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Trifluoroacetic Anhydride Promoted Tandem Conjugate Addition of Boronic Acids/Acetal Ring Opening†

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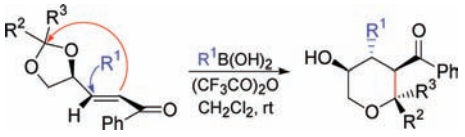
ABSTRACT



A new stereoselective tandem reaction consisting of the metal-free conjugate addition of boronic acids followed by an intramolecular ring opening of a cyclic acetal has been disclosed. Optically pure polysubstituted tetrahydropyrans have been synthesized diastereoselectively by this new reaction. Two new C−C bonds and up to three stereocenters are formed in a single step, allowing the generation of quaternary stereocenters.

The conjugate addition of carbon nucleophiles to electron-deficient alkenes constitutes one of the most relevant synthetic methods for C−C bond formation.[1] Among the different reagents that have been developed for this purpose, boronic acids have attracted a great deal of attention due to their low toxicity, thermal stability, and ample compatibility with functional groups that are normally labile to other organometallic nucleophiles.[2] Direct conjugate addition of boronic acids is normally precluded by their low nucleophilicity, and activation is normally required. This has been achieved by transmetalation to transition metals, mainly Rh and Pd, in catalytic cycles.[3,4] Although less common, promotion of the conjugate addition reaction of boronic acids by organic molecules has also been

† Dedicated to Prof. Carmen Nájera (Universidad de Alicante) in honor of her 60th birthday.

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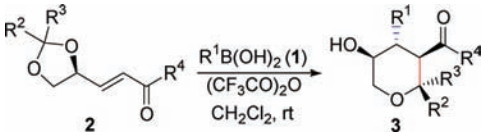
Table 1. Tandem Conjugate Addition/Acetal Ring Opening[a]



entry	**1** (R^1)	**2**	R^2, R^3	R^4	**3** (dr)[b]	yield[c] (%)
1	**1a** (PhCH=CH)	**2a**	Me, Me	Ph	**3aa** (>98:02)	80
2	**1b** (biphenyl-CH=CH)	**2a**	Me, Me	Ph	**3ba** (>98:02)	70
3	**1c** (*p*-F-C_6H_4CH=CH)	**2a**	Me, Me	Ph	**3ca** (>98:02)	85
4	**1d** (*p*-Me-C_6H_4CH=CH)	**2a**	Me, Me	Ph	**3da** (>98:02)	70
5	**1e** (*p*-Cl-C_6H_4CH=CH)	**2a**	Me, Me	Ph	**3ea** (>98:02)	75
6	**1f** (*p*-MeO-C_6H_4CH=CH)	**2a**	Me, Me	Ph		
7	**1a** (PhCH=CH)	**2b**	-$(CH_2)_5$-	Ph	**3ab** (>98:02)	75
8	**1b** (biphenyl-CH=CH)	**2b**	-$(CH_2)_5$-	Ph	**3bb** (>98:02)	75
9	**1c** (*p*-F-C_6H_4CH=CH)	**2b**	-$(CH_2)_5$-	Ph	**3cb** (>98:02)	75
10	**1a** (PhCH=CH)	**2c**	Me, Et	Ph	**3ac** (90:10)[d]	80
11	**1c** (*p*-F-C_6H_4CH=CH)	**2c**	Me, Et	Ph	**3cc** (95:05)[d]	65
12	**1d** (*p*-Me-C_6H_4CH=CH)	**2c**	Me, Et	Ph	**3dc** (90:10)[d]	75
13	**1a** (PhCH=CH)	**2d**	Me, Me	Me		
14	**1g** (Ph)	**2a**	Me, Me	Ph	[f]	

[a] Reaction conditions: **1** (1.25 equiv), **2** (1.0 equiv), $(CF_3CO)_2O$ (3.0 equiv), CH_2Cl_2 (1.7 mL/mmol), rt, 18 h. [b] Determined by integration of the ^1H NMR spectra ($CDCl_3$, 300 MHz) of the reaction crudes. [c] Isolated yield after column chromatography. [d] Diastereomers separated by column chromatography. [f] **1f** (4.0 equiv).

reported, either in stoichiometric[5] or catalytic variants.[6] Generation of radicals from boronic acids and their derivatives has also been used to effect some 1,4-additions.[7]

Among the different types of conjugate addition reactions, tandem processes are particularly attractive,[8] as these methods permit the construction of several C−C bonds in a one-pot process and the simultaneous generation of various stereocenters without isolation of intermediates. We disclose herein a new stereoselective tandem reaction which consists of the conjugate addition of boronic acids followed by the intramolecular ring opening of acetals[9] under metal-free conditions (trifluoroacetic anhydride-promotion). Two new C−C bonds and up to three stereocenters are formed in this single-step process, which allows the generation of quaternary sterocenters. Optically pure polysubstituted tetrahydropyran rings are synthesized diastereoselectively.

These constitute important synthetic targets, as the tetrahydropyran skeleton is found among a wide variety of biologically relevant natural products and pharmaceutically active ingredients. Consequently, considerable efforts have been made in recent times toward the stereoselective preparation of these compounds.[10]

The results of the conjugate addition of several boronic acids **1** to compounds **2** are given in Table 1. The addition of boronic acids **1a**−**d** to the isopropylidene acetal **2a** in the presence of trifluoroacetic anhydride afforded exclusively the corresponding tetrahydropyrans in high yield and as a single diastereomer (entries 1−5).

On the other hand, no reaction was observed when the reaction was carried out with boronic acid **1f** (entry 6). Extensive protodeborylation of this electron-rich boronic acid in the presence of the trifluoroacetic acid generated in the process may account for this result.[2] When the isopropylidene acetal was replaced by a cyclohexylidene acetal (compound **2b**), tetrahydropyran formation also took place in high yield and diastereoselectivity (entries 7−9).

We observed that this reaction was also of use for the stereoselective generation of a quaternary stereocenter in a highly efficient fashion (entries 10−12). For this purpose, we chose compound **2c** as starting material,[11] with a very small difference in the electronic or steric character of R^2 (Me) and R^3 (Et). We found that these reactions took place with good dr. Only two of all possible diastereomers were generated, which only differed in the relative disposition of R^2 and R^3. In particular, we noticed that the reaction of **2c**

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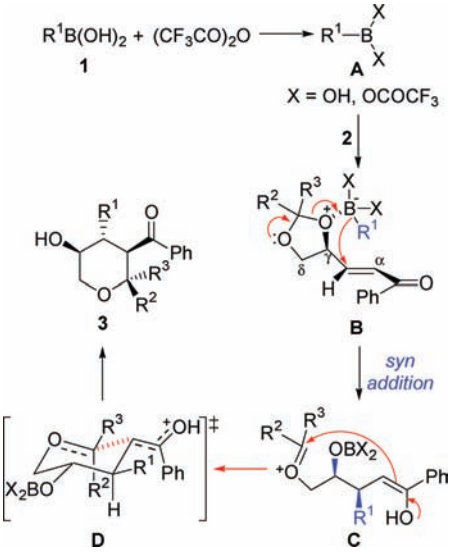
(11) Compound **2c** was used as a 1:1 mixture of diastereomers, epimers at carbon-2 of the [1,3]dioxolan-4-yl moiety.

with the electron-deficient boronic acid **1c** gave the corresponding tetrahydropyran **3cc** (entry 11) with very high dr.

On the other hand, no reaction was observed for the methyl ketone **2d** (entry 13) under similar conditions. The reaction of **2a** with phenylboronic acid **1g** (entry 14) led to deprotection of the acetal group of the starting material together with the conjugate addition product of **1f** to the latter (10% yield, 50:50 of epimers at the β-carbon).

A reaction mechanism which accounts for the formation of compounds **3** and the observed stereochemistry is proposed in Scheme 1. Reaction of $(CF_3CO)_2O$ with the boronic acid **1** may give a mono- or a diacylboronate[12] intermediate **A**, where the Lewis acidity of the boron atom is enhanced with respect to **1**. Coordination of this species[13] with the γ-oxygen of **2** gives intermediate **B**. The intramolecular delivery (*syn*-addition, *vide infra*) of the R^1 group will be facilitated by the lone pair on the δ-oxygen, leading to intermediate **C**. Intramolecular ring-closure finally accounts for the formation of compounds **3**.

Scheme 1. Proposed Mechanism



With regard to the stereochemistry, the conjugate addition of carbon nucleophiles to acyclic γ-alkoxysubstituted-α,β-unsaturated carbonyl compounds to afford either the *syn* or the *anti* products has been amply documented.[14,15]

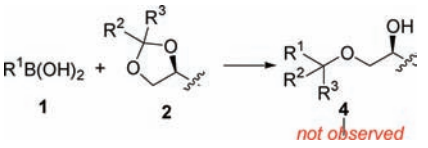
The stereochemistry has been found to depend on both the substrate and reagent structures. In this reaction, we have observed a highly selective *trans* relative disposition between R^1 and OH in the final cyclic product **3**. This is consistent with a substrate-controlled chelated *syn* conjugate addition step, as depicted on intermediate **B** (Scheme 1).

The final cyclization can be envisioned by an approach of the enolate to the sp^2 carbon of the electrophilic moiety in a chairlike transition state **D**. The pseudoequatorial disposition of the substituents minimizes the steric interaction between R^1 and the enolate, affording a *trans* relative disposition of R^1 and COPh in the tetrahydropyrans **3.**

In the case of the reactions with **2c** as starting material,[11] the high dr in the generation of the quaternary stereocenter can be understood by placement of the smallest substituent (R^2 = Me) in a pseudoaxial disposition.

Finally, it is also worth mentioning that formation of ethers **4** *via* cross-coupling of the boronic acids with the acetal function (Scheme 2) was not observed under these reaction conditions.[13]

Scheme 2. Formation of Ethers **4**



In conclusion, we have disclosed an unprecedented tandem process initiated by the conjugate addition of a boronic acid under metal-free conditions that affords polysubstituted tetrahydropyran rings in high dr and permits the formation of quaternary stereocenters. The reaction generates two C−C bonds and up to three stereocenters in a one-pot process. The corresponding tetrahydropyrans are prepared enantioselectively, as the reactions are carried out using enantiopure reactants easily derived from the chiral pool. The functionalization present in these tetrahydropyrans **3** can be further manipulated, thus adding synthetic value to the process.

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Supporting Information Available. Experimental procedures, characterization of all new compounds and assignment of the stereochemistry. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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