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Asymmetric Organocatalytic Monofluorovinylations

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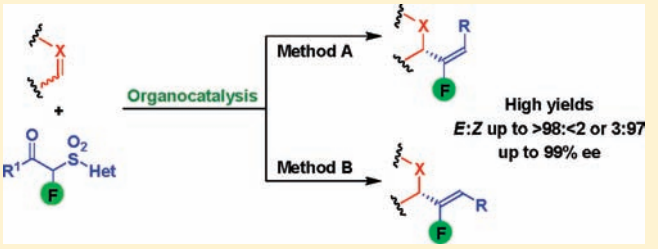
Supporting Information

ABSTRACT: The development of highly enantio- and diastereoselective organocatalytic monofluorovinylations is presented. Based on the application of α-fluoro-β-keto-benzothiazolesulfones, the formal addition of a monofluorovinylic anion synthon to a range of acyclic and cyclic enones, as well as imines, is shown. These procedures give selective access to both *E*- and *Z*-isomers of the monofluorovinylated products, which are isolated as the pure diastereoisomers in good to excellent yields with up to 99% ee. Furthermore, the application of this concept for the formation of highly enantioenriched bicylic compounds containing a monofluorovinyl moiety is also described. In addition, a mechanistic rationale for the observed *E*:*Z*-selectivities is presented.



INTRODUCTION

Introducing fluorine into organic molecules can have a profound effect on their pharmacokinetic and pharmacodynamic properties, and as such, the preparation of fluorine analogues of biologically active compounds have been the subject of intense research.[1] Due to the electronegativity of the fluorine atom, its presence on an alkene changes the electron distribution of the alkene moiety, mimicking the dipolar nature of an amide bond.[2] In this regard, monofluoroalkenes have long been known as stable bioisosteres of amide bonds with respect to conformational interconversion and hydrolysis (Figure 1).[2b,3] Recently, this has led to several publications concerning the replacement of amide bonds with monofluoroalkenes in biologically active compounds.[3a,4]

Although methods for the formation of monofluoroalkenes have seen a number of developments in recent years,[5] procedures for forming optically active monofluoroalkenes with an α-stereocenter are still scarce.[6] As such, to the best of our knowledge, the catalytic enantioselective addition of monofluoroalkenes to a prochiral electrophile is unprecedented, although the formed products are highly desirable, as the configuration of the stereocenter adjacent to the monofluoroalkene has previously been shown to be of importance for biological activity.[7] In addition, as *E*- and *Z*-monofluoroalkenes are possible bioisosteres for *cisoid*- and *transoid*-amide bonds, respectively (Figure 1), the introduction of monofluoroalkenes with a high control of *E*/*Z*-selectivity is potentially of great synthetic and pharmaceutical interest but remains a challenging task, especially concerning the formation of the *E*-isomers.[5]

We surmised that these problems could be overcome by developing an enantioselective organocatalytic[8] addition of a monofluorovinylic anion synthon to a prochiral electrophile. As outlined in the retrosynthetic analysis (Figure 2), such a synthon might be the α-fluoro-β-keto-heteroarylsulfone **1**,[9] which upon reduction of the ketone moiety in **1** could undergo a Julia−Kocienski-like transformation.[10]

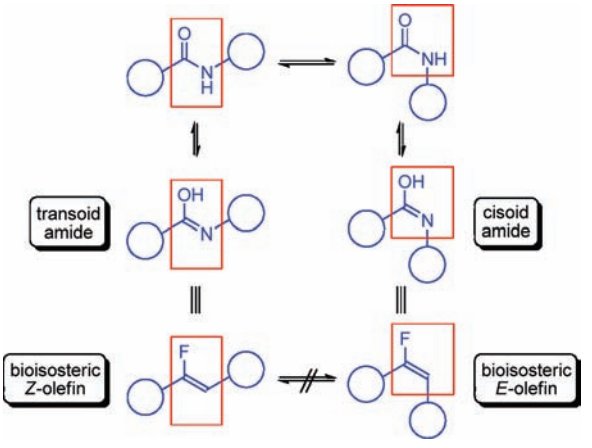


Figure 1. Monofluoroalkenes as nonisomerable, nonhydrolyzable isosteres of amide bonds.

Here, we report the development of the first, highly enantio- and diastereoselective monofluorovinylations of enones and imines. The products are formed as either *E*- or *Z*-isomers from a common intermediate and are generally isolated as the pure isomer. Furthermore, a rationale for the stereochemical outcome is presented. In addition, the developed procedure is also demonstrated to be useful for the formation of optically active bicylic monofluorovinyl compounds.

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As proof of concept, we speculated whether it would be possible to employ the easily accessible α-fluoro-β-keto-benzothiazolesulfones **1** as nucleophiles for the asymmetric organocatalytic monofluorovinylation of cyclic and acyclic enones **2** (Figure 3), as well as imines (vide infra). Following the addition, the adduct formed might selectively be converted into the *E*- and *Z*-monofluoroalkenes ***E*-3** and ***Z*-3**, by reduction of the ketone moiety. In analogy with the commonly accepted mechanism for the Julia–Kocienski reaction,[10] we assume that the diastereochemistry in the formation of **3** is solely based on the diastereoisomeric ratio between the α-sulfone moiety and the reduced ketone (***E*-A** or ***Z*-A**, Figure 3). Therefore, the diastereoselectivity of the reduction determines the *E*:*Z*-ratio of the produced alkene **3**. In order to access both ***E*-3** and ***Z*-3** from the common intermediate, we endeavored to develop two different one-pot reduction protocols, leading to **3** with selective control of the *E*- or *Z*-configuration of the monofluoroalkene moiety.

RESULTS AND DISCUSSION

Reactions of Cyclic and Acyclic Enones. Having established that the addition of α-fluoro-β-keto-benzothiazolesulfone **1a** (Figure 3, R = Ph) to the iminium ion-activated cyclohexenone

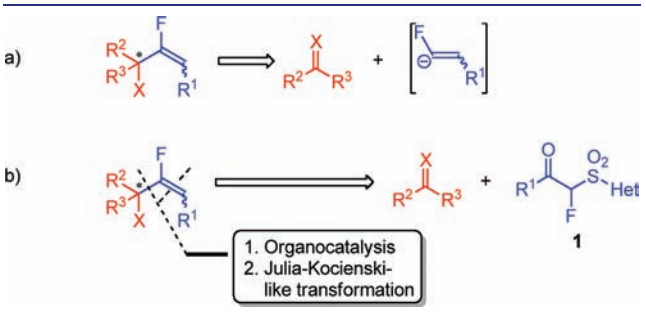

Figure 2. Schematic representation of (a) the enantioselective addition of a monofluorovinylic anion synthon and (b) the presented enantioselective organocatalytic approach for the formation of optically active monofluoroalkenes. Het = heteroarylsulfone.

2a can be performed with 99% ee at 45 °C by reaction in 1,4-dioxane utilizing 10 mol % primary amine[11] **4** as the organocatalyst, we turned our attention to the subsequent reduction needed to form selectively the *E*- or *Z*-isomer of the monofluorovinyl product **3**. Reducing intermediate **5aa** with $NaBH_4$ at room temperature gives the desired product **3aa** with an *E*:*Z*-ratio of 50:50 (Table 1, entry 1). It is observed that cooling alone does not solve this selectivity problem (entry 2); however, the employment of $LiBH_4$ as reducing agent at lowered temperature improves the selectivity substantially. It was found that at 0 °C ***E*-3aa** can be formed with an excellent *E*:*Z*-ratio of >98:<2 by reducing **5aa** with $LiBH_4$ in a 1:1 mixture of 1,4-dioxane and MeOH in a one-pot procedure (entry 3).

In order to obtain primarily the *Z*-isomer of **3aa**, it is essential to lower the amount of alcohol and change the reducing agent to $NaBH_4$. Furthermore, the addition of $ZnCl_2$ improves the selectivity toward the desired isomer (Table 1, entry 4 vs entry 5). Other salts such as $CaCl_2$ and $CeCl_3$ do not show the same effect. Employing sterically more demanding alcohols is advantageous (entries 5–8), and the product ***Z*-3aa** can be formed with an *E*:*Z*-ratio of 10:90 by addition of neopentanol (2,2-dimethyl-1-propanol) using $NaBH_4$ as reducing agent and $ZnCl_2$ as additive at ambient conditions (entry 8), thereby practically reversing the diastereoselectivity in this step. Moreover, we decided to employ a simple oxidation of the alcohol moiety in **3** to the corresponding ketone with Dess–Martin periodinane (DMP), as this allows for the separation of the *E*- and *Z*-diastereoisomers of the oxidized products **6** by flash column chromatography, hereby enhancing the synthetic utility of these reactions.

Having established reaction conditions for the organocatalytic step and subsequent reduction, we investigated the scope of the reaction (Table 2). Commencing with the *E*-selective reduction, it was found that both enantiomers of the product ***E*-6aa** can be isolated in 71–72% yield with enantioselectivities of 99% and 96% ee, respectively, by employment of quasi-enantiomeric catalysts **4** (*epi*-9-amino-quinidine) and ***quasient*-4** (*epi*-9-amino-quinine).

Substituents on the electrophile are also well tolerated as seen by the employment of 5,5-dimethylcyclohex-2-enone (**2b**) yielding product ***E*-6ab** in 60% yield with an enantiomeric excess

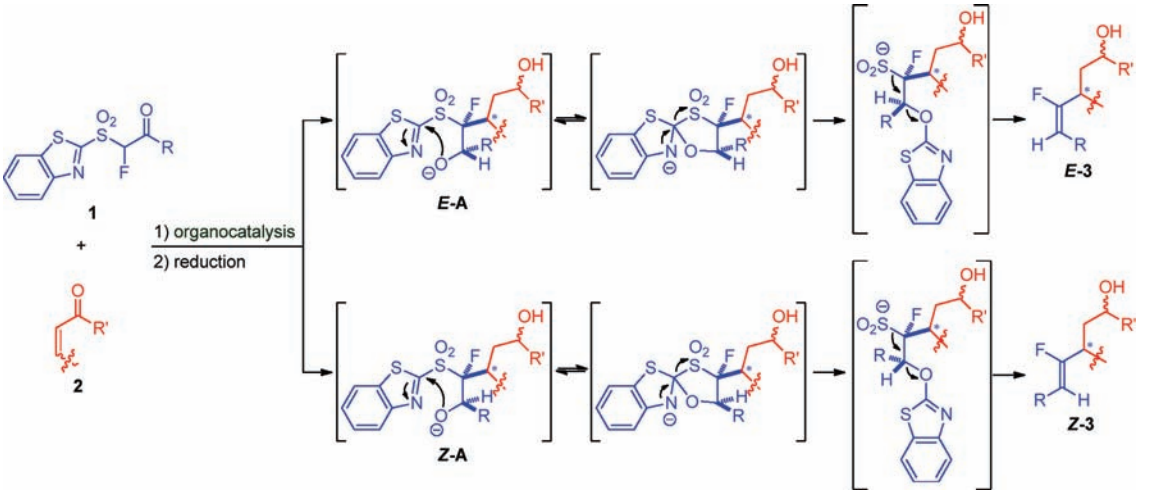

Figure 3. Mechanistic proposal for the diastereoselective formation of the monofluoroalkene moiety.

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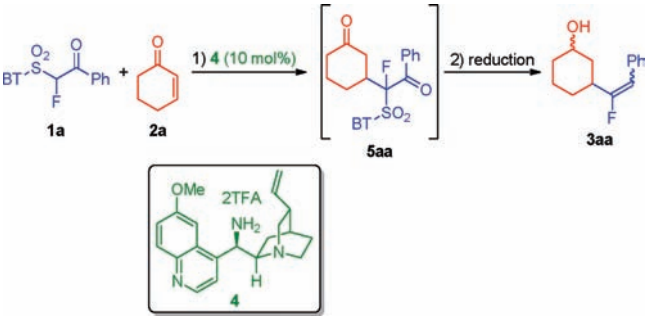
Table 1. Optimization of the *E*:*Z*-Ratio of the Monofluorovinylation[a]



entry	dioxane: alcohol	temp [°C]	reductant [10 equiv]	additive [3 equiv]	*E*:*Z*[b]
1	1:1 (MeOH)	rt	$NaBH_4$	–	50:50
2	1:1 (MeOH)	0	$NaBH_4$	–	50:50
3	**1:1 (MeOH)**	**0**	**$LiBH_4$**	–	**>98:<2**
4	10:1 (*i*PrOH)	rt	$NaBH_4$	–	26:74
5	10:1 (*i*PrOH)	rt	$NaBH_4$	$ZnCl_2$	13:87
6	10:1 (MeOH)	rt	$NaBH_4$	$ZnCl_2$	20:80
7	10:1 (EtOH)	rt	$NaBH_4$	$ZnCl_2$	16:84
8	**neopentanol[c] in dioxane**	**rt**	**$NaBH_4$**	**$ZnCl_2$**	**10:90**

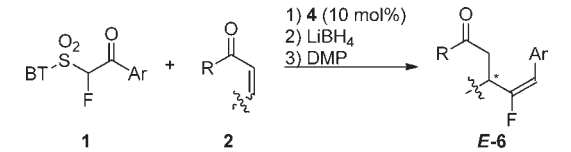
[a] All reactions performed one-pot with: step 1: **1a** (0.10 mmol), **2a** (0.20 mmol), **4** (0.01 mmol) in 1 mL of 1,4-dioxane at 45 °C. Step 2: conditions in Table 1 applied. Full conversion obtained in both steps in all cases. [b] Determined by ^{19}F NMR. [c] 20 equiv to **1a** (v/v dioxane/alcohol ≈ 4.6:1). BT = benzothiazole.

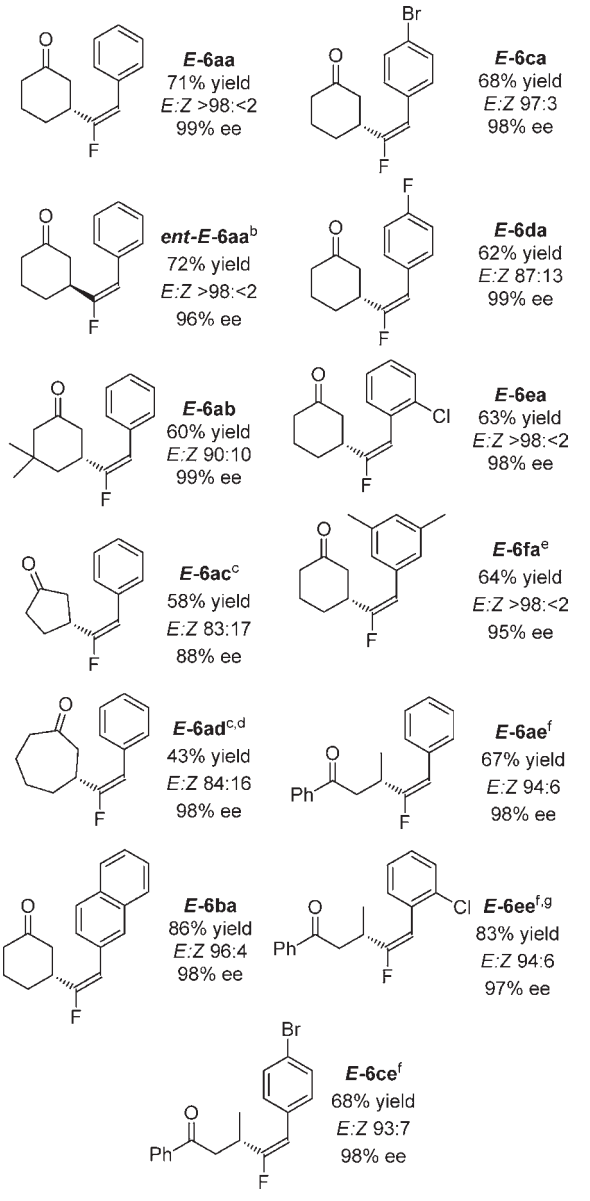
of 99% ee. Both ring-expanded and -contracted electrophiles can be employed, forming products ***E*-6ac** and ***E*-6ad** in 58% and 43% yield, with 88% and 98% ee, respectively. In all cases, the products are formed in good to excellent diastereomeric ratios (from 83:17 up to >98:<2), and the products can be isolated as the pure *E*-isomer. Acyclic enones are also feasible substrates for this reaction, as shown by the employment of *trans*-crotonophenone **2e**. The products ***E*-6ae**–***E*-6ee** are formed in 67–83% yield with enantiomeric excesses of 97 and 98% ee, respectively. As compared to the cyclic substrates, the *E*:*Z*-ratio is maintained at an excellent level of up to 94:6.

Investigating the scope with respect to the nucleophiles **1**, it was found that nucleophile **1b** bearing a 2-naphthyl moiety can be employed forming ***E*-6ba** with excellent stereoselectivities and isolated in 86% yield. Substituents on the aromatic moiety can be of either electron-withdrawing or -donating character, and independent of their position, the products ***E*-6ca**–***E*-6fa** are isolated in 62–68% yield with enantioselectivities between 95% and 99% ee. Alkyl-substituted nucleophiles can also be employed; however, due to degradation in the reduction step, the product was only isolated in 33% yield as a 3:1 mixture of *E*-*Z*-isomers for the *n*-propyl variant tested.

The scope with respect to the *Z*-selective formation of products ***Z*-6** is outlined in Table 3, and proved to be as broad as the one presented above for the *E*-selective protocol. As such, the products ***Z*-6** can be formed with *E*:*Z*-ratios of up to 10:90

Table 2. *E*-Selective Formation of Optically Active Monofluorovinyl Compounds *E*-6[a]





[a] All reactions performed with: step 1: **1** (0.20 mmol), **2** (0.40 mmol), **4** (0.02 mmol) in 1,4-dioxane (2 mL) at 45 °C. See Supporting Information for further details. *E*:*Z*-ratios determined by ^{19}F NMR. Yields are isolated yields of the pure *E*-isomer. Ee determined by CSP-HPLC. [b] ***quasient*-4** used as catalyst. [c] 20 mol % catalyst **4** employed at 60 °C. [d] Reaction stops at 80% conversion (determined by ^{1}H NMR). [e] Performed at 50 °C. [f] Performed with: step 1: **1** (0.10 mmol), **2e** (0.40 mmol), ***quasient*-4** (0.02 mmol) in 1,4-dioxane (0.5 mL) at 60 °C. See Supporting Information for further details. [g] Isolated as a mixture of the *E*:*Z*-isomers.

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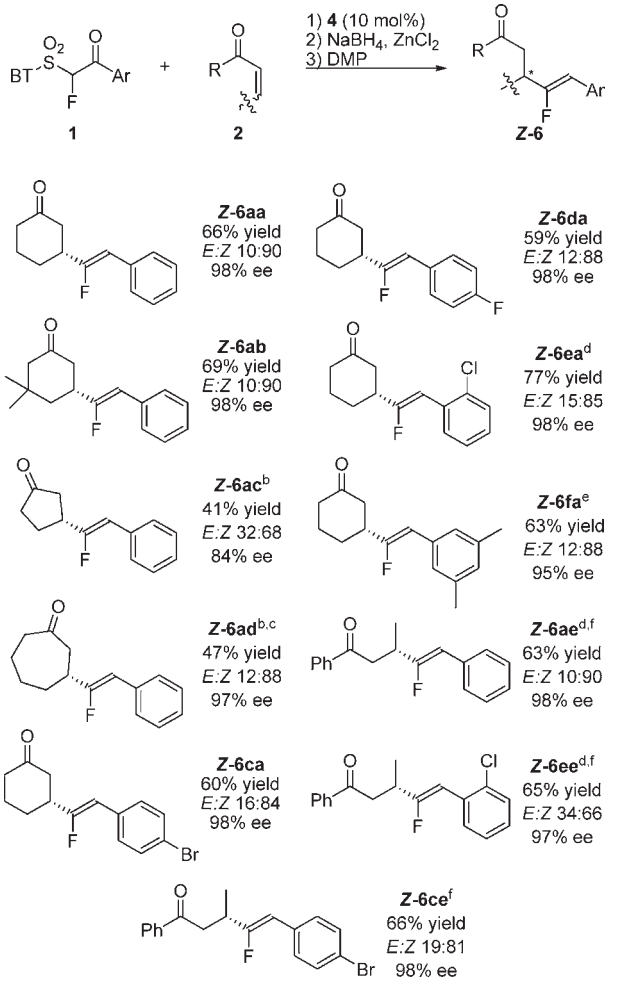
Table 3. *Z*-Selective Formation of Optically Active Monofluorovinyl Compounds *Z*-6[a]



[a] All reactions performed with: step 1: **1** (0.20 mmol), **2** (0.40 mmol), **4** (0.02 mmol) in 1,4-dioxane (2 mL) at 45 °C. See Supporting Information for further details. *E*:*Z*-ratios determined by ^{19}F NMR. Yields are isolated yields of the pure *Z*-isomer. Ee determined by CSP-HPLC. [b] 20 mol % catalyst **4** employed at 60 °C. [c] Reaction stops at 80% conversion (determined by ^{1}H NMR). [d] Isolated as a mixture of the *E*:*Z*-isomers. [e] Performed at 50 °C. [f] Performed with: step 1: **1** (0.10 mmol), **2e** (0.40 mmol), ***quasient*-4** (0.02 mmol) in 1,4-dioxane (0.5 mL) at 60 °C. See Supporting Information for further details.

and isolated as the pure *Z*-isomer in up to 69% yield with up to 98% ee, proving that the developed procedure gives access to both *E*- and *Z*-isomers of the obtained products.

The absolute configuration of the obtained products was determined by X-ray crystallography of ***E*-6ca** (see Supporting Information for further details).

Formation of Enantioenriched Bicylic Compounds Containing a Monofluorovinyl Moiety. The bicyclo[2.2.2]oct-5-en-2-ones motif is present in a number of natural products,[12] and analogous compounds have been successfully used as intermediates in the synthesis of decaline compounds.[13] Envisioning that novel optically active monofluorinated bicyclo[2.2.2]oct-5-en-2-ones **7** might be formed by an intramolecular aldol reaction followed by a Smiles rearrangement (Figure 4),[9f] we subjected

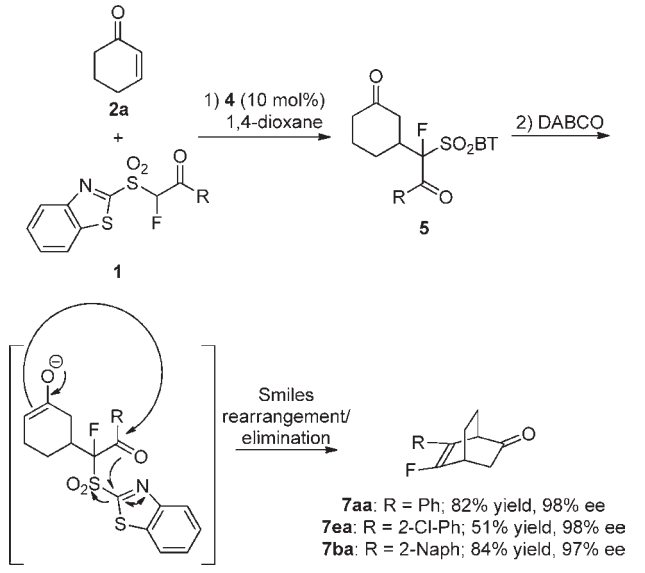


Figure 4. Formation of monofluorinated bicyclo[2.2.2]oct-5-en-2-ones (see Supporting Information for detailed reaction conditions).

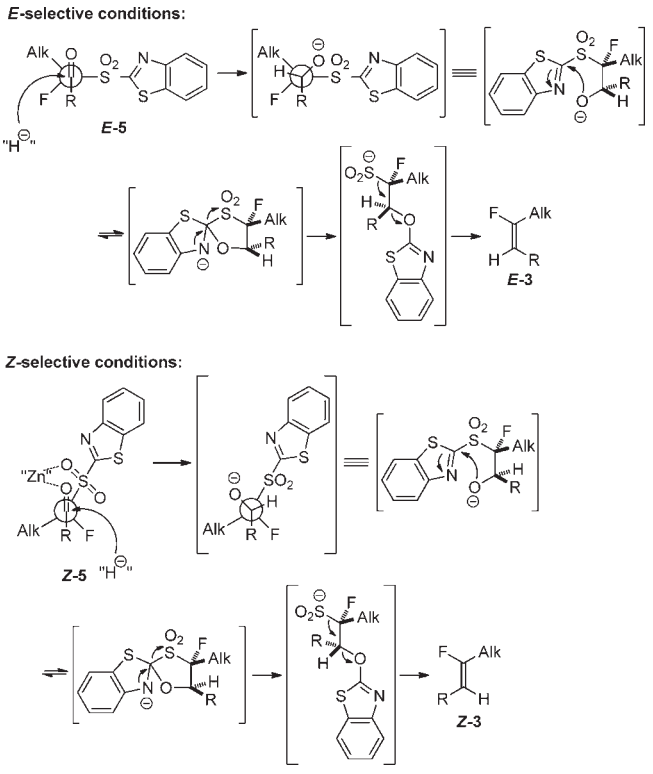


Figure 5. Mechanistic rationale for the observed *E*:*Z*-selectivities.

the adduct **5aa** to a variety of bases. Aqueous solutions of carbonate bases are successful in forming product **7aa**; however, a desulfonylated side-product is consistently formed, presumably by the addition of water to the heteroaryl moiety, thus resulting in a diminished yield of ~50% for **7aa**. To circumvent this problem, organic bases can be employed, and to our delight, the desired product **7aa** was formed exclusively when adding

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DABCO to the solution containing **5aa** in a one-pot manner. As seen in Figure 4, the products **7**, containing a tetrasubstituted monofluoroalkene, can be formed with a variety of aryl substituents on the double bond. Hence, both ortho substituents (**7ea**) as well as the larger 2-naphthyl substituent (**7ba**) are well-tolerated.

Mechanistic Proposal. As a mechanistic rationale for the *E*:*Z*-ratio in **6** (Tables 2 and 3) we assume the diastereoselectivity of the reduction of intermediate **5** to determine the *E*:*Z*-ratio of the alkene formed. As this reduction is an addition to a carbonyl adjacent to an α-chiral center, we suggest that the stereochemical outcome can be explained by the Felkin-Ahn and Cram chelation models. Under Felkin-Ahn conditions, one would expect the most electron-withdrawing substituent to be aligned perpendicular to the carbonyl moiety in the most reactive conformation of **5**. This provides a stabilization of the carbonyl-LUMO by σ^*(C-EWG) and π^*(CO) overlap, rendering the carbonyl more reactive toward nucleophilic attack. Figure 5 shows in the upper scheme a model with the sulfone moiety in this position, based on the observed stereochemical outcome. This leads to monofluoroalkene ***E*-3** as attack of the hydride equivalent is presumed to occur only in the conformer where the fluorine atom is present near the Bürgi−Dunitz trajectory, as this minimizes the steric repulsion. Under chelation control, intermediate **5** would be forced out of its most reactive conformation, as chelation between the carbonyl, Zn(II), and the heteroarylsulfone moiety is now favorable (Figure 5, bottom). Attack from the least hindered side does provide the monofluoroalkene with *Z*-configuration as observed experimentally. As seen in the figure, the proposed mechanism for the reduction step does not involve the fluorine atom in particular, as its sole role is to be the least bulky substituent. If this mechanism is correct, reduction of a nonfluorinated adduct under the developed conditions should result in similar control of *E*:*Z*-selectivity. As such, to provide further evidence to the proposed mechanism, a control experiment was performed with a nonfluorinated precursor. The analogous outcome strongly supports the proposed mechanism, as application of the aforementioned reduction conditions provide access to either ***E*-8** or ***Z*-8** (Figure 6). Futhermore, these experiments reveal that our developed reduction protocols can be extended and optimized to yield nonfluorinated products **8** with both *E*- and *Z*-configuration, enhancing our previously reported procedures.[9d]

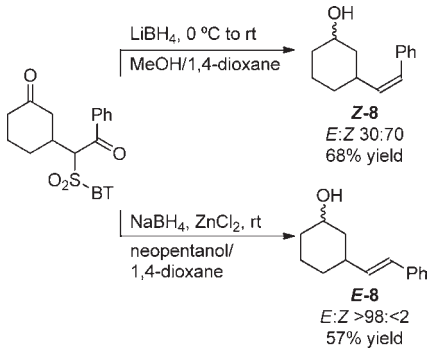


Figure 6. Employment of nonfluorinated nucleophiles in the addition and reduction steps. *E*:*Z*-Ratios are based on ^{1}H NMR of the crude samples. ***Z*-8** was isolated as a mixture of the *E*:*Z*-isomers, and the yields are given for two steps and based on the nucleophile.

Reactions of Imines. The successful development of monofluorovinylations of cyclic and acyclic enones prompted us to investigate the possibility of developing a protocol for the stereoselective formation of monofluorovinylated peptide analogues. As outlined in Figure 7, we anticipated that formation of such compounds could be accomplished by initial phase-transfer catalyzed (PTC)[14] addition of nucleophiles **1** to imines formed from precursors **9**,[15] followed by reduction of the obtained adduct by procedures similar to those developed above.

By employing tetrabutylammonium bromide (TBAB) as catalyst the monofluorovinylation procedure could be successfully extended to include imine electrophiles. The products are formed in good yields with high *E*:*Z*-selectivities, independent of the side chain present. As shown, the valine, leucine, alanine, and methionine derivatives are easily accessible, and the products are isolated as the pure diastereomer. Moreover, the presence of an easily removable carbamate protection group, either *tert*-butyl (Boc) or benzyl carbamate (Cbz), makes these products ideal for employment in further reactions, e.g. peptide-coupling reactions.

We next endeavored to further develop these reactions into asymmetric organocatalytic versions. Screening a range of reaction conditions (see Supporting Information for further details) led to the development of an asymmetric organocatalytic formation of monofluorovinylated dipeptide analogues (Figure 8). Whereas ***Z*-10aa**, bearing an aromatic sidechain, can be isolated only with a moderate enantiomeric excess of 64% ee, the aliphatic side chain of imine precursor **9b** proved more suitable for the developed catalytic system. As such, the leucine derivate ***E*-10ab** can be isolated in 83% yield with an enantiomeric excess of 84% ee, employing the quinine-derived catalyst **11**.

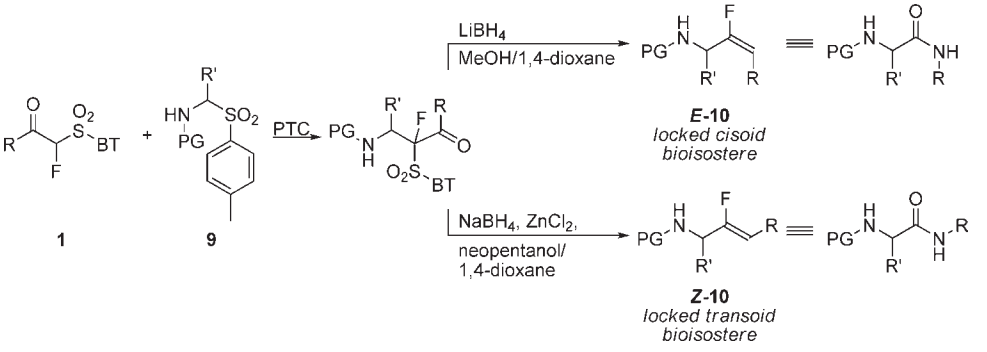
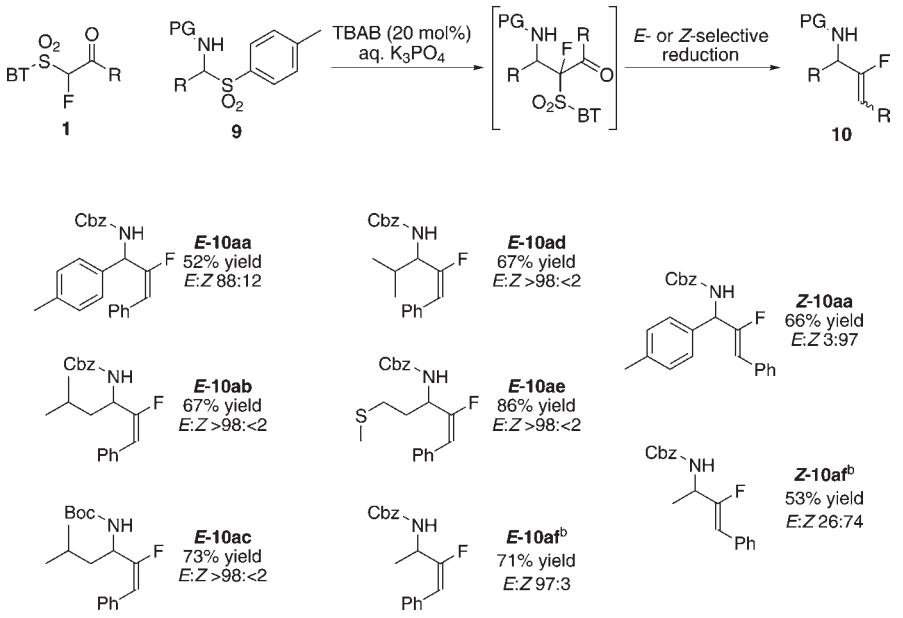


Figure 7. Development of a highly stereoselective formation of dipeptide analogues **10**. PG = protection-group.

Table 4. Stereoselective Formation of Monofluorovinylated Dipeptide Analogues 10[a]



[a] All reactions performed with: step 1: **1** (0.10 mmol), **9** (0.20 mmol), TBAB (0.02 mmol) in CH_2Cl_2 (0.5 mL) with 120 μL of conc. aq K_3PO_4 at room temperature. See Supporting Information for further details. *E*:*Z*-ratios determined by ^{19}F NMR. Yields are isolated yields of the pure isomer. [b] Step 1 performed in water−ice bath. Boc = *tert*-butyl carbamate. Cbz = benzyl carbamate.

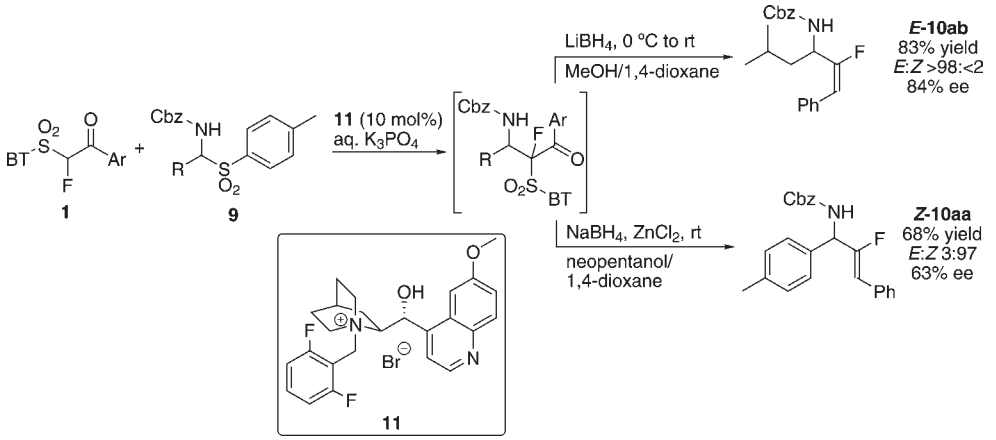


Figure 8. Employment of nucleophiles **1** in the asymmetric organocatalytic formation of dipeptide analogues **10**. Reactions performed as in Table 4 at −30 °C with catalyst **11** (10 mol %) instead of TBAB. See Supporting Information for further details.

CONCLUSION

In summary, we have developed a range of α-fluoro-β-keto-benzothiazolesulfones applicable for highly stereoselective monofluorovinylations. As proof of concept, we have employed these nucleophiles in the formal organocatalytic addition of monofluorovinyl moieties with both *E*- and *Z*-configuration to a range of cyclic and acyclic enones. The resultant products are formed from a common intermediate with up to excellent *E*:*Z*-ratios, and in general isolated as pure diastereomers in good to excellent yields (up to 86%) as well as enantiopurities (up to 99% ee). Suggested mechanisms based on classical models provide a rationale for the *E*:*Z*-selectivities observed experimentally. Moreover, a series of interesting, optically active monofluorinated bicyclo[2.2.2]oct-5-en-2-ones have been synthesized by utilization of these novel nucleophiles. Furthermore, extension of the concept by employing imine electrophiles allowed us to develop an asymmetric organocatalytic formation of monofluorovinylated dipeptide analogues.

ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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