Peptide Mimics

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# Diastereomeric Fluoroolefins as Peptide Bond Mimics Prepared by Asymmetric Reductive Amination of α-Fluoroenones**

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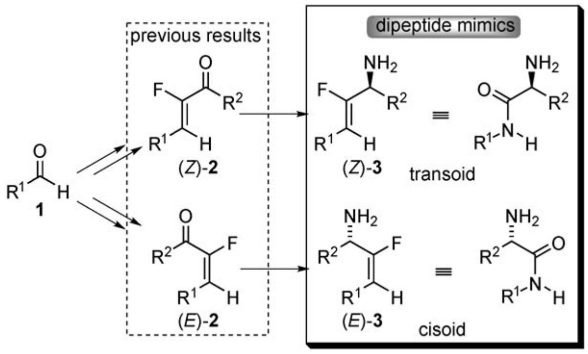
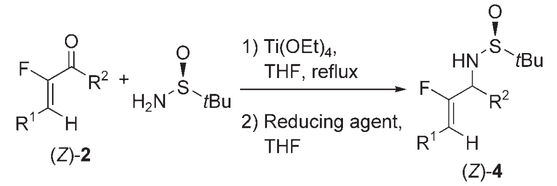
Among the numerous peptide bond analogues, monofluorinated olefins are considered to be ideal mimics because of their close steric and electronic similarities.[1] Moreover, fluoroolefins are not affected by chemical or enzymatic hydrolysis.[1c,d,2] Another important feature is the lack of rotational freedom of this peptidic bond isostere: "transoid" and "cisoid" conformation effects can be estimated separately. Since the pioneering work of Allmendinger et al.,[2b] useful synthetic methods have been developed to prepare fluoroolefins as peptide bond analogues. These include classical olefination reactions (aldol,[3] Horner–Wadsworth–Emmons,[1d,4] and Peterson[5] reactions) and elegant defluorination reactions.[6] Nevertheless, stereochemical control of the fluoroalkene configuration as well as the chiral centers α to the double bond are still important issues to be addressed.

In our project we proposed a stereoselective and mild method to obtain both *E* and *Z* isomers of the dipeptide mimics **3**. Our strategy was based on an efficient Negishi-type reaction with easily accessible bromofluoroalkenes,[7] allowing us access to both *Z* and *E* fluoroenones **2** (Scheme 1).[8] At this stage, we were interested in short sequences to transform unsaturated ketones **2** into chiral allylic primary amines **3**, which are potential dipeptide mimics. To our knowledge, no reductive aminations of α-fluoro α,β-unsaturated ketones **2** had been described. Moreover, there are only few examples of either nonstereoselective[9] or asymmetric[10,11] amination reactions of enones in the literature. Since our first attempts as enantioselective reduction studies gave only moderate results,[12] we turned our attention to diastereoselective processes. Only two chiral agents have been used for the diastereoselective reduction of enones : α-methylbenzylamine[11a,b] and Ellman's sulfinamide.[11c] The facile deprotection of the latter and the high diastereoselectivity induced by this auxiliary prompted us to test this method.[11c,13] Herein we report the first diastereoselective reductive amination of α-fluoroenones **2** and their transformation into dipeptide mimics.



***Scheme 1.*** Fluoroolefins **3** as amide mimics and the general synthetic method developed.

Preliminary tests were made with the aromatic compound **2a**. A one-pot procedure for sulfinyl imine synthesis[14] and subsequent reduction was developed, and we obtained compounds **4** in good yields and high diastereoselectivities (Scheme 2, Table 1). When the imines were purified and isolated before reduction, no significant change in the diastereoselectivity was observed, indicating that the presence of $Ti(OEt)_4$ does not affect the reduction process. Different metal hydrides were tested for the reductive amination of compound **2a**. Common coordinating reagents such as $NaBH_4$, $BH_3$, 9-borabicyclo[3.3.1]nonane (9-BBN), and diisobutylaluminum hydride (DIBAL-H) furnished amines **4a** in yields up to 79% and with excellent diastereoselectivities of up to 97% *de* for the crude mixture (entries 1–4, Table 1). It should be noted that in each case a single chromatographic purification on silica gel afforded the almost diastereomerically pure product (up to 99% *de*). When the Ellman (*S*)-sulfinamide was used as a reagent and DIBAL-H as the reducing agent, the resulting crystals of **4a** displayed the absolute *S* configuration at the created stereogenic center (X-ray analysis).[15]



***Scheme 2.*** Diastereoselective reductive amination of α-fluoro α,β-unsaturated ketones **2**.

At that stage, we postulated that modulations in the steric bulk and in the electronic properties of the metal hydride

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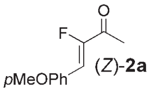
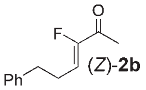
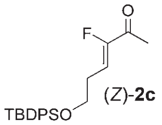
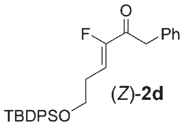
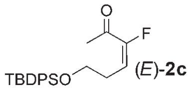
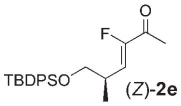
***Table 1:*** Diastereoselective reduction of fluoroenones **2**.

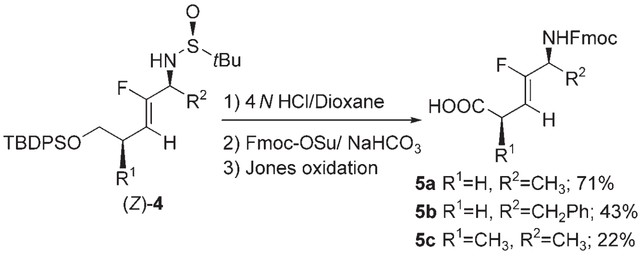
| Entry | Fluoroenone **2**[a] | Reducing agent (−78 °C) | **4**, Yield[b] | *de*[c,d] |
|---|---|---|---|---|
| 1 |  (*Z*)-**2a** | $NaBH_4$ | (*S*,*S*,*Z*)-**4a**, 67 | 94 (89) |
| 2 | | $BH_3$ | (*S*,*S*,*Z*)-**4a**, 48 | 96 (93) |
| 3 | | 9-BBN[e] | (*S*,*S*,*Z*)-**4a**, 77 | 91 (89) |
| 4 | | DIBAL-H | (*S*,*S*,*Z*)-**4a**, 79 | 99 (97) |
| 5 | | $LiBHEt_3$ | (*S*,*R*,*Z*)-**4a**, 64 | 96 (70) |
| 6 | | L-Selectride | (*S*,*R*,*Z*)-**4a**, 72 | 97 (95) |
| 7 | | K-Selectride | (*S*,*R*,*Z*)-**4a**, 63 | 94 (79) |
| 8 |  (*Z*)-**2b** | DIBAL-H | (*S*,*S*,*Z*)-**4b**, 57 | 98 (96) |
| 9 | | L-Selectride | (*S*,*R*,*Z*)-**4b**, 46 | 99 (94) |
| 10 |  (*Z*)-**2c** | DIBAL-H | (*S*,*S*,*Z*)-**4c**, 65 | 98 (95) |
| 11 | | L-Selectride | (*S*,*R*,*Z*)-**4c**, 67 | 96 (95) |
| 12 |  (*Z*)-**2d** | DIBAL-H | (*S*,*S*,*Z*)-**4d**, 58 | 99 (98) |
| 13 | | L-Selectride | (*S*,*R*,*Z*)-**4d**, 57 | 99 (98) |
| 14 |  (*E*)-**2c** | DIBAL-H | (*S*,*S*,*E*)-**4c**, 60 | 99 (96) |
| 15 | | L-Selectride | (*S*,*R*,*E*)-**4c**, 86 | 99 (98) |
| 16 |  (*Z*)-**2e** | DIBAL-H | (*R*,*S*,*S*,*Z*)-**4e**, 61 | 99 (96) |
| 17 | | L-Selectride | (*R*,*S*,*R*,*Z*)-**4e**, 62 | 99 (91) |

[a] TBDPS = *tert*-butyldiphenylsilyl.[b] Yield of isolated product. [c] The *de* values were determined from the $^{19}F$ NMR spectra of isolated products. [d] The *de* value of the crude product is given in brackets. [e] The reaction was conducted at 0 °C and yielded an inseparable mixture of 9-BBN derivative and **4**. The yield of **4** given (77 %) is estimated.

could lead to a reversal of the diastereofacial selectivity, like that described by Ellman and Kochi.[16] Such variations in the stereochemical outcome of the addition of carbon nucleophiles to sulfinyl imines[17] and reduction of *tert*-butanesulfinyl imine bearing a hydroxy group in β position[18] have already been reported. Indeed, with poorly coordinating and bulky reagents such as $LiBHEt_3$, L-Selectride, and K-Selectride, the opposite (*R*) stereomer could be obtained in yields of up to 72 % and diastereoselectivities of up to 95 % *de* for crude mixtures and up to 97 % *de* for purified products (entries 5–7, Table 1). In the course of our study a similar reversal of diastereofacial selectivity was described by Andersen et al. for the reduction of ketone-derived sulfinyl imines.[19] To explain their results, they postulated different transition states depending on the nature of the reducing agent. The same approach can be applied to our compounds: a six-membered-ring transition state should be favored by chelation of the metal hydride to the sulfoxyde moiety, allowing the hydride delivery to occur at the *Si* face. When bulkier and non-coordinating reagents are employed, steric control and the classical Cram's rule could explain the generation of the opposite stereomer.[17–19]

We then tried to extend the method to aliphatic compounds using DIBAL-H and L-Selectride as the reducing agents. The phenylethyl derivative (*Z*)-**2b** and compound (*Z*)-**2c**, a precursor of the Ala-$\Psi$[(*Z*)CF=CH]-Gly dipeptide mimic, gave good yields and excellent diastereoselectivities (entries 8–11, Table 1). Very good results were also obtained with compound (*Z*)-**2d**, a precursor of the Phe-$\Psi$[(*Z*)CF=CH]-Gly derivative, showing that an increase in the steric hindrance of the ketimine moiety does not affect the reduction (entries 12 and 13, Table 1)). The reduction process applied to the cisoid peptide mimic precursor (*E*)-**2c** was not affected by the double-bond geometry and led to excellent results (entries 14 and 15, Table 1)). Lastly, we tested the chiral precursor (*Z*)-**2e** and observed no mismatch effects for the reduction process. Indeed, results were still good in terms of yield (> 60 %) and excellent in terms of diastereoselectivity (up to 99 % *de*). It should be noted that for all these substrates, the reversal of stereoselectivity depending on the reducing reagent was effective (see Table 1).

In our ongoing project aimed to develop a general route to peptidomimetics bearing the fluoroolefin isostere $\Psi$[CF=CH], we performed a three-step procedure—a double deprotection step, protection of the amine group with an 9-fluorenylmethyloxycarbonyl (Fmoc) moiety, and oxidation of the alcohol to the carboxylic acid—to prepare dipeptide mimics ready for automated synthesis (Scheme 3). Ala-Gly and Phe-Gly peptidomimetics were obtained in 71 % and 43 % overall yields, respectively. The Ala-Ala peptide mimic was generated in a lower 22 % overall yield as a result of less effective deprotection and Fmoc protection steps. Finally, three dipeptide mimics were synthesized in a chiral manner: Fmoc-Ala-$\Psi$[(*Z*)CF=CH]-Gly, Fmoc-Ala-$\Psi$[(*Z*)CF=CH]-Ala, and Fmoc-Phe-$\Psi$[(*Z*)CF=CH]-Gly.



***Scheme 3.*** Synthesis of dipeptide analogues. Fmoc-OSu = 9-fluorenylmethyloxycarbonyl-*N*-hydroxysuccinimide.

In summary, we have reported the first efficient asymmetric reductive amination of fluoroenones to give potential fluoropeptide isosteres precursors. Using different reducing agents, we developed stereoselective routes to both diastereomers from the same chiral nonracemic sulfinyl imine. The method could be applied to aromatic as well as aliphatic compounds without erosion of yields and stereoselectivities. Moreover, neither the fluoroolefin geometry nor the presence of chiral center on the C-terminal moiety affected the reduction selectivity. Finally, we applied this methodology to the synthesis of three chiral dipeptide analogues: Fmoc-

Ala-*Ψ*[(*Z*)CF=CH]-Gly, Fmoc-Ala-*Ψ*[(*Z*)CF=CH]-Ala, and Fmoc-Phe-*Ψ*[(*Z*)CF=CH]-Gly.

## *Experimental Section*

General procedure for the conversion of fluoroenones **2** into fluoro-*tert*-butylsulfinamides **4**: A solution of 0.5 M $Ti(OEt)_4$ (2 equiv), (*S*)-*tert*-butylsulfinylamine (2 equiv), and fluoroenone **2** (1 equiv) in dry THF was prepared under argon and heated to reflux for 2 h. The mixture was allowed to cool to room temperature and then cooled to −78 °C. DIBAL-H (1 M in toluene, 4 equiv) was then added dropwise, and the mixture was stirred for 1 h. After the reaction was complete ($^{19}$F NMR spectrum of the reaction mixture was monitored), MeOH was added at −78 °C. The mixture was then allowed to warm to room temperature. The resulting solution was then poured into an equal volume of brine with rapid stirring. The resulting suspension was then filtered through a plug of Celite, and the filter cake was washed with EtOAc. The filtrate was washed with brine, the organic layer was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic portions were dried, filtered, and concentrated under reduced pressure. The residue was then purified by chromatography on silica gel (EtOAc/cyclohexane 1:1), affording the desired *tert*-butylsulfinamide **4**.

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**Keywords:** asymmetric synthesis · fluoroenones · fluoroolefins · peptidomimetics · reductive amination

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