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Simple, Stable, and Versatile Double-Allylation Reagents for the Stereoselective Preparation of Skeletally Diverse Compounds

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Multifunctional reagents that display chemodivergent reactivity are of great interest for the preparation of novel organic compounds using diversity-oriented and target-oriented synthesis. There are still very few multifunctional reagents that provide high diastereo- and enantiocontrol in a variety of bimolecular and multicomponent reactions, and that are stable, safe, and easy to prepare. In this respect, a few examples were reported of chiral double-allylation reagents of type I[1] and type II[2] based on boron and silicon (Figure 1). Addition of such reagents onto a carbonyl substrate unveils an intermediate that features a second allylmetal unit. Even beyond the need for providing high stereocontrol, there are major chemoselectivity issues in the design of double-allylation reagents. Indeed, the second allylmetal intermediate could compete with the initial reagent and react indiscriminately with the electrophile to give mixtures of products.

There is no general approach to the preparation and use of nonracemic α-functionalized reagents of type III.[3] Here, we describe the first optically active α-trialkylsilylmethyl allylboronates of type III, and we report that their chemodivergent reactivity can be controlled with ease to generate a broad range of useful and diverse products such as propionate units, polysubstituted furans, vinylcyclopropanes, and larger carbocycles.

In our design of a reagent of type III, we anticipated that boron and silicon could be judiciously positioned to react independently with a variety of electrophiles. We first targeted α-trialkylsilylmethyl allylboronate reagents such as **1** (Scheme 1). Their allylic boron unit should add chemoselectively to a first electrophile, such as an aldehyde, without interference from the allylsilane of the addition product. Indeed, additions of 3-substituted allylic trialkylsilanes to carbonyl compounds require activation from strong Lewis acids at relatively high temperatures.[4] Furthermore, the resulting allylic silanes are known to display a broad reactivity that would confer a wide applicability to reagent **1**.[5] A straightforward method for the preparation of optically pure **1** was achieved using a simple Matteson homologation of pinanedioxy ethyleneboronic ester,[6] followed by in situ addition of trimethylsilylmethyl−MgBr (Scheme 1). This "one-pot" preparation provided a 70% yield of reagent **1**, which is robust enough for chromatographic purification and long-term storage. It is noteworthy that pinanediol is available in both enantiomeric forms at a reasonable price.

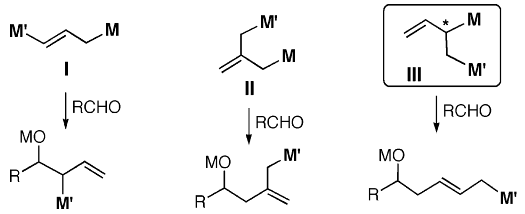


Figure 1. General types of bimetallic double-allylation reagents.

Scheme 1. One-Step Preparation of Optically Active Reagent **1**

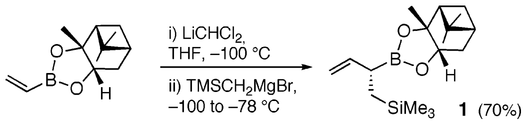
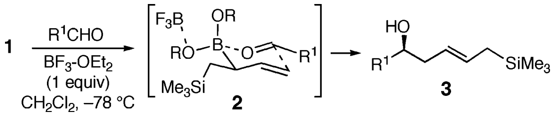


Table 1. Scope of Aldehyde in Additions with Reagent **1**[a]



entry	R¹	product	yield (%)[b]	*E*:*Z*[c]	ee (%)[d]
1	Ph(CH$_2$)$_2$	**3a**	77	>30:1	95
2	*n*-C$_7$H$_{15}$	**3b**	70	>30:1	98
3	*i*-Pr	**3c**	63	>30:1	96
4	BnOCH$_2$	**3d**	70	>25:1	91
5	Ph	**3e**	72	>30:1	95
6	(*E*)-PhCH═CH	**3f**	75	>30:1	79
7	(*E*)-MeCH═CH	**3g**	81	>30:1	96
8	(*n*-C$_5$H$_{11}$)CC	**3h**	85	>30:1	95

[a] Time: 12 h. Typical scale: 0.2−1.0 mmol at 0.2 M. See Supporting Information for more details. [b] Isolated yields. [c] Measured by ^{1}H NMR analysis of crude products. [d] Measured by chiral HPLC of free alcohol, except entries 2, 3, 7, and 8, where an isocyanate derivative was employed.

We found that reagent **1** adds onto aldehydes under uncatalyzed conditions to give the expected homoallylic alcohols, however, with a disappointingly low *E*/*Z* selectivity.[7] In contrast, the low-temperature Lewis acid-catalyzed allylboration manifold[8] provided the products **3** in very high *E*/*Z* selectivity and excellent enantioselectivities (Table 1).[7] Since most products are obtained in over 95% ee and α-substituted allylic boronates are known to transfer chirality with near perfection,[9] the optical purity of reagent **1** is inferred to be >98%. The outstanding *E* selectivity is of crucial importance because the *Z* isomer of **3** is epimeric at the carbinol[9] and would require a separation in the event of a lower selectivity. This issue is avoided with the Lewis acid-promoted conditions, and remarkably, no double-allylation products from further reaction of the allylic silane **3** were observed. A wide range of aliphatic and unsaturated aldehydes are suitable substrates. As depicted in transition structure model **2**, the enantiofacial selectivity is controlled by the configuration of the reagent's α-carbon center and the preference for a pseudo-equatorial orientation of the substituent. The influence of the pinanedioxy unit is likely negligible.[8d] The high degree of *E*/*Z* selectivity can be tentatively explained by a late transition state[10] involving coordination of the Lewis acid to a boronate oxygen.[11]

This new preparation of intermediates **3** is direct and more *E*/*Z* selective compared to previous methods, which involve a cross-metathesis of allylTMS on terminal homoallylic alcohols.[12] The potential versatility of reagent **1** is linked to the rich chemistry of allylic silanes **3**.[5] For example, a condensation with aldehydes afforded the all-cis trisubstituted furans **5**−**7** in very high diastereo- and enantioselectivity (eq 1). The diastereoselectivity is explained by the pseudo-diequatorial arrangement of R^1 and R^2 in transition state model **4**.[13] Remarkably, the unprecedented use of ketones in

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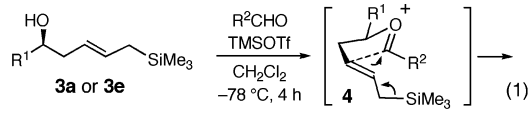
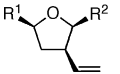
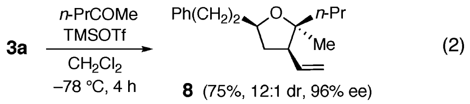
this reaction provides 1,1,2,4-tetrasubstituted furans in high yields and acceptable diastereoselectivities (eq 2). Preliminary results also indicate that a sequential one-pot three-component reaction between **1** and two aldehydes is possible.[14]





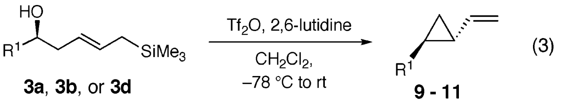
5 - 7

5 $R^1 = Ph(CH_2)_2$, $R^2 = Ph$ (75%, >25:1 dr, 93% ee)
6 $R^1 = Ph(CH_2)_2$, $R^2 = n\text{-}C_7H_{15}$ (82%, >30:1 dr, 95% ee)
7 $R^1 = Ph$, $R^2 = BnOCH_2$ (72%, 25:1 dr, 91% ee)



8 (75%, 12:1 dr, 96% ee)

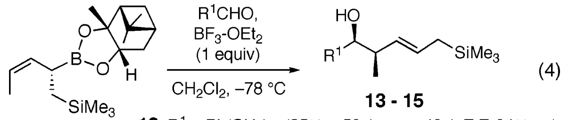
Transformation of the hydroxyl group of products **3** into a triflate triggers, upon warming, the formation of vinylcyclopropanes in high enantio- and diastereoselectivity (eq 3).[12] These vinylcyclopropanes are highly valued synthetic intermediates.[15]



3a, **3b**, or **3d** → **9 - 11**

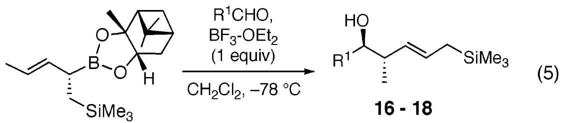
9 $R^1 = Ph(CH_2)_2$ (81%, 20:1 dr, 93% ee)
10 $R^1 = n\text{-}C_7H_{15}$ (72%, 15:1 dr, 95% ee)
11 $R^1 = BnOCH_2$ (56%, 11:1 dr, 90% ee)

The *Z* and *E* crotyl reagents **12** were prepared in high yields from the corresponding 2-propenylboronic esters.[14] Their addition onto aldehydes afforded the *syn* propionate products **13**−**15** and *anti* diastereomers **16**−**18** in high yields and high selectivity (eqs 4 and 5). These adducts undergo the same reactions as allylsilanes **3** to form the corresponding methylated furans and cyclopropanes.[14]



***Z*-12** → **13 - 15**

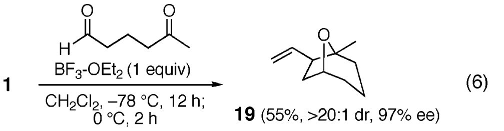
13 $R^1 = Ph(CH_2)_2$ (85%, >50:1 *syn*, >40:1 *E*:*Z*, 94% ee)
14 $R^1 = BnOCH_2$ (90%, >30:1 *syn*, >25:1 *E*:*Z*, 96% ee)
15 $R^1 = Ph$ (94%, >50:1 *syn*, >40:1 *E*:*Z*, 93% ee)



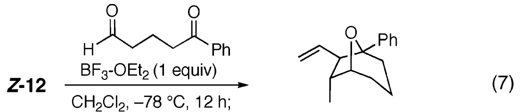
***E*-12** → **16 - 18**

16 $R^1 = Ph(CH_2)_2$ (85%, >50:1 *anti*, >40:1 *E*:*Z*, 95% ee)
17 $R^1 = BnOCH_2$ (80%, >40:1 *anti*, >30:1 *E*:*Z*, 98% ee)
18 $R^1 = Ph$ (98%, >50:1 *anti*, >40:1 *E*:*Z*, 95% ee)

The use of dicarbonyl substrates can provide several opportunities for accessing carbocycles and other ring systems. For example, reagents **1** and (*Z*)-**12** add onto ketoaldehydes to give the oxabicyclic products **19** and **20** via a double-allylation cascade (eqs 6 and 7).



19 (55%, >20:1 dr, 97% ee)



20 (77%, >30:1 dr, 98% ee)

In summary, we have disclosed a new family of simple and efficient double-allylation reagents: the α-trimethylsilylmethyl allylboronate **1** and the crotylboronates **12**. These stable bimetallic reagents add onto a wide range of aldehydes to afford a direct access to hydroxyl-functionalized allylic silanes in very high *E*/*Z* selectivity and excellent enantioselectivity. The use of the Lewis acid-catalyzed allylboration manifold was key to the overall selectivity of this process. Through the hydroxyl-functionalized allylsilane products, reagents **1** and **12** can be exploited in chemodivergent syntheses of various compound classes such as propionate units, polysubstituted furans, vinylcyclopropanes, and larger carbocycles. Other transformations of allylic silanes such as oxidations[5b] and Pd-catalyzed reactions[16] can be envisaged. Thus, reagents **1** and **12** are expected to find multiple applications in natural product synthesis and diversity-oriented synthesis.

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Supporting Information Available: Full experimental details, a proof of absolute stereochemistry (on compound **18**), additional examples, and NMR spectral reproductions for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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