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S_N2' Boron-Mediated Mitsunobu Reactions – A New One-Pot Three-Component Synthesis of Substituted Enamides and Enol Benzoates

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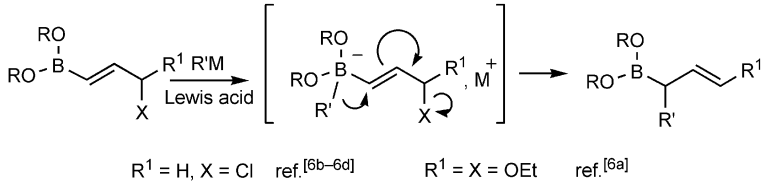
The conversion of (3-hydroxy-1-propen-1-yl)boronates to substituted enamides and enol benzoates is readily achieved in a one-pot procedure consisting of a regiocontrolled Mitsunobu reaction with convenient nucleophiles, followed by allylboration of aldehydes.

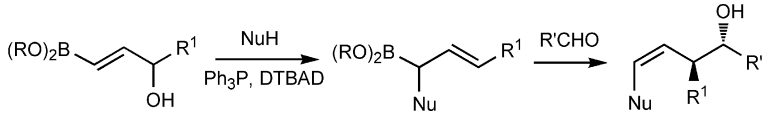
Introduction

Since the initial report of the acylation of secondary alcohols with carboxylic acids in the presence of triphenylphosphane and diethyl azodicarboxylate,[1] the Mitsunobu reaction has became a powerful and widely used procedure for the synthesis of a range of derivatives.[2] These reactions are generally restricted to nucleophiles generated from carboxylic acids, phenols, or N–H acidic compounds, such as sulfonamides or cyclic imides. Inversion of configuration usually occurred, while, quite recently, few examples of Mitsunobu reactions with retention of configuration appeared in the literature, most commonly with hindered substrates.[3] Concerning the regiochemical course observed with allylic substrates, Mitsunobu displacements usually proceeded with high S_N2 regioselectivity, and products arising from S_N2' have been only observed in rare cases.[4,5]

On the other hand, several examples of vinylogous Matteson reactions have been already reported, where "ate" species, resulting from the addition of a Grignard reagent to a boron atom, underwent anionic 1,2-shift to afford α-substituted allylboronates (Scheme 1).[6] These compounds represent an important structural class of organoboron derivatives widely employed in organic chemistry to prepare homoallylic alcohols with good to excellent levels of stereocontrol.[6–8]



Scheme 1. Synthesis of α-substituted allylboronate by an S_N2' reaction; $(RO)_2B$ = Bpin, R′ = alkyl.



Scheme 2. One-pot Mitsunobu reaction/allylboration sequence; R, R′ = alkyl, aryl.

As an extension of our recent work related to boron-mediated substitution reactions, we report herein the results of the study on the Mitsunobu reaction of (3-hydroxy-1-propen-1-yl)-boronic esters and the subsequent one-pot addition of aldehydes to the resulting allylboronates (Scheme 2).

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Results and Discussion

Starting vinylboronates **3a**–**e** were first synthesized from the corresponding commercially available propargylic alcohols according to literature procedures.[9] Protection of the propargylic alcohols as their trimethylsilyl derivatives was followed by hydroboration with pinacolborane to afford allylic alcohols **2**. All these alkenes have a controlled (*E*) double-bond stereochemistry due to the hydroboration step. Finally, deprotection was achieved with acetic acid in THF to give vinylboronates **3** (47–82%); **3f** was prepared by allylboration of the corresponding aldehyde **4** in a 69% yield (Scheme 3, Table 1).

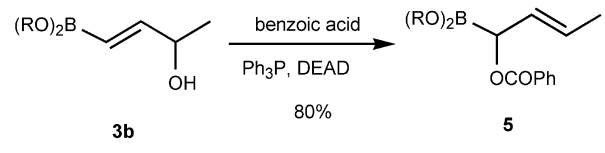
Table 1. Synthesis of vinylboronates **3**.

Entry	R^1	R^2	Yield (%)[a]		
			1	**2**	**3**
a	H	H	96	41	47
b	CH_3	H	94	58	82
c	C_5H_{11}	H	73	53	67
d	Ph	H	95	41	65
e	CH_3	CH_3	70	50	74
f	$CH_2CH{=}CH_2$	H	–	–	69[b]

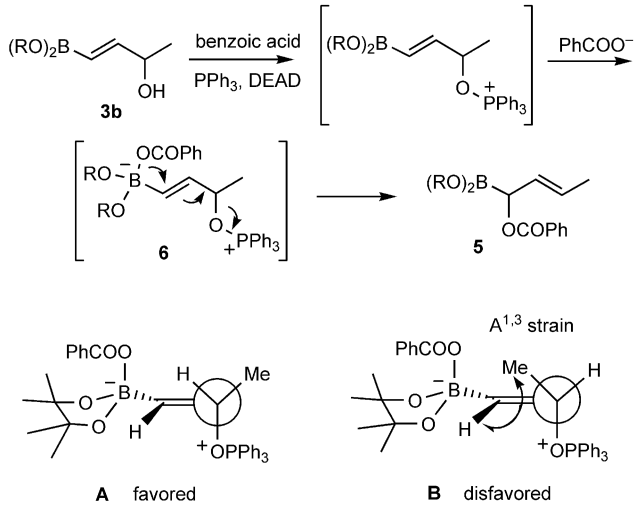
[a] Isolated yields after distillation or purification by column chromatography. [b] From **4** and pinacol allylboronate.

Boronate **3b** was first selected as test substrate. Its treatment with benzoic acid in the presence of triphenylphosphane and diethyl azodicarboxylate (DEAD) only led to the S_N2' Mitsunobu product **5** as a single (*E*) isomer (80% yield, calculated by ^1H NMR spectroscopy with $PhCH_2Ph$ as internal reference) (Scheme 4). The reaction is highly (*E*)-stereoselective (^1H NMR, $J_{HC=CH}$ = 14.5 Hz).[10]

The origin of the stereo- and regioselectivities is not completely clear, but the following mechanism can be proposed. Triphenylphosphane first combines with DEAD to generate a phosphonium intermediate that converts the alcohol oxygen atom to a leaving group, as in classical Mitsunobu reactions.[11] Addition of the benzoate anion to the boron atom leads to the borate **6** that rearranges by an anionotropic 1,2-shift to afford **5**. Taking into account Midland's report,[12] which assumed that the 1,2-migration occurred in an S_N2' manner, *anti* to the leaving group, the obtention of a single (*E*) isomer can be therefore rationalized by the presence of an allylic 1,3-strain in transition state **B** involving the methyl group (Scheme 5).

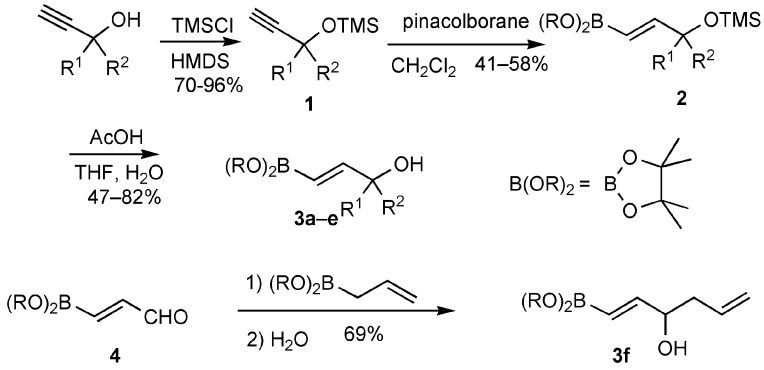


Scheme 4. Mitsunobu reaction of **3b** with benzoic acid.

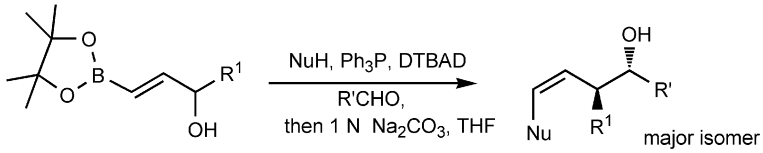


Scheme 5. Proposed mechanism for the S_N2' Mitsunobu reaction.

With this result in hand, a series of experiments were conducted to determine the optimal conditions for this reaction. Several solvents and temperatures were investigated, as the use of di-*tert*-butyl azodicarboxylate (DTBAD) instead of DEAD or DIAD.[13] However, although we found that **5** could be purified by column chromatography, partial decomposition occurred on silica gel. As our initial attempt was to use these compounds as allylating reagents, we decided to carry out the sequence Mitsunobu reaction/allylboration as a one-pot procedure.[14] Various boronates **3a**–**3f** were therefore treated with benzoic acids, phenols or tosylamides and aldehydes in the presence of triphenylphosphane and di-*tert*-butyl azodicarboxylate (Scheme 6).



Scheme 3. Synthesis of α-substituted allylboronates **3**.



3 **7–18**

Scheme 6. S_N2' Mitsunobu reaction/allyboration sequence.

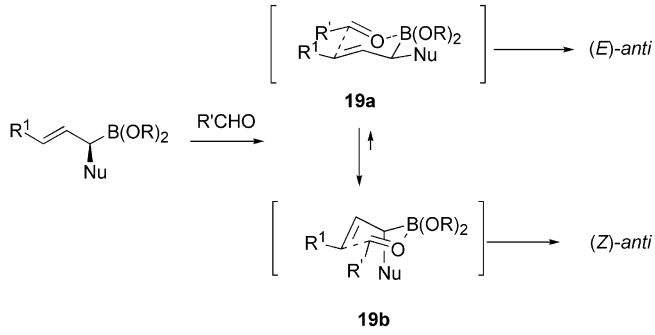
Several examples of homoallylic alcohols **7**–**18** are shown in Table 2. A variety of boronates **3** showed a clean and efficient reaction with benzoic acids, phenol or *N*-tosylamines; the aldehyde component may be aliphatic or aromatic. However, we noted that no defined product could be isolated in the case of **3a** ($R^1 = R^2 = H$), whereas the starting material was recovered unchanged in the case of **3e** (R^1 and $R^2 \neq H$). The diastereomeric ratios were measured on the crude mixtures by ^1H NMR spectroscopy. The (*Z*)-*anti* products were always formed with a high level of diastereoselectivity, in agreement with literature data.[15] The origin of this stereoselectivity can be explained from two competing chair-type transition states as shown in Scheme 7. As it was already mentioned in the literature, with polar α-substituents, dipolar effects tend to predominate[6d,8i] that favored transition states with a pseudoaxial C–Nu bond and led to a major (*Z*)-*anti* isomer.

Table 2. Synthesis of (*Z*)-homoallylic alcohols **7**–**18** from boronates **3**.

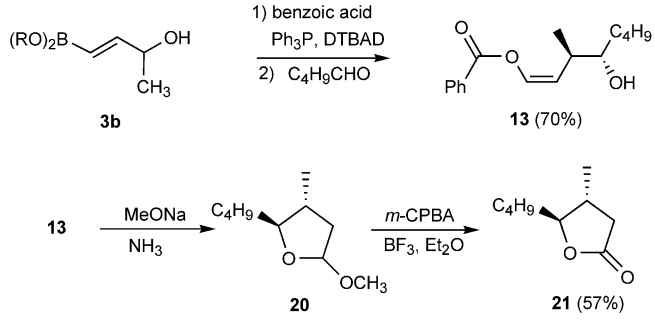
Product	R^1	NuH	Aldehyde	Yield (%)[a]	Ratio *anti*/*syn*[b]
7	Me	$PhCO_2H$	PhCHO	78	92:8
8	Me	$PhCO_2H$	$4\text{-}O_2NC_6H_4CHO$	79	95:5
9	*n*-pent	$PhCO_2H$	PhCHO	69	>99
10	Ph	$PhCO_2H$	$4\text{-}O_2NC_6H_4CHO$	40	>99
11	Me	$PhCO_2H$	$PhCH_2CH_2CHO$	57	96:4
12	Me	$PhCO_2H$	PrCHO	63	>99
13	Me	$PhCO_2H$	BuCHO	70	97:3
14	allyl	$PhCO_2H$	$4\text{-}O_2NC_6H_4CHO$	67	>99
15	Me	$4\text{-}O_2NC_6H_4CO_2H$	BuCHO	62	97:3
16	Me	$4\text{-}O_2NC_6H_4CO_2H$	PhCHO	67	97:3
17	Me	PhOH	PhCHO	46	97:3
18	Me	$PhCH_2NHTos$	PhCHO	53	>99

[a] Isolated yields after silica gel chromatography. [b] Inspection of the ^1H NMR spectra of the crude products indicates the presence of 2–4% of the *syn* isomers.

The stereochemistry of the double bonds of the major products was attributed to be (*Z*) from ^1H NMR data ($J_{HC=CH}$ = 6.4–7.5 Hz). The relative *anti* configuration of the two stereogenic centers of **7**–**16** was assigned by comparison with the partial ^1H NMR spectroscopic data reported by Cossy et al.[16] and by analogy with the OMOM and OCb analogues.[15a,17] The structure of **13** was secured by its conversion to the known *trans*-whisky lactone **21**,[18] by reaction with NaOMe and oxidation of the resulting lactol ether **20** with *m*-CPBA in the presence of BF_3–Et_2O, as summarised in Scheme 8.[16,19] Compound **17** has already been prepared by another route,[15d] and, in the case of the α-sulfonamido homoallylic alcohol **18**, the ^1H NMR spectroscopic data are in full agreement with those reported by Hoffmann and co-workers for a very similar compound.[15c]



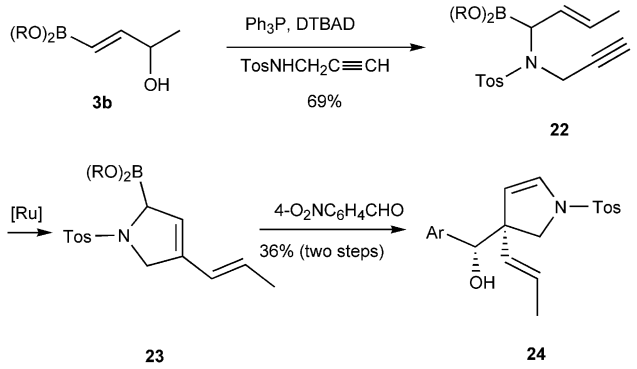
Scheme 7. S_N2' postulated competing transition states in the allylation step.



Scheme 8. Synthesis of *trans*-whisky lactone from boronate **3b**.

Subsequently, to illustrate another aspect of the synthetic potential of allylboronates **3**, we also explored the ruthenium-catalysed cycloisomerisation reaction of an enyne derivative prepared according to the sequence described above.

The boronate **22** was first synthesised from **3b** and *N*-tosylpropargylamine in a 69% yield. In the presence of Grubbs II catalyst, it was readily converted to corresponding cyclic diene **23**, which gave, after the one-pot addition of *p*-nitrobenzaldehyde, the corresponding homoallylic alcohol **24** in a moderate 36% yield (Scheme 9).[20,21] The use of such process thus allows to easily synthesise pyrrolidines possessing a quaternary stereogenic center of defined geometry.[22]



Scheme 9. Mitsunobu/metathesis/allylboration sequence.

Conclusions

We have demonstrated that the presence of a boronic ester group efficiently governed the regiochemical course of a Mitsunobu reaction. On the basis of this behaviour, we developed three-component reactions of (3-hydroxy-1-propen-1-yl)boronates, benzoic acids, phenol or *N*-tosylamines and aldehydes to access enamides and enol benzoates with high diastereoselectivity.[22] Further works will be devoted to more detailed mechanistic investigations and to the asymmetric version of this sequence.

Experimental Section

Mitsunobu Reaction/Allylboration Sequence. General Procedure: To a solution of vinyl boronate **3** (1 mmol) in dry THF (7 mL) under argon, were added successively triphenylphosphane (315 mg, 1.2 mmol), the nucleophile (1.2 mmol) and di-*tert*-butyl azodicarboxylate (276 mg, 1.2 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 15 h. The aldehyde (1.5 mmol) was then added, and the reaction mixture was stirred for 15 h. Saturated Na_2CO_3 solution (5 mL) was added, and the mixture was stirred for 15 h. The solvent was evaporated in vacuo. The residue was dissolved in ethyl acetate and washed twice with H_2O. The organic phase was dried with $MgSO_4$. The residue was purified by silica gel chromatography (cyclohexane/ethyl acetate = 95:5 to 80:20) to afford the homoallylic alcohols in 40–79% yield.

Supporting Information (see footnote on the first page of this article): Full experimental procedures and characterization data for compounds **3**–**24**.

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[10] The presence of small amounts of the (*Z*) isomer (ca. 6% by ^{1}H NMR spectroscopy) cannot be excluded since a set of signals, which could be attributed to this isomer [mainly a doublet at δ = 4.95 ppm, C*H*B(OR)$_2$], was observed in the crude product. Due to the chemical instability of such allylboronates, it has not been possible to isolate this minor compound by chromatography in order to confirm its structure.

[11] See ref.[2a], p. 1343.

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[14] All the reactions were carried out in two steps: First, addition of DTBAD to a solution of the alcohol **3**, triphenylphosphane and nucleophile, followed after completion of the reaction (usually 15 h at room temp.) by the addition of the aldehyde. In the case of **7**, we obtained the same results in term of yield, purity and diastereoisomeric ratio when the aldehyde was present at the beginning of the reaction.

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[20] Compound **24** is a mixture of two diastereomers (9:1). For the major isomer, if the (*E*) geometry was clearly established by ^{1}H NMR spectroscopy ($J_{HC=CH}$ = 15.7 Hz), the relative configuration of the quaternary center and the carbon atom α to the hydroxy group was not secured, but only proposed on the basis of the expected Zimmerman–Traxler transition state observed with similar structures (see refs.[8f,8j]).
[21] A concomitant deborylation of **23**, which led to the formation of *N*-tosyl-3-vinylpyrrole (R. Settambolo, R. Lazzaroni, T. Messeri, M. Mazzetti, P. Salvadori, *J. Org. Chem.* **1993**, *58*, 7899–7902), was also observed (18%).
[22] For a recent review on these significant intermediates in organic synthesis, see: M. Ryosuke, K. Shuvin, *Acc. Chem. Res.* **2008**, *41*, 292–301.

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