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Stereoselective Desymmetrization of *gem*-Diborylalkanes *via* "*trifluorination*"

Nivesh Kumar, Reddy Rajasekhar Reddy, and Ahmad Masarwa*

Dedication ((optional))

Abstract: An efficient and general method for the chemoselective synthesis of unsymmetrical *gem*-diborylalkanes is reported. This method is based on a novel late-stage desymmetrization via nucleophilic *"trifluorination"*, providing chiral *gem*-diborylalkanes bearing a trifluoroborate group. The reaction offers a highly modular and diastereoselective approach to synthesize *gem*-diborylcyclopropanes. The utility of the *gem*-diborylalkane building blocks was demonstrated by selective post-functionalization of the trifluoroborate group. These functionalizations include inter- and intra-Pd-catalyzed Suzuki−Miyaura coupling reactions.

gem-Diborylalkanes have recently emerged as a versatile class of intermediates for preparing alkylboron compounds via chemoselective transformations.[1] These bisnucleophilic compounds (termed sp^3-geminated organodimetallics)[2] have increasingly attracted much attention from synthetic chemists,[1a, 3] particularly for constructing C–C bonds, *e.g.*, the pioneering work reported by Shibata in which he developed the first Pd-catalyzed Suzuki−Miyaura cross-coupling of 1,1-diborylalkanes.[4] Although many traditional approaches to the formation of C–C bonds have been made available by using symmetrical *gem*-diboryalkanes (*e.g.*, **10** Scheme 1D),[5] methods for cross coupling with unsymmetrical *gem*-diboryalkanes[6] *via* C–B bond activation have not been satisfactorily addressed and could unveil new opportunities for sequential bond formation. As such, advances that accomplish the selective synthesis of unsymmetrical *gem*-diborylalkanes and their transformation have the potential to drastically improve the synthesis of organic molecules.

As a part of a general program to investigate the reactivity and selectivity of *gem*-diborylalkanes in cross-coupling transformations, we sought to prepare variants bearing a mono-trifluoroborate-salt group (**11**) because, unlike boronic-esters, e.g., the Bpin group, mono-alkyl-trifluoroborate salts are known to be easily activated and to undergo rapid transmetalation with transition metal complexes.[7] In general, owing to their air-, moisture-, shelf -, and thermal stability, as well as their occurrence as free-flowing crystalline solids, mono-trifluoroborate-salts have now become extremely popular reagents in synthesis.[8] Their geminal analogues could offer new opportunities for reactivity. This holds promise for expanding the range of boron-based cross-coupling partners.[9]

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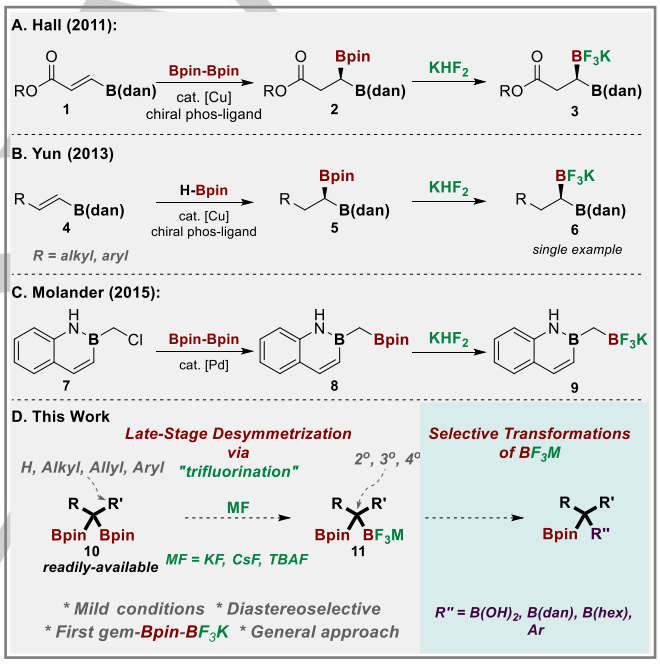
Most of the *gem*-diborylalkanes bearing boronic acid or ester groups (e.g., **10**) are readily and commercially available.[10] However, until very recently, there has been a lack of versatile and efficient synthetic methods to access *gem*-borylalkanes containing a trifluoroborate group (e.g., **11**, Scheme 1D). To date, there are only three reported methods for the synthesis of secondary and tertiary *gem*-diborylalkanes of which one of the groups is a trifluoroborate salt (**3, 6, 9**, Scheme 1).[11]



Scheme 1. Overview for the synthesis of *gem*-diborylalkanes possessing trifluoroborate salts.

In this context, Hall[11b, 12] reported the first preparation of a chiral, enantioenriched 1,1-diboronyl-BF_3K compound (**3**) through a stepwise sequence of a copper-catalyzed conjugate addition of the B_2pin_2 reagent to a 1,8-diaminonaphthalenyl (dan) 3-boronyl enoate (**1**), followed by the reaction of the diboryl product (**2**) with KHF_2 (Scheme 1A). Similarly, in 2013, Yun[13] reported the asymmetric synthesis of 1,1-diborylalkanes –BF_3K (**6**) via regio- and enantioselective copper(I)-catalyzed hydroboration of borylalkenes (**4**) and the subsequent reaction of the product (**5**) with KHF_2 (Scheme 1B). Recently, in 2015, Molander[11a] developed a method for the synthesis of an achiral class of potassium 2-(trifluoroboratomethyl)-2,1-borazaronaphthalenes (**9**). It is noteworthy that in order to obtain the BF_3K group in **3, 6,** and **9**, unsymmetrical *gem*-diborylalkanes bearing groups that differed in reactivity were employed. For example, B(dan) is a

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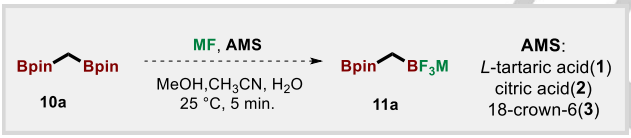
protected boronic acid with lower reactivity[14] towards KHF_2 as compared to Bpin.

Although these commendable methods provide an elegant means to access *gem*-diborylalkanes-BF_3K, they are inherently limited as (1) a large number of synthetic steps are required for their preparation, (2) the use of environmentally unfriendly conditions, e.g., KHF_2 salts that etch glass, (3) the geminal-borylated carbon in **11** can only be secondary or tertiary, (4) the geminal-borylated carbon can only be replaced with alkyl groups, and (5) because a special masked boron moiety is required, none of the existing examples (**3**, **6**, **9**) use the more synthetically useful Bpin group.[11b] Therefore, it became clear to us that a milder, more efficient, and general methodology for simplifying the synthesis of this class of *gem*-diboryalkanes was necessary.

To this end, we envisioned that a desymmetrization-based [15] approach of symmetrical *gem*-diborylalkanes could provide an attractive solution (Scheme 1D). This goal could be accomplished through a nucleophilic *"trifluorination"*[16] of *gem*-diborylalkanes, as illustrated in Scheme 1D.[17] To achieve this aim, we sought to employ conditions similar to those developed by Lloyd-Jones[18] for the conversion of mono-boronic acids to trifluoroborate potassium salts (Table 1). Initially, we examined the commercially available *gem*-diborylmethane **10a**. We were pleased to observe **11a** as the sole product after a 5 min reaction time, under green and mild conditions using either KF (entry 3), CsF (entry 5), or TBAF (entry 9) as salts and an alkali metal sponge[18] (AMS), e.g., *L*-tartaric acid (entry 3) or citric acid (entry 7). The product was obtained by precipitation, thus making product isolation rapid and simple. Notably, product **11** was not obtained in the presence of KHF_2 or in the absence of AMS (entries 1–2). Moreover, the selectivity and yield of **11** are not affected when an excess of MF or AMS is used.

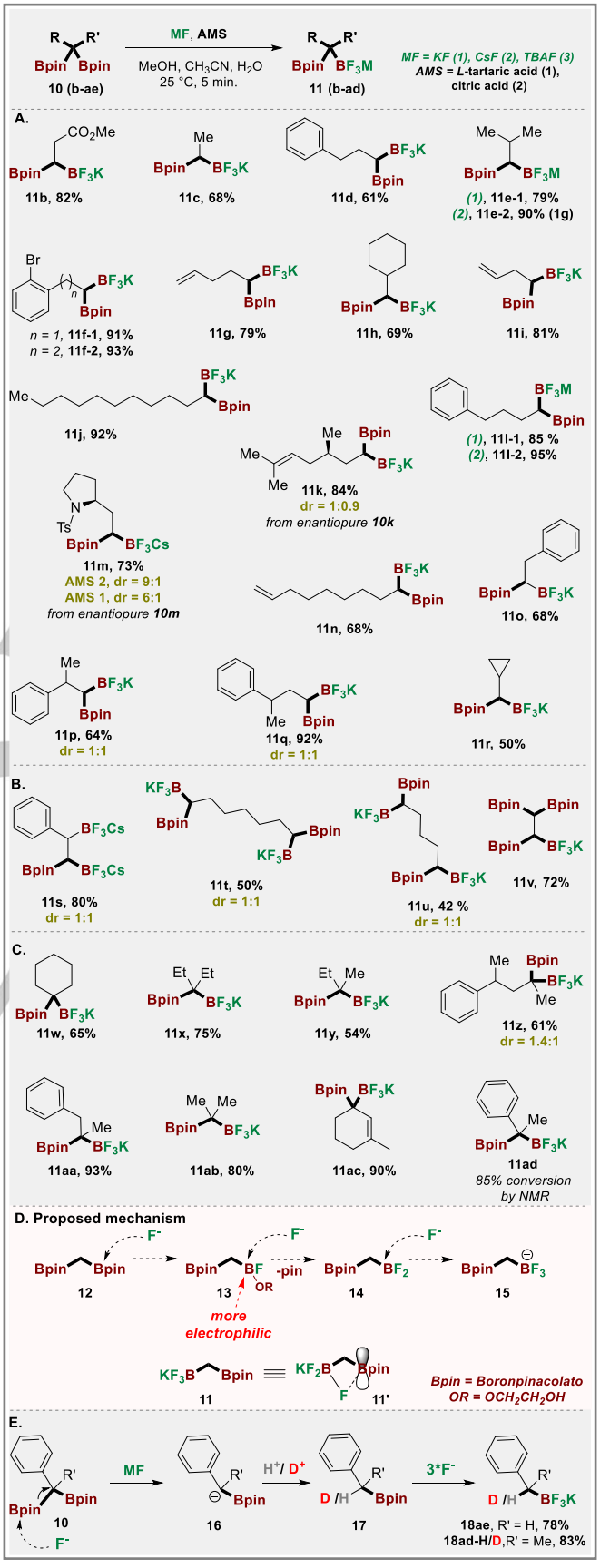
Table 1. Optimization of the reaction conditions[a-b]



Entry	MF	AMS	Yield[%]	Entry	MF	AMS	Yield[%]
1	KHF_2	-	0[c]	6	LiF	**1**	13
2	KF	-	0	7	KF	**2**	90
3	KF	**1**	86	8	KF	**3**	60
4	AgF	**1**	0	9	TBAF	-	FC[d]
5	CsF	**1**	92	10	KHF_2	**1**	0[c]

[a]Reactions were carried out with 0.5 mmol of **10a** and 1.025 mmol of **AMS** at room temperature. [b]Isolated yields. [c]Decomposition of the starting material. [d]Full conversion (FC) by ^1H NMR.

Under the optimized conditions, the scope of the desymmetrization reaction was examined (Scheme 2). Our results show that we can selectively convert symmetrical *gem*-diborylalkanes possessing alkyl, allyl, and aryl groups (up to 37 examples; **10**) with secondary, tertiary, quaternary, and cyclic groups into unsymmetrical *tri*fluoroborated *gem*diborylalkanes (**11b-ad**). Moreover, when polyborylated compounds (**10s**, **10t**, **and 10u**) with two groups of *gem*-diboryls were used, the *"trifluorination"* reaction chemoselectively desymmetrized both sites to obtain **11t** and **11u** in good yields (Scheme 2B).



Scheme 2. Scope of the desymmetrization reaction via nucleophilic *"trifluorination"* and rationalization for the selectivity.

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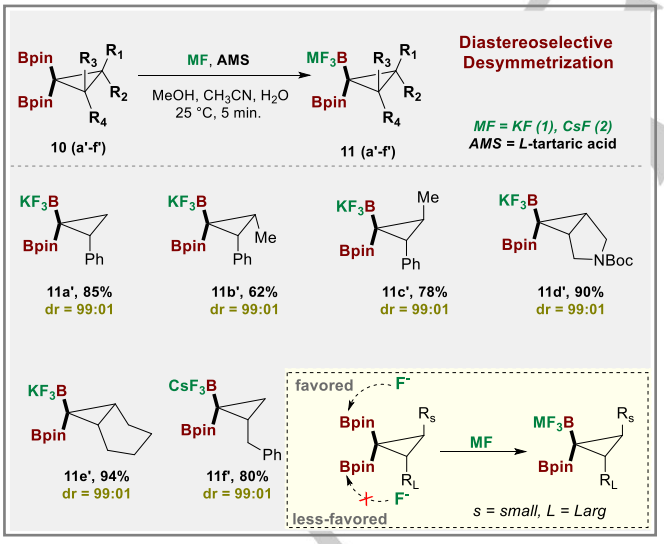
However, when *tetra*borylated-ethane **10v** was treated with excess KF under the reaction conditions, **11v** was obtained as a single product. Upon scale-up, the KF/L-tartaric acid process was equally as efficient and easy to carry out, thus generating, for example, 1 g (90%) of **11a** and 1 g (95%) of **11e** (Scheme 2A). Interestingly, when enantiopure *gem*diboryl-proline **10m** was subjected to the reaction conditions using AMS (citric acid or L-tartaric acid), a diastereoselectivity of 9:1 or 6:1, respectively (see **11m,** Scheme 2A) was observed. This is likely the result of a directing group effect for the tosyl-substituted proline.

We believe that the mechanism[17-18] underlying the selectivity – *i.e., the observation* of *only the mono-BF_3K product, while the other boron substituent remains untouched* – arises from "*tandem*" in the fluorination step in which the first nucleophilic fluoride attacks the vacant p-orbital of one of the boron centers of **12** (Scheme 2D), As a result, this fluorinated-boron (see **13**) becomes more electrophilic; hence, it forces the second and then the third nucleophilic fluorides to attack only the originally fluorinated boron center (**12-15**, Scheme 2D). Consequently, the generated borate (BF_3) moiety in (**11**) develops a partial negative charge on the fluorides, and this partial negative charge stabilizes the flanking Bpin group[19] toward subsequent attack by fluoride, this stabilization may undergo through bridging fluoride structure (see **11'**, Scheme 2D).[20] [4]

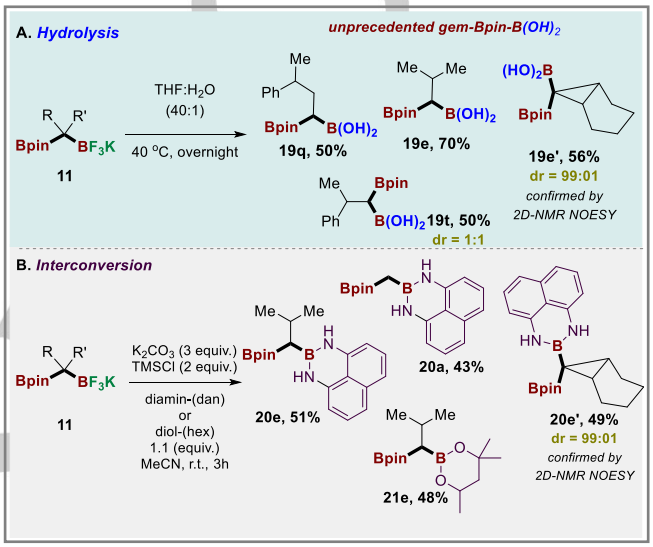
In the case of R = Ph (in **10ae**, **10ad**), different conditions (i.e., **11ad** observed by ^{11}BNMR using MeCN) had to be employed because of the competing formation of a protodeboronation side product (**18,** Scheme 2E).[5m, 21] This α-protodeboronation product (**18**) is believed to arise from a scenario involving a discrete doubly stabilized anion **16**, which is protonated (or deuterated) at the α-position,[5j] at which point the remaining Bpin group undergoes *trifluorination* (Scheme 2E).



Scheme 3. Diastereoselective desymmetrization of *gem*-diborylcyclopropanes **10** (**a'-f'**) and the rationale for the diastereoselectivity.

Importantly, the desymmetrization process also displays diastereoselectivity when applied to *gem*-diborylcyclopropanes (**10a'-f',** Scheme 3).[22] The structure and relative configuration of the diastereomers of diborylatedcyclopropanes[22b] (**11a'-f'**) were unambiguously determined by a 2D-NMR NOESY and COSY studies of **11a'-f'**, and are consistent with a nucleophilic "*trifluorination"* of the Bpin group on the less sterically hindered face of the cyclopropane (Scheme 3, yellow-box).[23] Remarkably, even when both faces of the cyclopropane are only slightly sterically differentiated, e.g., Ph vs. Me in the *trans*-Ph-Me cyclopropene **10c**, the desymmetrization afforded product **11c'** as a single diastereomer.

Having these valuable *gem*-diborylalkanes-BF_3K (**11**) in hand, we sought to demonstrate their synthetic utility in selective transformations of the BF_3M group as described in Scheme 4 and 5.[5j, 21b, 21c]

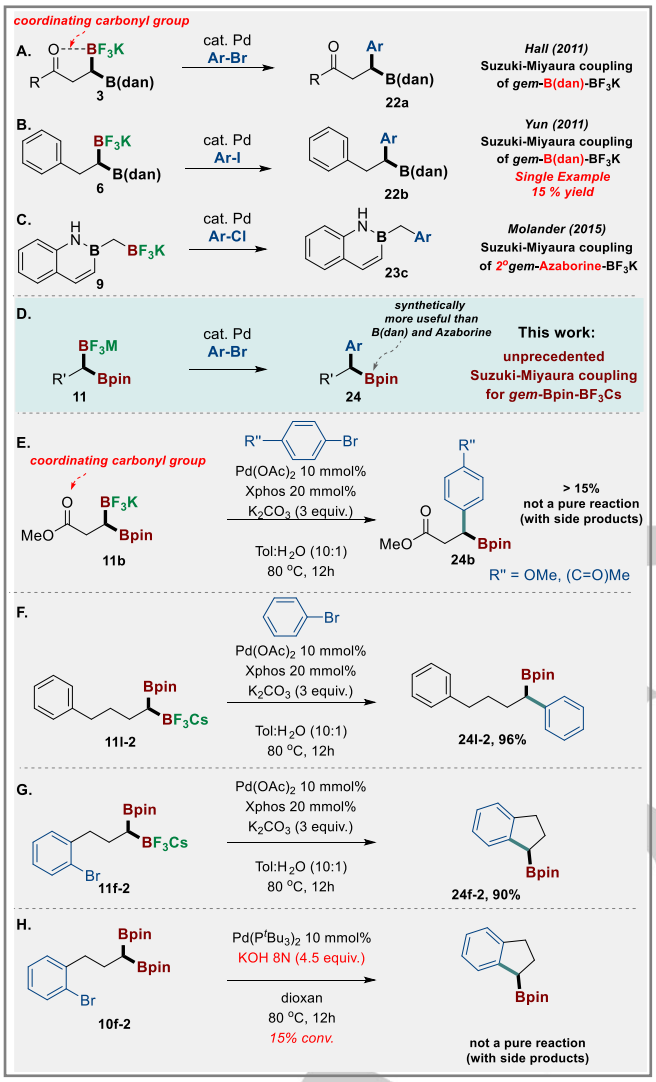


Scheme 4. Selective transformations of *gem*-Bpin-BF_3K (**11**).

We were intrigued to observe that *gem*-diborylalkanes (**11**) could be selectively converted, for the first time, into *gem*-diboryls containing a boronic-acid moiety ($B(OH)_2$) (see **19**) through a simple hydrolysis process as described in Scheme 4A.[24] Gratifyingly, the *gem*-diborylalkanes-BF_3K (**11**) can be directly converted to different unsymmetrical *gem*-diborylalkanes (**20-21,** Scheme 4B).[25]

Next, we tried the Pd-catalyzed inter- and intra-molecular Suzuki–Miyaura cross coupling reaction on **11** (Scheme 5D). Such a cross coupling reaction has been reported by Hall,[12] Yun,[13] and Molander[11a] on different systems with *gem*-B(dan)-BF_3K and *gem*-azaborine-BF_3K (Schemes 5A-C). However, no reports exist for a reactant bearing the *gem*-Bpin-BF_3M groups. These compounds could offer an opportunity to overcome some limitations of the previously reported methods including low yield,[13] the need for coordinating groups,[12b] and for using a strong bases such as KOH[4] (Schemes 5A-C, highlighted in red). Subjecting **11b** to the same reaction conditions reported by Hall[12a] revealed **24b** in negligible yield with many side products e.g. the proto-deboronation product (Scheme 5E). However, **11l** without a coordinating carbonyl group affords the cross-coupling product **24l** with excellent yield (Scheme 5F).[5m] Moreover, the intramolecular cross coupling reaction of **11f-2** afforded a clean cyclization-product (**24f-2**) in good yield (Scheme 5G). However, in comparison reactions with *gem*-Bpin-Bpin (**10f-2**) under the same reactions conditions, or under the reaction conditions of

Shibata[20] using KOH as a base, product **24f-2** was either not obtained or observed with very low conversion along with the proto-deboronation side product, respectively (Scheme 5H). These observations demonstrate the critical role of the *gem*-Bpin-BF_3M unit of **11** on mild, efficient and selective transformations without a need of a coordinating carbonyl group and providing a direct access to the product containing the Bpin functionality intact, which is considered more synthetically useful than B(dan) and azaborine groups.[12b]



Scheme 5. Selective inter- and intra-molecular Suzuki−Miyaura cross-coupling of (**11**).

In summary, we have developed the first desymmetrization method of *gem*-diborylalkanes *via* nucleophilic *"trifluorination"*, thus allowing the transformation of symmetrical *gem*-diBpin-alkanes into *gem*-diborylalkanes containing trifluoroborate groups. Compared to the reported methodologies involving KHF_2, this reaction constitutes a mild, general, and convenient approach to synthesize a variety of differently substituted *gem*-diborylalkanes possessing a trifluoroborate moiety. This process exhibits high diastereoselectivity when *gem*-diborylcyclopropanes are desymmetrized. The trifluoroborate (in **11**) groups can be selectively transformed into a collection of unsymmetrical *gem*-diborylalkanes, which underline the usefulness of **11** as intermediates for the general method for interconversion of *gem*-boronic acid. Moreover, selective inter- and intra-molecular Suzuki−Miyaura cross-coupling has been described using mild conditions. Studies to achieve an enantioselective desymmetrization transformation using chiral phase transfer catalyst,[26] as well as new transformations of *gem*-diborylalkanes bearing a BF_3M group are currently under investigation and will be reported in due course.

Acknowledgments ((optional))

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Keywords: *gem*-diborylalkanes • desymmetrization • organotrifluoroborate-salts • cyclopropanes • Suzuki−Miyaura cross-coupling

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[26] using *L*-tartaric acid with **10m** and **10k**, gave **11m** and **11k** with a low ee % of 10% and > 5% respectively.

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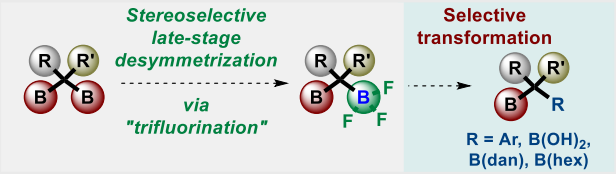

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Stereoselective Desymmetrization of gem-diborylalkanes via "trifluorination"

"*3*F-*" desymmetrized *gem*-diboryls: In this work we have developed an efficient method for the chemo-, regio-, and diastereo-selective synthesis of *gem*-diborylalkanes. It is based on a novel late-stage desymmetrization method via nucleophilic *"trifluorination"*; it gains access to chiral *gem*-diborylalkanes possessing trifluoroborate salts. The knowledge gained provided us with an in-depth understanding of their reactivity for additional transformations. This enabled us to develop optimized reaction conditions for their BF_3 functionalization.