

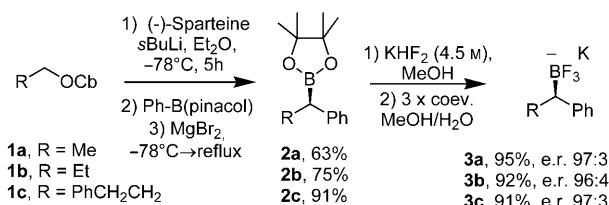
Homogeneous Catalysis

Complete Stereoretention in the Rhodium-Catalyzed 1,2-Addition of Chiral Secondary and Tertiary Alkyl Potassium Trifluoroborate Salts to Aldehydes**

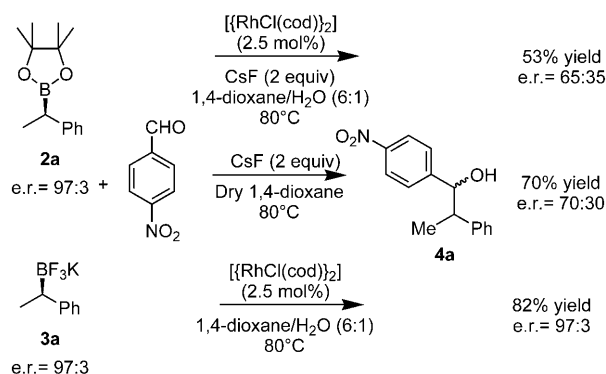
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The Rh-catalyzed 1,4-addition^[1] and 1,2-addition^[2] of boronic acids to Michael acceptors and aldehydes, first reported by Miyaura and co-workers just over a decade ago, has spawned a major area of research.^[3] The 1,4-addition reaction, in particular, has rapidly moved from methodological studies to applications in synthesis.^[4] Although less well developed, the 1,2-addition reaction has also enjoyed significant development. For example, it has been found that alternative metals to Rh^[5] can be used (Pd, Ni, Cu, Ru),^[6] and that the more-stable potassium organotrifluoroborates can be employed in place of boronic acids.^[7] However, all of these reactions are limited to the use of sp²-carbon boron derivatives (aryl- or alkenylboronic acids, esters, or organotrifluoroborate salts).^[8] Presumably, alkyl boron derivatives suffer from a slower rate of transmetalation and the potential for rapid β -hydride elimination from the sp³ metalloalkyl intermediate.^[9] These two effects would conspire to render such substrates unsuitable in this type of coupling reaction,^[10] although Crudden and co-workers recently reported a breakthrough in the Suzuki coupling of secondary benzylic boronic esters.^[11,12] Nevertheless, we recognized the significant potential that would ensue if we could induce alkyl boron derivatives to couple to electrophiles. Herein we describe our success in achieving this goal and furthermore demonstrate complete stereoretention in reactions involving not only secondary but also tertiary chiral alkyl derivatives.

We elected to study the reactions of secondary benzylic boron derivatives because they were expected to undergo more rapid transmetalation. They were easily prepared in high enantioselectivity by the reaction of Hoppe's lithiated carbamates with aryl/alkyl boronic esters by using methodology that we recently reported (Scheme 1).^[13] We also converted the boronic esters into the corresponding trifluoroborate salts to test both classes of substrates. However, reactions of boronic ester **2a** with *p*-NO₂C₆H₄CHO



Scheme 1. Synthesis of secondary potassium trifluoroborate salts. Cb = *N,N*-diisopropylcarbamoyl, coev = co-evaporation.



Scheme 2. Reaction of boronic ester **2a** or trifluoroborate salt **3a** with 4-nitrobenzaldehyde. cod = cycloocta-1,5-diene.

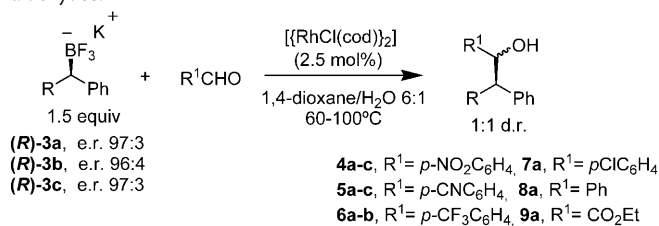
either showed limited reactivity in the presence of [RhCl(cod)]₂ or direct reaction was observed with CsF accompanied by substantial racemization in both cases (Scheme 2).

We therefore turned our attention to the trifluoroborate salts, particularly as Batey et al. had reported that they show greater reactivity than boronic acids because they undergo more rapid transmetalation.^[7a] With this switch we were immediately rewarded with success. Using the commercially available catalyst [RhCl(cod)]₂ (2.5 mol %) at 80°C in 1,4-dioxane/H₂O (6:1), the reaction of **3a** with *p*-NO₂C₆H₄CHO gave the adduct in 82% yield and with complete stereoretention (Scheme 2). The reaction was applied to a range of aldehydes, and different temperatures were tested to maximize the enantioselectivity and minimize proto-deboration. Strongly activated aldehydes were found to react efficiently at 60–100°C (Table 1, entries 1–3) and so we chose 80°C to determine the scope of the reaction (Table 1, entries 2 and 4–6). However, less-activated aldehydes suffered low yields at this temperature, because of competing protonation (Table 1, entry 6) and so reactions were conducted at 60°C instead (Table 1, entry 7). At this temperature, non-activated

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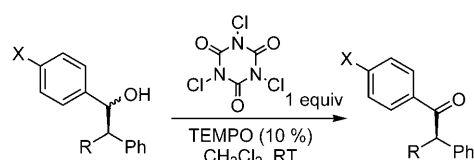
Table 1: 1,2-Addition of the potassium trifluoroborate salts (*R*)-**3a–c** to aldehydes.^[a]

Entry	R	R ¹	T [°C]	t [h]	Product yield (%) ^[b]	Stereoet. [%] ^[c]
1	Me	<i>p</i> -NO ₂ C ₆ H ₄	60	6	4a , 78	> 99
2	Me	<i>p</i> -NO ₂ C ₆ H ₄	80	4	4a , 82	> 99
3	Me	<i>p</i> -NO ₂ C ₆ H ₄	100	4	4a , 86	> 99
4	Me	<i>p</i> -CNC ₆ H ₄	80	6	5a , 93	> 99
5	Me	<i>p</i> -CF ₃ C ₆ H ₄	80	6	6a , 86	> 99 ^[d]
6	Me	<i>p</i> -ClC ₆ H ₄	80	8 ^[e]	7a , 33	> 99
7	Me	<i>p</i> -ClC ₆ H ₄	60	15 ^[e]	7a , 49	> 99
8	Me	Ph	60	15 ^[e]	8a , 28	> 99
9	Me	CO ₂ Et	80	4 ^[f]	9a , 61	97
10	Et	<i>p</i> -NO ₂ C ₆ H ₄	80	4	4b , 96	> 99
11	Et	<i>p</i> -CNC ₆ H ₄	80	6	5b , 72	> 99
12	Et	<i>p</i> -CF ₃ C ₆ H ₄	80	6	6b , 61	> 99
13	(CH ₂) ₂ Ph	<i>p</i> -NO ₂ C ₆ H ₄	100	8	4c , 66	> 99 ^[g]
14	(CH ₂) ₂ Ph	<i>p</i> -CNC ₆ H ₄	100	8	5c , 61	> 99 ^[g]

[a] A mixture of aldehyde (0.3 mmol), RBF₃K (0.45 mmol), and [RhCl(cod)]₂ (2.5% mol) in deoxygenated 1,4-dioxane/H₂O (6:1; 1.65 mL) was stirred at 60–100°C. [b] Yield of isolated product. [c] Stereochemical retention is meant to imply the degree of retention relative to the starting material rather than retention versus inversion. Determined by HPLC on a chiral stationary column (see the Supporting Information). [d] The absolute configuration was assigned by comparison of the corresponding ketone **10** (Scheme 3) with literature data: see Ref. [17]. All others are assigned by analogy. [e] Starting aldehyde remained after 8 h, but all the trifluoroborate salt was consumed and the product of proto-deboronation was observed. At higher temperature (80–100°C), a lower yield was obtained, but without loss of enantioselectivity [f] Four equivalents of aldehyde were used with respect to (*R*)-**3a**. [g] The e.r. value was determined on the corresponding ketone after oxidation using TEMPO (Scheme 3).

aldehydes only gave low yields (Table 1, entry 8). Glyoxylates were suitable aldehyde partners giving the 1,2-adduct in moderate yield (Table 1, entry 9). The more-hindered salts **3b** and **3c** could also be employed with the activated aldehydes, thus demonstrating the scope in the trifluoroborate salt partner (Table 1, entries 10–14).^[14] In all cases, and with all of the aldehydes examined, essentially complete retention of configuration was obtained at the fragile benzylic center. Chiral benzylic organometallic reagents are notoriously unstable towards racemization, but we have shown that the benzylic organorhodium (or organoboron, see below) intermediate is configurationally stable even at 100°C.^[15]

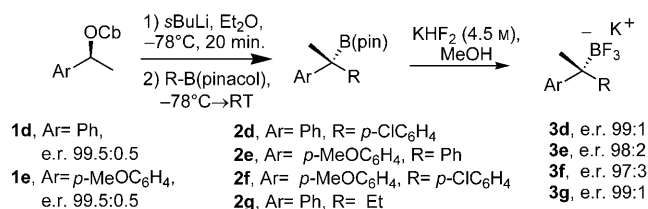
As expected, no control of the carbinol center was observed and a 1:1 mixture of diastereoisomers was isolated. Nevertheless, the alcohols could be oxidized to the corresponding ketones **10–12** without any detectable racemization using TEMPO (Scheme 3).^[16] Furthermore, by correlation of the chiral ketone **10** with the literature we were able to confirm that the addition of the secondary trifluoroborate salt occurred with retention of configuration.^[17]



6a, R = Me, X = CF₃ **10**, R = Me, X = CF₃, 84%, e.r. 96:4
4c, R = CH₂CH₂Ph, X = NO₂ **11**, R = CH₂CH₂Ph, X = NO₂, 84%, e.r. 96:4
5c, R = CH₂CH₂Ph, X = CN **12**, R = CH₂CH₂Ph, X = CN, 97%, e.r. 95:5

Scheme 3. TEMPO-mediated oxidation of the alcohols **6a**, **4c**, and **5c**. TEMPO = 2,2,6,6-tetramethyl-1-piperidinoxyl (free radical).

Having successfully demonstrated that chiral secondary alkyl trifluoroborate salts could couple with aldehydes,^[14] we considered extending the methodology to the even more challenging tertiary substrates. These were easily prepared, in high enantioselectivity through a related lithiation–borylation reaction, again by using methodology that we recently reported (Scheme 4).^[18]

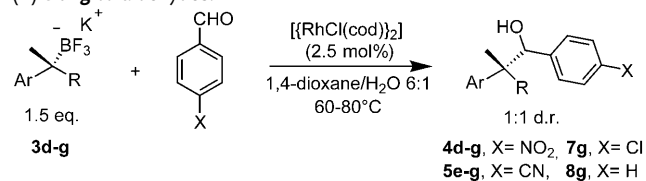


Scheme 4. Synthesis of chiral tertiary potassium trifluoroborate salts. Pin = pinacol.

Remarkably, the enantioenriched diarylalkyl trifluoroborate salts **3d–f** were able to couple with aldehydes in the presence of the same rhodium catalyst without interference from β-hydride elimination and without erosion in the enantioselectivity of this exceptionally fragile stereogenic center. This process was general for a range of trifluoroborate salts, although as before was limited to relatively reactive aldehydes (Table 2, entries 1–6). Perhaps, even more surprising was the success in coupling the dialkylaryl trifluoroborate salt **3g** with aldehydes (Table 2, entries 7–10) since it would be expected to undergo slower transmetalation and more rapid β-hydride elimination than the secondary arylalkyl trifluoroborate salt. Furthermore, these processes generate quaternary stereogenic centers with essentially perfect enantioselectivity. The reaction of such hindered boron derivatives, the complete transfer of chirality of especially fragile stereocenters, and the lack of β-hydride elimination are all noteworthy features of the novel chemistry.

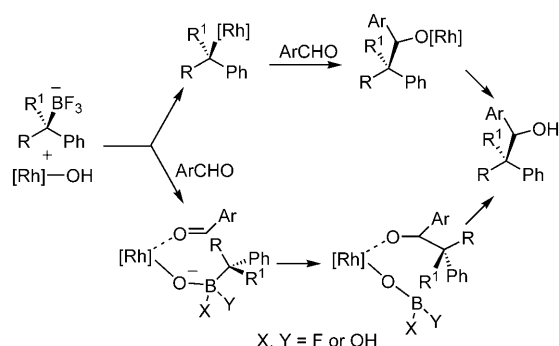
The mechanism of the reaction is intriguing. By analogy with 1,4- and 1,2-addition of boronic acids to electrophiles,^[1c,2] one would expect initial transmetalation to rhodium followed by 1,2-addition (Scheme 5). An alternative mechanism is that the hydroxy–rhodium complex coordinates to the boron derivative and aldehyde followed by direct formation of a C–C bond. The latter mechanism would account for the complete stereoretention and the lack of β-hydride elimination.

Table 2: 1,2-Addition of the tertiary chiral potassium trifluoroborate salts (**3 d–g**) to aldehydes.^[a]



Entry	Trifluoroborate salt (3 d–g) Ar	R	X	T [°C]	t [h]	Yield [%] ^[b]	Stereoret. [%] ^[c]
1	Ph	<i>p</i> -ClC ₆ H ₄	NO ₂	60	6	4 d , 84	> 99
2	Ph	<i>p</i> -ClC ₆ H ₄	NO ₂	80	2	4 d , 68	> 99
3	<i>p</i> -MeOC ₆ H ₄	Ph	NO ₂	60	6	4 e , 82	> 99
4	<i>p</i> -MeOC ₆ H ₄	Ph	CN	60	6	5 e , 76	> 99
5	<i>p</i> -MeOC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	NO ₂	60	20	4 f , 89	> 99
6	<i>p</i> -MeOC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	CN	60	24	5 f , 71	> 99
7	Ph	Et	NO ₂	80	2	4 g , 87	> 99
8	Ph	Et	CN	80	2	5 g , 90	> 99
9	Ph	Et	Cl	60	15 ^[d]	7 g , 44	> 99
10	Ph	Et	H	60	15 ^[d]	8 g , 35	> 99 ^[e]

[a] A mixture of aldehyde (0.3 mmol), RBF₃K (0.45 mmol), and [[RhCl(cod)]₂] (2.5 mol%) in deoxygenated 1,4-dioxane/H₂O (6:1; 1.65 mL) was stirred at 60–100°C. [b] Yield of isolated product. [c] Stereochemical retention is meant to imply the degree of retention relative to the starting material rather than retention versus inversion. Determined by HPLC on a chiral stationary phase (see the Supporting Information). [d] Starting aldehyde remained after 15 h, but all the trifluoroborate salt was consumed and proto-deboronation was the main side reaction. [e] The e.r. value was determined on the corresponding ketone. The absolute configuration of **8 g** (entry 10) was assigned by comparison with literature data: see Ref. [19]. All others are assigned by analogy.



Scheme 5. Possible mechanisms for 1,2-addition.

tion observed, which present unusual features had initial transmetalation to rhodium taken place.^[20]

In conclusion, we have shown that secondary and tertiary alkyl trifluoroborate salts couple with aldehydes in the presence of [[RhCl(cod)]₂] in good yield and with complete retention of stereochemistry of the initial chiral trifluoroborate salt. In fact, the complete retention of stereochemical information during the transformation of a chiral organometallic compound is rather rare in organic chemistry. The lack of β -hydride elimination is also especially noteworthy and bodes well for future application to other classes of reactions. Studies in this area are currently in progress.

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