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α-Crotyl-α-difluoroboranyloxy-amides: Structure and Reactivity of Isolable Intermediates in Stereospecific α-Ketol Rearrangements

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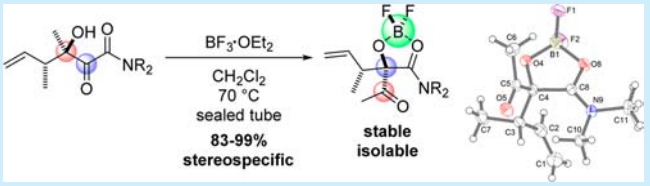
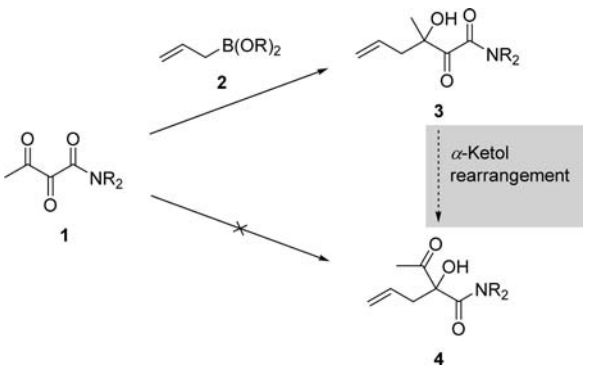
Supporting Information

ABSTRACT: The stereospecific BF_3-mediated α-ketol rearrangement of β-hydroxy-α-ketoamides yields isolable 2-difluoroboranyloxy-3-keto-amides. X-ray and NMR analysis reveal a carbonyl coordination of the boron by the amide not the ketone. The boron complexes are air-stable solids, can be purified by silica gel chromatography, and exhibit novel reactivity in bromination and superior stereoselectivity in dipolar cycloaddition reactions.



Vicinal tricarbonyl compounds are valuable building blocks in organic synthesis for the construction of complex target molecules such as natural products and potent motifs in medicinal chemistry.[1,2] In the case of unsymmetrical vicinal tricarbonyl compounds such as *vic*-diketoamides **1**, a regioselective approach to differentiate the attack of carbon nucleophiles at one of the two keto functionalities present is decisive.[3] The allylboration of diketoamides **1** with allylboronates **2** occurs solely with β-regioselectivity and results in the formation of β-hydroxy-α-ketoamides **3**.[4] However, α-allylation product **4** could be attained from β-allylation product **3** by means of α-ketol rearrangement (Scheme 1).[5] Expanding the

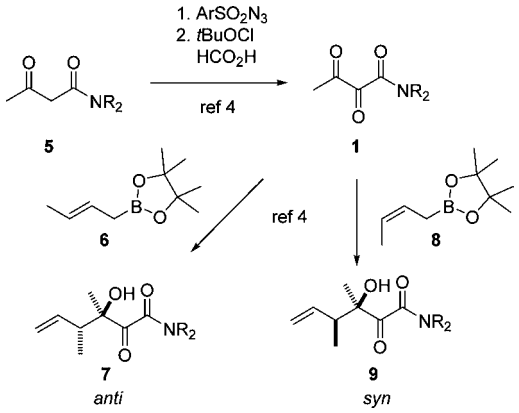
Scheme 1. Regioselective Allylation of *vic*-Diketoamides



allylboration to a crotylboration allows the study of the diastereoselectivity/specifity in addition to the regioselectivity challenge. Here we report on the efficient stereospecific BF_3-mediated α-ketol rearrangement of various β-hydroxy-α-ketoamides into α-hydroxy-β-ketoamides. Besides structural characterization of the corresponding difluoroalkoxyborane intermediates, their synthetic utility was investigated.

The starting point for the synthesis of the *vic*-diketoamides was the β-ketoamides **5**. A Regitz diazo transfer followed by *t*BuOCl-oxidation furnished the *vic*-diketoamides **1**.[4] Crotylboration of the latter with (*E*)-crotyl boronate **6** exclusively led to β-hydroxy-α-ketoamides **7** with high *anti*-diasteroselectivity (single diastereomer). The reaction of **1** with (*Z*)-crotyl boronate **8** gave β-addition products **9** with *syn*-diastereoselectivity (d.r. 91:9 for Weinreb amide **9f**) (Scheme 2).[4]

Scheme 2. Stereospecific Access to β-Hydroxy-α-ketoamides



Reaction of β-hydroxy-α-ketoamides **7** with stoichiometric amounts of $BF_3{\cdot}OEt_2$ resulted in the formation of the difluoroalkoxyboranes **10** (Scheme 3). Compounds **10** can be purified by silica gel chromatography and are bench-stable solids. For the present case, the amide oxygen acts as a strong binding ligand to boron and leads to isolable boron complexes of type **10**. A variety of *N*,*N*-dialkylamides **7a**−**e** gave the corresponding difluoroalkoxyboranes **10a**−**e** in very good yield. The difluoroalkoxyboranes were converted by methanolysis into the β-hydroxy-α-ketoamides **11** in nearly quantitative yield.

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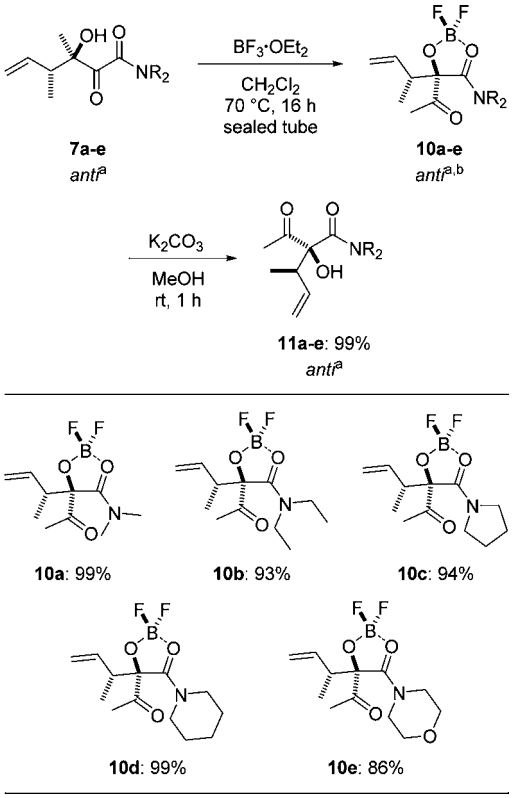
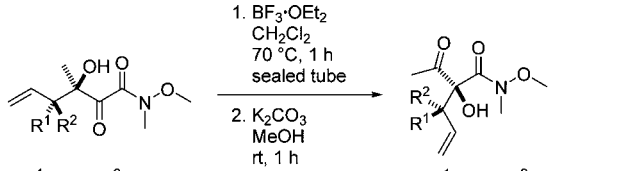
Scheme 3. BF_3-Mediated α-Ketol Rearrangement and Subsequent Methanolysis



[a]Single diastereomer as measured by ^{1}H NMR. [b]Confirmed by X-ray single crystal structure analysis.

The strict stereospecificity of the rearrangement was determined by a combination of NMR and X-ray analysis (Scheme 4). The *anti*-β-hydroxy-α-ketoamide **7f** gave the *anti*-α-hydroxy-β-ketoamide **11f**, while the *syn* compound **9f** led to the *syn* product **12** exclusively.

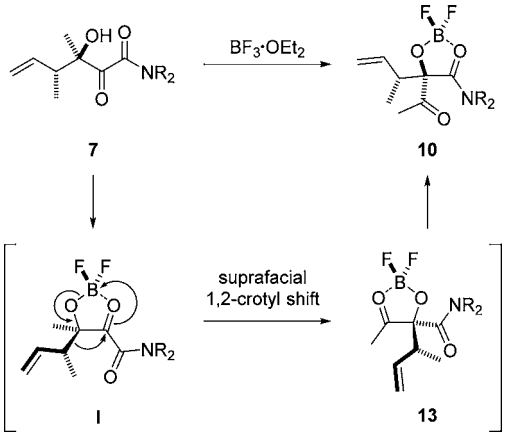
Scheme 4. Stereospecifity of the Rearrangement



[a]Single diastereomer as measured by ^{1}H NMR. [b]Confirmed by X-ray single crystal structure analysis.

Mechanistically, the 1,2-migration of the crotyl group from the β- into the α-position can be described as a suprafacial α-ketol rearrangement (Scheme 5).[5] Reaction of α-hydroxy-β-ketoamide **7** with BF_3·OEt_2 leads to intermediate **I** which is transformed by the stereospecific 1,2-crotyl shift into the α-crotylation product **13**. Subsequently, the keto oxygen is replaced by the more basic amide oxygen (**13** → **10**, vide infra). Related rearrangements have been reported for the β-hydroxy-α-ketoester,[6,7] but the corresponding difluoroalkoxyboranes have not been isolated and characterized before.[8]

Scheme 5. Mechanistic Considerations for the α-Ketol Rearrangement



A priori, coordination of the boron by the amide carbonyl **10** or the ketone carbonyl **13** is conceivable. X-ray crystal structures revealed the stabilizing and chelating role of the oxygen of the amide group in the solid state. For all 11 difluoroalkoxyboranes described herein,[9] the X-ray crystal structures exhibit the sole complexation by the amide oxygen (Figure 1 and Supporting Information). Whereas the B–F

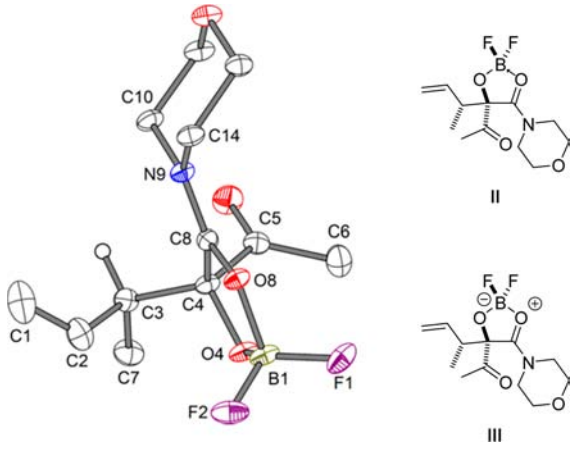


Figure 1. X-ray crystal structure of rearrangement product **10e**. Hydrogen atoms are omitted for clarity.

bond lengths are similar (B–F1 1.372 to 1.394 Å, average 1.381 Å; B–F2 1.368 to 1.399 Å, average 1.378 Å), different distances for the covalent B–O bond (1.408 to 1.452 Å, average 1.437 Å) and the coordinate B–O bond (1.519 to 1.550 Å, average 1.536 Å) are observed. The bonding situation between the boron substituent and the amide carbonyl group can be described by **II** or **III**.

In solution, evidence for the exclusive coordination of the amide oxygen to the boron center at room temperature was provided by ^{13}C NMR spectroscopy. ^{19}F–^{13}C-Through-space coupling was observed for *anti*-**10a–f** in all cases at C2, C3, C5, and C6 (Figure 2a; for numbering of the crystal structure of **10e**, see Figure 1) with coupling constants in the range of $^{TS}J_{FC}$ = 1.3 to 3.8 Hz. Neither quarternary carbon C4 nor amide carbon C8 shows signal splitting in any case. Therefore, scalar *J*-coupling through the chemical bonds can be ruled out as a source of the ^{13}C NMR signal splitting. In all cases, ^{19}F–^{13}C-through-space coupling resulted in doublet splitting rather than

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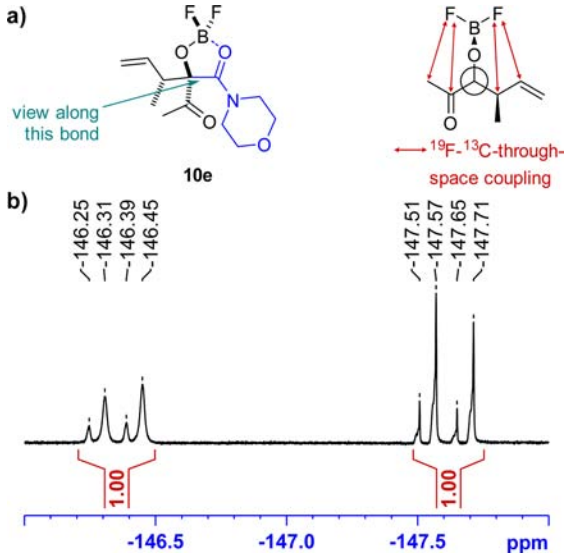


Figure 2. a: Illustration of ^{19}F−^{13}C-through-space couplings. In the depicted Newman projection, morpholine amide (blue) is omitted for clarity. b: ^{19}F NMR spectrum (470 MHz, $CDCl_3$) of rearrangement product **10e** at room temperature relative to external $CFCl_3$.

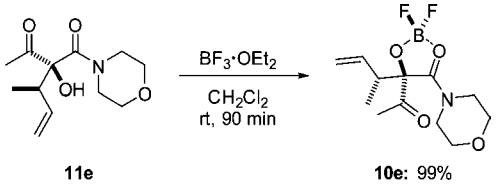
doublet−doublet or triplet splitting of the aforementioned ^{13}C NMR signals. This indicates the absence of rotation around the covalent O−B bond and points to a firm coordinative O−B bond of the amide oxygen resulting in a rigid 1,3,2-dioxaborole structure. With atoms C10, C14, N9, C8, C4, O8, O4, and B1 forming a plane, F1 is located above C5 and C6 on the one side of the plane and F2 is located above C2 and C3 on the opposite side. Crystal structure F−C distances range from 3.5 Å (F1−C6 and F2−C2) to 4.0 Å (F1−C5 and F2−C3). Owing to the configurative inversion at C3, Weinreb analogue *syn*-**10f** does not show ^{19}F−^{13}C-through-space coupling at C2 (distance 4.6 Å) but at C7 (distance 3.6 Å, $^{TS}J_{FC}$ = 0.8 to 0.9 Hz).

Noteworthy is the ^{19}F NMR of **10e** (Figure 2b): It consists of two sets of signals, one arising from the ^{11}B species (80%), the other from the ^{10}B species (20%). As a result of the diastereotopicity of the fluorine atoms, two doublets are observed ($\Delta\delta$ = 0.70 to 1.26 ppm, $^{2}J_{FBF}$ = 63 to 70 Hz). These observations additionally support the existence of a strong coordinative O−B bond and a rigid 1,3,2-dioxaborole scaffold.

The 2-difluoroboranyloxy-amides were also accessible in nearly quantitative yield by adding $BF_3{\cdot}OEt_2$ to a solution of the α-hydroxy-amide in methylene chloride at room temperature as shown for the case **11e** → **10e** in Scheme 6.

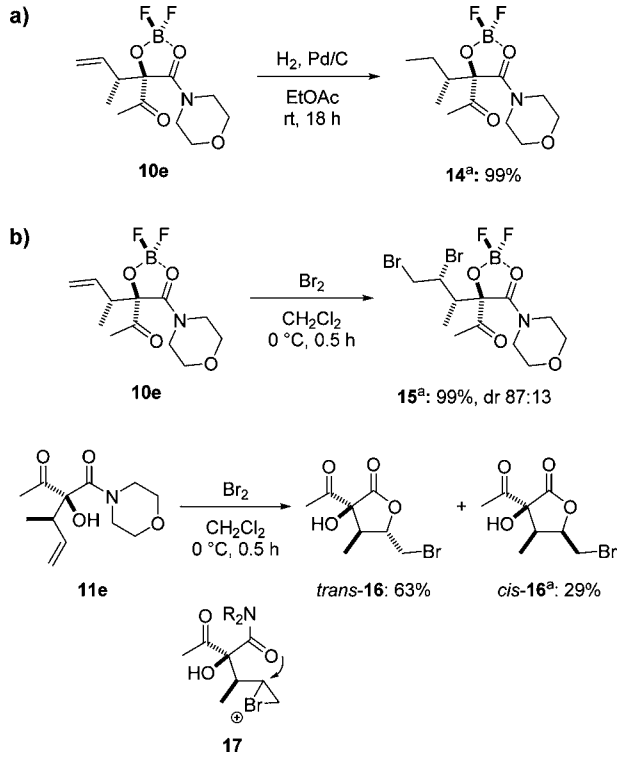
The specific chemical reactivity of the novel 2-difluoroboranyloxy-amides was investigated next. Compound **10e** was chosen as a trial system for studies with respect to stability and selective functionalization. Attempts to address the keto functionality selectively leaving the boron functionality intact

Scheme 6. Direct Formation of the 1,3,2-Dioxaborole from the α-Hydroxy-amide



were unsatisfying (ketone reduction with $NaBH_4$ and $NaBH(OAc)_3$, nucleophilic addition of a phenyl Grignard reagent, phenyllithium). Oxidative conditions (epoxidation, dihydroxylation) produced complex reaction mixtures and decomposition of the alkoxyborane. The catalytic hydrogenation of alkene **10e** cleanly gave alkane **14** leaving the borane functionality untouched (Scheme 7a). In the case of

Scheme 7. Reaction Scope of α-Crotyl-α-difluoroalkoxyboranyl-amides



[a]Confirmed by X-ray single crystal structure analysis.

bromination, different reactivity was observed for the boron complex compared to the corresponding α-hydroxy-amide (Scheme 7b). Treatment of compound **10e** with bromine led to dibromide **15** in excellent yield and an 87:13 diastereomeric ratio. In contrast, the reaction of the free alcohol **11e** gave a mixture of the bromolactones **16** with poor diastereoselectivity via an intramolecular attack of the amide group at the cyclic bromonium ion **17**.

Furthermore, the 1,3-dipolar cycloaddition reaction of difluoroalkoxyborane **10e** with benzonitrile oxide generated from benzohydroximinoyl chloride **18** gave difluoroalkoxyborane isoxazoles **19** in an excellent 91% overall yield with very good *anti*-diastereoselectivity (d.r. 91:9). In contrast, the same reaction conditions applied to the corresponding α-hydroxy-amide **11e** yielded the cycloaddition product **20** in 78% overall yield with moderate diastereoselectivity (d.r. 72:28) plus 21% of the double cycloaddition product **21** (Scheme 8). While *anti*-**19** and *syn*-**19** could not be separated chromatographically, R_f-values of *anti*-**20** and *syn*-**20** differ greatly. BF_2 complexes **19** can easily be purified by crystallization.

In summary, we have developed an efficient and high-yielding stereospecific method for the α-ketol rearrangement of β-hydroxy-α-ketoamides which provides diastereoselective access to α-hydroxy-β-ketoamides starting from vicinal

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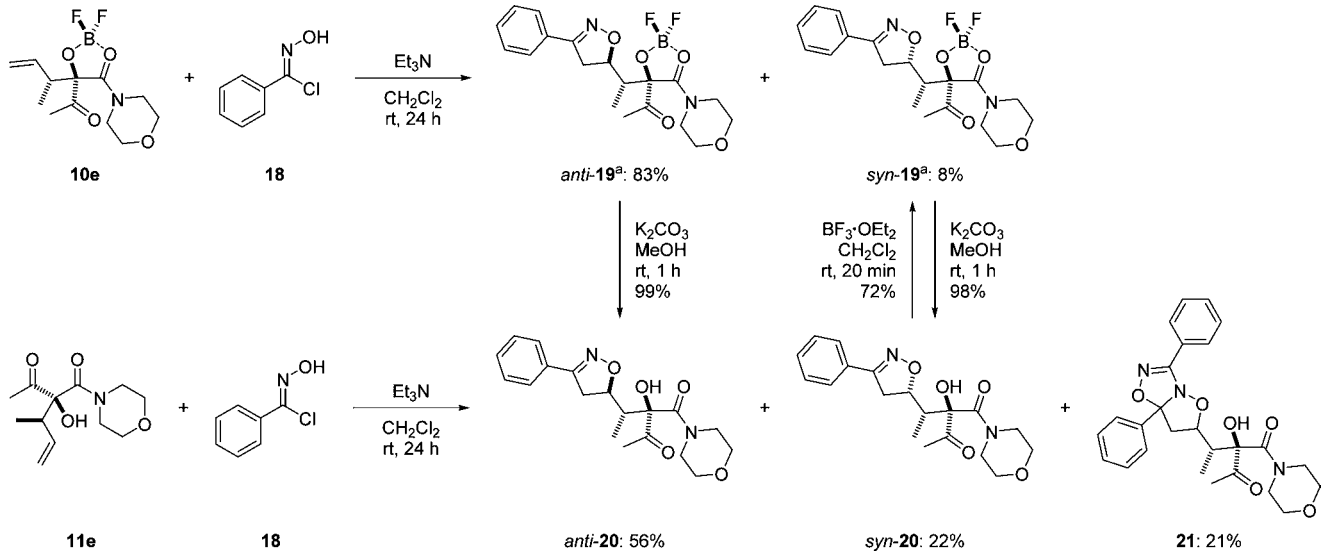
Scheme 8. 1,3-Dipolar Cycloaddition Reactions



[a]Confirmed by X-ray single crystal structure analysis.

tricarbonyl compounds **1** → **3** → **4**. The novel class of difluoroalkoxyborane intermediates of type **10** was studied structurally by X-ray and NMR analysis revealing an exclusive amide carbonyl coordination mode. The synthetic utility of these compounds was proven by novel reactivity in the case of bromination and superior stereoselectivity for the 1,3-dipolar cycloaddition. The novel boron functionality could be a useful protective group for α-hydroxy-amides.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectroscopic and analytical data, and crystallographic information file (CIF) for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01427.

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Notes

The authors declare no competing financial interest.

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(9) That is *anti*-**10a-f**, *syn*-**10f**, **14**, **15**, *anti*-**19**, and *syn*-**19**.

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