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γ-Silylboronates in the Chiral Brønsted Acid-Catalysed Allylboration of Aldehydes

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The use of functionalised allylboronic esters in the catalytic enantioselective allylboration of aldehydes is described for the first time. γ-Silylallyl pinacolate derivatives give rise to α-silyl homoallylic alcohols in high yields, with complete diastereoselectivities and high enantioselectivities, in most of the cases. The usefulness of such intermediates is showcased by their transformation into fluorinated allylic alcohols.

The fifty-years old allylboration reaction is still one of the most useful methods in organic synthesis.[1,2] In a single operation a new carbon-carbon bond is formed, a new stereogenic center created and two versatile functionalities, namely an alcohol and a C-C double bond, installed in the proximity of one another. Moreover, the use of γ-substituted allylborane derivatives (crotylboronates being the most widely used) regio- and stereospecifically provides two consecutive stereocenters.[3] For all these features, the allylboration reaction, and related transformations, have attracted the attention of some of the most important synthetic organic chemists of the second half of the last century who developed chiral allylborating reagents allowing the preparation of homoallylic alcohols with a very high degree of stereocontrol, which propelled the use of this reaction in natural product total synthesis.[4,5] The new century has witnessed the advent of long sought-for catalytic enantioselective allylboration reactions.[6] Among them, the chiral Brønsted acid catalysed allylation developed by Antilla stands out for its experimental simplicity, efficiency and environmentally benign nature.[7-9] Despite the impressive development achieved in the field, to the best of our knowledge the use of γ-functionalized allylborating reagents in asymmetric catalysis has been *completely overlooked*. Reagents of this kind give rise to vicinally funtionalised homoallylic alcohols in a regio- and diastereospecific manner. The synthetic versatility of allylsilanes inspired us to initiate our study on γ-functionalised allylboronates with the corresponding silylated analogues (Figure 1). Chiral derivatives of this kind have extensively been used by Roush and others for the synthesis of 1,2- and 1,4-diols, among other building blocks.[10] In addition, Krische recently reported an iridium catalysed silylallylation using SEGPHOS as chiral ligand for the synthesis of analogous α-silyl homoallylic alcohols.[11] Herein, we report our preliminary results on the use of γ-silyl allylboronic pinacolate derivatives in asymmetric catalysis for the first time (Figure 1).

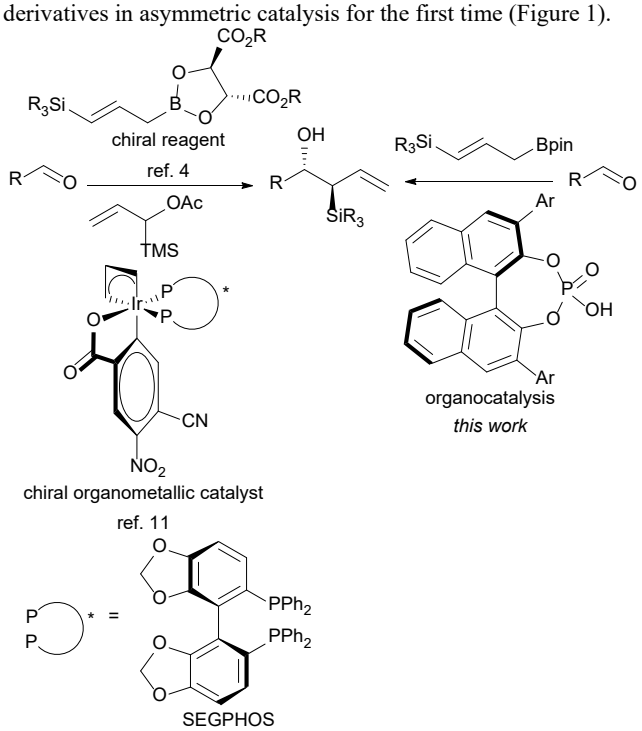
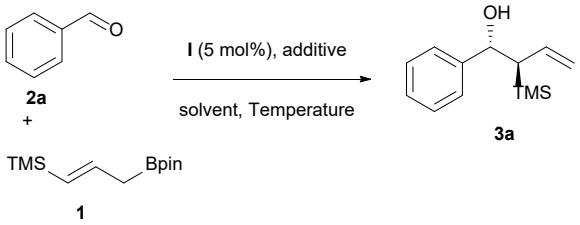
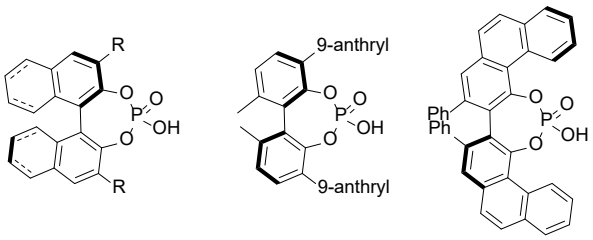


Figure 1. Our organocatalytic approach to α-silyl homoallylic alcohols.

Prompted by the availability of TMSallylBpin (**1**) in just one step from the corresponding commercially available allylic alcohol[12] we decided to study its performance in the chiral Brønsted acid catalysed allylboration reaction using benzaldehyde **2a** as the model substrate (Table 1).

Table 1. Optimisation of the reaction conditions





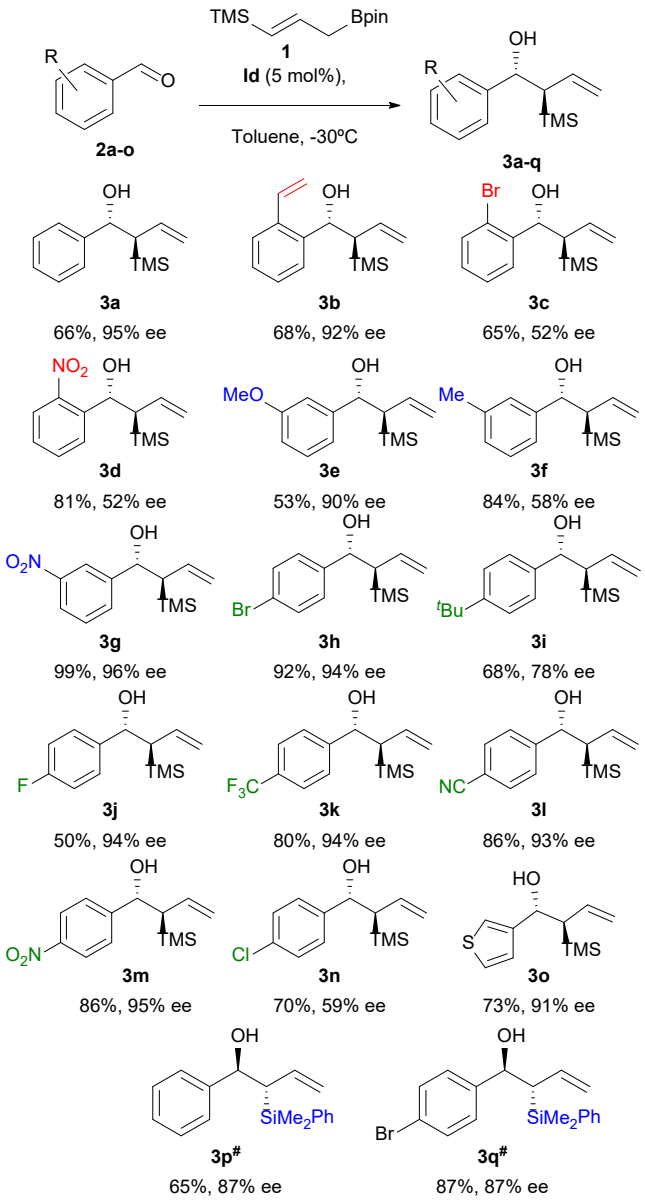
Ia, R = 2,4,6-(^{i}Pr)$_3$-C$_6$H$_2$
Ib, R = 3,5-(CF$_3$)$_2$-C$_6$H$_3$
Ic, R = SiPh$_3$
Id, R = 9-anthryl
Ie, R = 9-anthryl (H$_8$)

If **Ig**

Entry	I	Addit.	Solv.	Temp. ºC	3a (%)	e.e. (%)
1	**Ia**	-	TolH	-30	74	36
2	**Ia**	-	DCM	-30	73	34
3	**Ia**	4ÅMS	TolH	-30	80	11
4	**Ib**	-	TolH	-30	71	6
5	**Ic**	-	TolH	-30	50	16
6	**Id**	-	TolH	-30	66	95
7	**Ie**	-	TolH	-30	50	90
8	**If**	-	TolH	-30	39	67
9	**Ig**	-	TolH	-30	42	2
10	**Id**	4ÅMS	TolH	-30	90	67
11	**Id**	-	DCM	-30	73	90
12	**Id**	-	TolH	-50	33	20
13	**Id**	-	TolH	25	64	84

The use of (*R*)-TRIP **Ia** under the optimised reaction conditions reported by Antilla[7a] afforded the expected α-silyl homoallylic alcohol **3a** in good yield and with complete diastereoselectivity, although with modest enantiocontrol (Table 1, entry 1). A comparable level of enantiocontrol was observed when DCM was used as solvent (Table 1, entry 2) and, intriguingly, the addition of 4Å MS proved deleterious for the enantioselectivity (Table 1, entry 3).[13] In view of these unsatisfactory results, we decided to explore other chiral Brønsted acid catalysts. A screening of common BINOL-derived phosphoric acids (Table 1, entries 4-6) allowed identifying **Id** as an effective catalyst affording the product in high enantiomeric excess without affecting the yield nor the diastereoselectivity (Table 1, entry 6). Regarding structurally related catalysts, partially hydrogenated **Ie** provided slightly lower enantiocontrol (Table 1, entry 7), while the biphenol derivative **If** proved less efficient (Table 1, entry 8). On the other hand, VAPPOL derivative **Ig**, showed an almost complete lack of enantiocontrol (Table 1, entry 9). Further optimisation of the reaction conditions did not lead to any improvement (Table 1, entries 10-13).

With these optimised conditions in hand (Table 1, entry 6), the scope and limitations of the new methodology were established (Scheme 1). Excellent *anti* selectivity (>95:5) was observed for all of the cases. Regarding the substitution pattern, as a general trend, substrates bearing substitution at the *ortho* position afford only moderate enantioselectivities (compare **3d** with **3g** and **3m** or **3c** with **3h**); however, good enantiocontrol is observed for *ortho*-vinyl derivative **3b**. The dependence of the enantioselectivity with the electronic nature of the substituents also seem to follow a general trend; while electron-withdrawing groups afford enantioselectivities above 90% (see **3g,h,j,k,l,m**), mild electron-donating groups do not exceed 80% (see **3f,i**).† Interestingly, the *m*-methoxy derivative is obtained in a relatively high 90% ee suggesting that the –I effect overrides the +R. Finally, the more robust dimethylphenylsilyl derivative could also be obtained although in modest 87% ee (**3p,q**).[#]



Scheme 1. Scope and limitations.

The relative and absolute stereochemistry of the two newly created stereocenters was unambiguously established by means of X-ray diffraction experiments on derivative **3m** (Figure 2). Those of others were surmised by analogy.

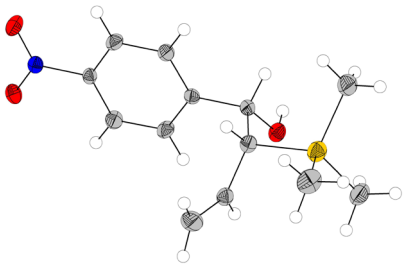


Figure 2. ORTEP diagram of compound **3m**.

As anticipated, the relative stereochemistry is *anti*, reflecting the *E* stereochemistry of the starting allylboronate. With regard to absolute stereochemistry, the *re*-face attack suggests that the reaction proceeds through a two-point transition state analogous to the one proposed by Goodman and Houk for allylboration (Figure 2, the absolute configuration changes due to priority considerations).[14] This transition state accounts for the observed lower enantioselectivity obtained with TRIP, since the bulky TMS group might clash with the tris(isopropyl)phenyl substituents of TRIP. Apparently, the less bulky 3,3'-bis(9-anthryl) derivative shows an optimum balance allowing enantiodifferentiation; the pinacol being still the most hindered substituent occupies the empty pocket while the TMS group must be accommodated in the sterically demanding pocket.

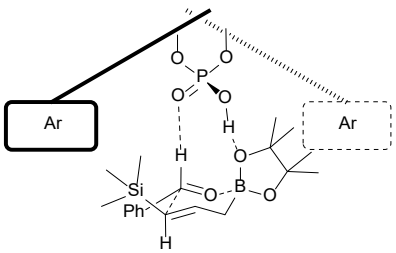
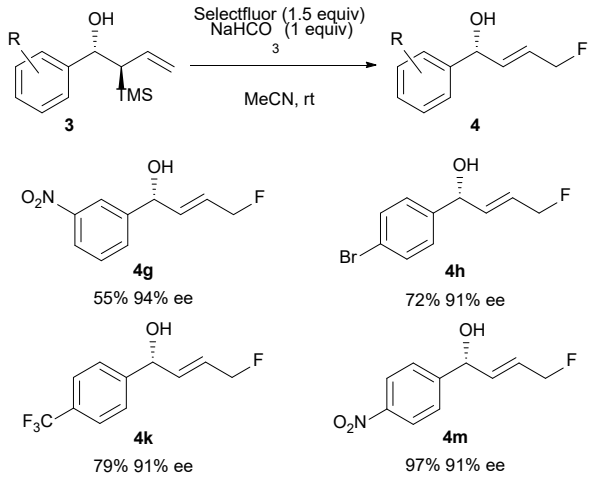


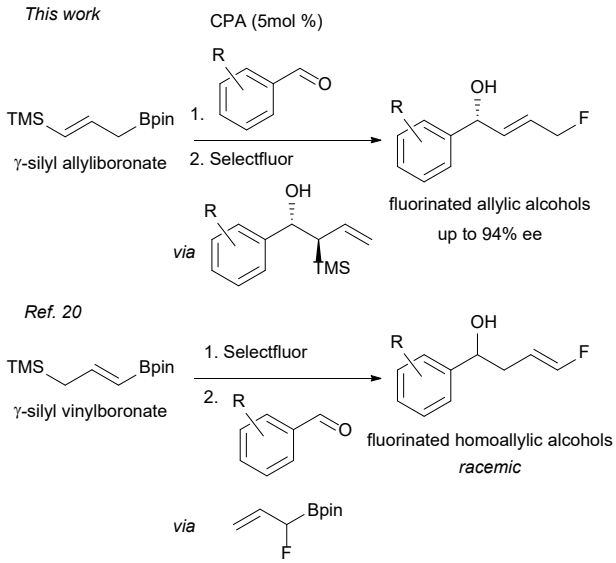
Figure 3. Suggested stereochemical model

Allylsilanes are very versatile reagents in organic synthesis.[15] Undoubtedly, Sakurai-like nucleophilic addition to carbonyl compounds represents the most popular reaction of synthetic value.[16] In a first approach, several reactions of this kind (Lewis or Brønsted acid catalysed allylation of carbonyl compounds) were assayed on α-silyl homoallylic alcohols **3**.[17] However, elimination was observed under each of the assayed reaction conditions.§ The high stabilisation of the β-silyl benzyl carbocation intermediate accounts for the observed incompatibility of compounds **3** with acidic reaction conditions. Therefore, buffered reaction conditions are required in order to avoid the kinetic and thermodynamically favoured Peterson elimination. Krische recently demonstrated that the DMDO-mediated oxidation of such scaffolds towards the corresponding 1,4-diols was a viable process under buffered conditions.[11] Hence, we wondered if the electrophilic allylic fluorination reported by Gouverneur could be used on our substrates, since acid catalysis is not necessary.[18,19] Disappointingly, the use of the original reaction conditions only achieved small amounts of the desired fluorinated product (>15%) along with the diene as the major product, even when the acetyl protected alcohol was used, indicating that Selectfluor behaves as a strong Lewis acid to promote the elimination. To our delight, treatment of **3g** with Selectfluor under buffered reaction conditions afforded product **4g** in good yield (72 %), as a single stereosiomer and with almost complete preservation of the optical purity.[18a] Next, the generality of this transformation was established using some of the α-silyl homoallylic alcohols shown in Scheme 1 (Scheme 2). Good yields with minor erosion of optical purity and complete *E*-selectivities were observed in all cases.



Scheme 2. Scope of the electrophilic fluorination.

To the best of our knowledge, this is the first available methodology for the synthesis of these versatile intermediates. Recently, the reversed reaction sequence (electrophilic allylic fluorination / allylboration) using isomeric γ-sylilvinylboronates has been described.[20] Hence, while our methodology affords enantioenriched fluorinated allylic alcohols, the complementary one gives rise to isomeric fluorinated homoallylic alcohols, in a racemic fashion (Scheme 3).



Scheme 3. Comparison of the two methodologies.

Conclusions

Since the pioneering work of Brown and Roush, the application of functionalised allylborating reagents in asymmetric synthesis has, for decades, been limited to the use of chiral boronate reagents. In this communication, the application of a γ-functionalised allylboronic ester in a catalytic enantioselective reaction has been reported for the first time. More specifically,

the chiral Brønsted acid catalysed allylboration of aromatic aldehydes with γ-silyl functionalised reagents has been achieved in good yields and with high enantioselectivities in most cases. The synthetic versatility of the thus-obtained α-silylhomoallylic alcohols has been extended to the synthesis of fluorinated allylic alcohols by means of electrophilic fluorination. Further studies aimed to broaden the scope of this transformation, specially to the use of readily oxidisable silyl groups as well as to the introduction of functionalities of other kinds, are currently underway in our laboratories and will be disclosed in due time.

Notes and references

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† With stronger electron-donating substituents, i.e. *p*-methoxy, the corresponding 1,3-diene arising from elimination of the TMSOH moiety was observed as the major product. Accordingly, products **3f** and **3i** are also prone to elimination. For this reason, only ^{1}H NMR spectrum is given for **3f** while small signals of the corresponding diene appear in the ^{13}C NMR spectrum of **3i**.

§ Elimination was also observed when aldehyde allylation was assayed under TBAF-mediated reaction conditions.[21] The Peterson elimination is known to proceed both under acidic and basic reaction conditions.

An independent optimisation was carried out for this substrate leading to the identification of the partially hydrogenated analogue of **Id**, H_8-3,3'-bis(anthryl)binolphosphoric acid **Ie**, as the optimum catalyst for this reaction (see ESI). The *S* enantiomer of the catalyst was used; thus, reversal in the absolute configuration of the final products is assumed.

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Electronic Supplementary Information (ESI) available: experimental procedures, characterization of all new compounds, copies of the spectra and chromatograms and CIF file for compound **3m**. See DOI: 10.1039/c000000x/

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