**	**2a**	99
10	2-furyl **1j**	**2a**	96
11	**1f**	3-thienyl **2d**	97
12	2-thienyl **1k**	1-naphthyl **2e**	71
13	**1b**	2-MeC$_6$H$_4$ **2f**	94

^{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]$_2$ and 3 mol% P(tBu)$_3$ at 60 °C in 2.5 ml toluene/water 3 : 2. ^{b} Isolated yield.
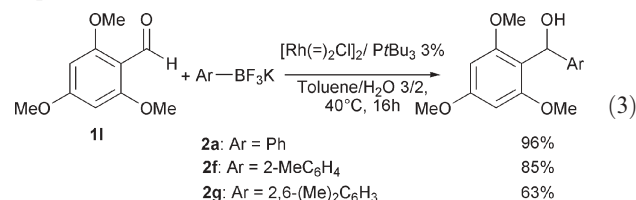
Interestingly, electron-rich aldehydes (entries 1 and 8–9) showed comparable high reactivity. In contrast to classical 1,2-additions of strong organometallic reagents, the present reaction is compatible with the presence of various functionalities, avoiding non-productive protection/deprotection steps. Indeed, unprotected phenol functionalities were tolerated in these conditions (entries 8 and 9) and 1,2-addition to salicylaldehydes **1h** and **1i** occurred in high yields, whereas similar reaction gave generally modest yields on such substrates.[12b,14b] Heteroaromatic aldehydes were also reactive and, once again, corresponding carbinols were obtained in high yields. Particularly, trifluoro(3-thienyl)borate **2d** showed a similar reactivity and 1,2-addition to **1f** gave the expected carbinol in 97% yield (entry 11). Even *ortho*-substituted potassium aryltrifluoroborates (naphthyl **2e** or 2-methylphenyl **2f**) participated, affording the addition adducts in 71 and 94% yield respectively (entries 12 and 13). Under these conditions, alkenyl-trifluoroborates reacted quantitatively but the corresponding carbinols were isolated in low yields due to the presence of aryl alkyl ketone, the latter probably resulting from direct isomerisation of the vinyl carbinol or from an addition/elimination followed by a hydride transfer process as described previously.[15,17]

As shown in the Table, reactions were generally conducted at 60 °C for practical purposes (short reaction times) and at this temperature nearly quantitative conversions to diarylcarbinols were usually observed in less than one hour, using two equivalents of trifluoro(organo)borate. But in many cases, reactions can be conducted at room temperature without altering the yields. For example, addition of potassium trifluoro(4-methoxyphenyl)borate (**2b**) to **1c** occurred under standard conditions at room temperature giving the expected 1,2-adduct in 97% yield (Eqn. (2)).

$$\textbf{1c} \; + \; \textbf{2b} \xrightarrow[\substack{\text{Toluene/H}_2\text{O 3/2,}\\ \textbf{Room Temp.}, 16h}]{[\text{Rh}(=)_2\text{Cl}]_2/\, P t\text{Bu}_3\; 3\%} \underset{97\%}{\text{F}_3\text{C}{-}\text{C}_6\text{H}_4{-}\underset{\text{OH}}{\text{CH}}{-}\text{C}_6\text{H}_4{-}\text{OMe}} \quad (2)$$
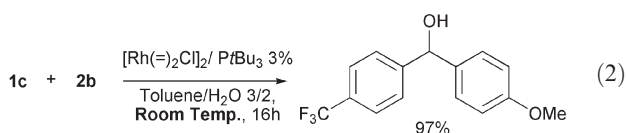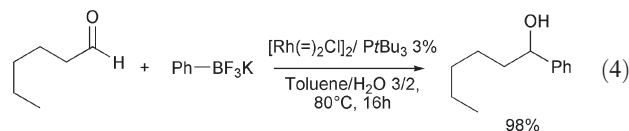
We also tested the effect of steric hindrance in the *ortho* position of the reaction partners. As shown before, a mono substitution in

the *ortho* position of one of the coupling partners did not alter their reactivity (see Table, entries 12 and 13). The feasibility of access to highly hindered diarylmethanols was evaluated using di-*ortho*-substituted and electron rich 2,4,6-trimethoxybenzaldehyde (**1l**) (Eqn. (3)). Under previous conditions, and conducting the reaction at 40 °C, di-, tri- and even tetra-*ortho*-substituted diarylmethanols could be obtained in high yields using potassium phenyl- (**2a**), 2-methylphenyl- (**2f**) and 2,6-dimethylphenyltrifluoroborate (**2g**) respectively. To our knowledge, this is the first time that such crowded diarylmethanols could be obtained using soft organometallics under very mild conditions in the presence of a rhodium catalyst in water, reactions being generally limited to mono-, and, in rare cases, di-substitution patterns under elevated temperatures.[14b,c]

$$\textbf{1l} \; + \; Ar{-}BF_3K \xrightarrow[\substack{\text{Toluene/H}_2\text{O 3/2,}\\ 40°\text{C, 16h}}]{[\text{Rh}(=)_2\text{Cl}]_2/\, P t\text{Bu}_3\; 3\%} \text{product} \quad (3)$$

2a: Ar = Ph — 96%
2f: Ar = 2-MeC$_6$H$_4$ — 85%
2g: Ar = 2,6-(Me)$_2$C$_6$H$_3$ — 63%

The described conditions are not limited to aromatic aldehydes and aliphatic ones do participate in this rhodium-catalyzed 1,2-addition. Indeed, reaction of potassium phenyltrifluoroborate with hexanal afforded the expected 1-phenylhexan-1-ol in 98% yield at 80 °C (Eqn. (4)). At lower temperature conversion was extremely low, even after prolonged reaction time.

$$\text{hexanal} \; + \; \text{Ph}{-}BF_3K \xrightarrow[\substack{\text{Toluene/H}_2\text{O 3/2,}\\ 80°\text{C, 16h}}]{[\text{Rh}(=)_2\text{Cl}]_2/\, P t\text{Bu}_3\; 3\%} \underset{98\%}{\text{1-phenylhexan-1-ol}} \quad (4)$$

In contrast to previously described methodologies, the addition of potassium aryltrifluoroborates to aldehydes, catalyzed by the association of a rhodium precursor and sterically hindered and basic tri-*tert*-butylphosphane, offers a huge flexibility, tolerating a wide range of substituents. This catalytic process allows Grignard type additions to aldehydes under mild organoaqueous conditions. The efficiency of the reaction was further demonstrated by the possibility of accessing highly crowded diarylmethanols and the compatibility with aliphatic aldehydes. Indeed, this methodology appears to be versatile and may provide new opportunities in organic synthesis, all the more so as it employs highly stable, easily accessible, and commercially available potassium trifluoro-(organo)borates, compared to their trivalent congeners. Furthermore, organoboron derivatives are now easily accessible *via* new methodologies involving the functionalisation of an aromatic C–H bond, preventing the use of reactive organometallics for their preparation.[18]

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