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Diastereocontrolled addition of organometallic reagents to S-chiral *N*-(*tert*-butanesulfinyl)-α-fluoroenimines

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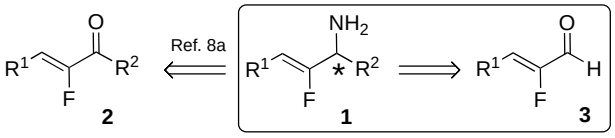
ABSTRACT

Grignard and organolithium reagents efficiently react with (*S*)-*N*-(tert-butanesulfinyl)-α-fluoroenimines to provide chiral allylamines in excellent yields and with diastereomeric ratios of up to 96:4. Acidic removal of the sulfinyl group and simple functional group transformations allow to get enantiopure fluoroolefin dipeptide mimics.

Fluorine is certainly the element that has experienced the greatest interest in the recent years as evidenced by the huge number of fluorinated synthetic pharmaceuticals, agrochemicals, and materials that had been synthesized.[1] In the field of medicinal chemistry, fluorinated molecules clearly have altered physicochemical properties when compared to non-fluorinated derivatives, and often with an improved therapeutic profile.[2] Among the very large variety of fluorine-containing compounds, functionalized fluoroolefins represents a motif that is an effective amide bond mimic. Indeed, the fluoroolefin moiety is both isosteric and isoelectronic to the amide function and its stability to chemical or enzymatic hydrolysis is high.[3] Relevant biologically active compounds that incorporate the fluoroolefin moiety include dipeptidyl peptidase inhibitors,[4] substance P analogues,[5] and adenylate cyclase production stimulators.[6]

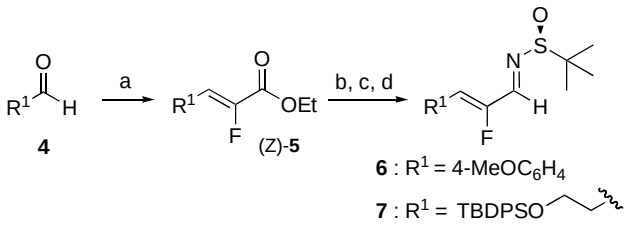
In our ongoing project devoted to the synthesis of new functionalized fluoroolefins, we required the asymmetric access to α-substituted-β-fluorinated allyl amines **1** (Scheme 1). Few methods have been described to produce enantioenriched molecules of type **1**.[5–7] Previously, we described an efficient access to compounds **1** via an asymmetric reductive amination of the corresponding α-fluoroenones **2** (Scheme 1).[8]

We herein report a complementary route to **1** from the more easily accessible fluoroenals **3** via the addition of Grignard and organolithium reagents to the C=N bond of chiral α-fluoroenimines **6** and **7** (Schemes 1 and 2).[9]



Scheme 1. Two synthetic pathways to chiral fluorinated allyl amines **1**.

Both aliphatic and aromatic aldehydes **4** were considered in our study. Ethyl dibromofluoroacetate reacted with aldehydes in the presence of diethylzinc to afford pure (*Z*) α-fluoroesters **5**.[10] Alternatively, (*Z*)-**5** could be obtained by a modified Julia olefination



Scheme 2. Synthesis of starting α-fluoroenimines **6** and **7**. Reagents and conditions: (a) FBr_2CCO_2Et, Et_2Zn, DCM, rt, 3h, 38–60%; (b) DIBAL-H, THF, −78 °C, 3 h, quant.; (c) SO_3·pyridine, DMSO, Et_3N, DCM, 0 °C, 82–89%; (d) (*S*)-(−)-*t*-butanesulfinamide, $Ti(OEt)_4$, THF, reflux, 1 h, 89–96%.

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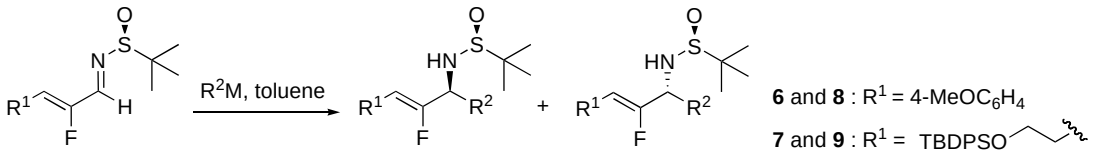
reaction from **4** and ethyl fluorobenzothiazolylsulfonyl acetate with DBU in the presence of $MgBr_2$.[11] Next, a two-step sequence of reduction and oxidation provided α-fluoro-α,β-unsaturated aldehydes **3**. The straightforward preparation of β-fluoroenimines **6** and **7** was carried out according to the well-established Ellman procedure with the aid of (*S*)-(−)-*tert*-butanesulfinamide (Scheme 2).[9a]

To determine suitable reaction conditions, we first carried out the addition of phenylmagnesium bromide to α-fluoroenimines **6** in various solvents (toluene, dichloromethane, and THF). Toluene provided the best yield and diastereomeric ratio (95%, 10:90 dr) while CH_2Cl_2 and THF gave lower yields (87% and 91%, respectively) and lower dr were observed in THF (35:65). Consequently, all experiments have been carried out in toluene. Representative results are listed in Table 1.[12] Importantly, all Grignard and organolithium reagents were added regioselectively at the imino carbon of α-fluoroenimines to give (S_S,*S*) and (S_S,*R*) diastereomers. Diastereomeric ratios were determined by ^{19}F NMR on the crude mixtures. It is worth noting that all diastereomeric mixtures could be purified by silica gel column chromatography to afford each product in a diastereomerically pure form. Attempts to react phenylzinc bromide with substrate **6** at various temperatures failed to get the addition product **8a**; **6** was recovered unchanged. In most cases, the yield of the desired addition product was high (>82%) except for Grignard reagents possessing a β-hydrogen atom. For this latter, reduction of the C=N bond occurred in quite high proportion, thus lowering the yield of the desired product (entries 11, 13, 22, and 24). To circumvent this side reaction, *i*-PrLi at −78 °C was used instead of *i*-PrMgCl at 0 °C allowing an increase in yield for compounds **8c** and **9c** to 98% and 91%, respectively (entries 12 and 23). We explored a number of Lewis acids as additive to enhance the yield and the diastereomeric ratio of the reaction. Thus, precomplexation of **6** or **7** with $AlMe_3$ (1.1 equiv) and reaction with PhMgBr did not allow the reaction to take place whereas the reaction with PhLi happened albeit without improvement of yield and dr (entries 2, 4, and 18). Interestingly, the diastereoselectivity was dramatically reversed, changing from 10:90 with PhMgBr to 67:33 with PhLi for substrate **6** (entries 1 and 3), and from 14:86 to 65:35 for substrate **7** (entries 17 and 19). Reversals of diastereoselectivity also applied to the reagents *i*-PrMgCl/*i*-PrLi (entries 11, 12, 22, and 23) and in a lower extend to MeMgBr/MeLi (entries 5–10). The opposite induction is obviously due to different transition states. Contrary to PhMgBr, the use of MeMgBr on the precomplexed substrate with $AlMe_3$ revealed that the reaction affords the desired product **8b** in high yield with higher dr, up to 6:94 (entry 7). The addition of MeLi required low temperature (−78 °C) and longer reaction time, but excellent yields are obtained although with poor diastereoselectivity (entries 9 and 10). With the aliphatic substrate **7**, in the presence of $AlMe_3$, product **9b** was also obtained in higher dr (10:90, entry 21). Under similar conditions $BF_3{\cdot}Et_2O$ failed to produce compound **8b** (entry 8). The scope of the reaction was further investigated in toluene, with or without $AlMe_3$. Benzyl, allyl, and vinyl Grignards were evaluated, all giving high product yields in the range 82–98% with moderate to high drs. In particular, allylMgBr provided the highest dr in our study in up to 4:96 for compound **8f** (entry 15).

The absolute configuration of the newly created stereogenic center was established by X-ray crystallography of the minor

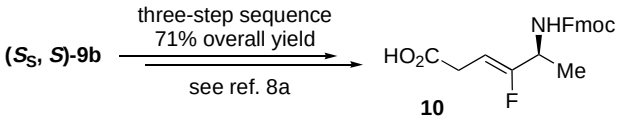
Table 1
Diastereoselective addition of Grignard and organolithium reagents to β-fluoroenimines **6** and **7**[12]



6, 7 **(S_S, *S*)-8, 9** **(S_S, *R*)-8, 9**

Entry	Substrate	R^2M (equiv)	*T* (°C)	Time (h)	Additive (1.1 equiv)	Product	Yield (%)	dr[a]
1	**6**	PhMgBr (1.1)	−30	2	—	**8a**	95	10:90
2	**6**	PhMgBr (1.1)	0	12	$AlMe_3$	**8a**	0	—
3	**6**	PhLi (1.6)	−78	3	—	**8a**	95	67:33
4	**6**	PhLi (2)	−78	0.75	$AlMe_3$	**8a**	100[b]	65:35
5	**6**	MeMgBr (1.1)	−30	30	—	**8b**	45	25:75
6	**6**	MeMgBr (1.1)	0	0.5	—	**8b**	93	11:89
7	**6**	MeMgBr (1.1)	0	0.75	$AlMe_3$	**8b**	82	6:94
8	**6**	MeMgBr (1.1)	0	48	$BF_3{\cdot}Et_2O$	**8b**	0	—
9	**6**	MeLi (2)	−78	5	—	**8b**	96	45:55
10	**6**	MeLi (2)	−78	5	$AlMe_3$	**8b**	96	53:47
11	**6**	*i*-PrMgCl (3)	0	0.7	—	**8c**	60	30:70
12	**6**	*i*-PrLi (3)	−78	1	—	**8c**	98	60:40
13	**6**	*i*-BuMgBr (1.5)	0	0.7	—	**8d**	27	30:70
14	**6**	BnMgCl (1.1)	0	1	—	**8e**	94	30:70
15	**6**	AllylMgBr (3)	0	1	—	**8f**	82	4:96
16	**6**	VinylMgBr (3)	0	0.5	—	**8g**	95	33:67
17	**7**	PhMgBr (1.1)	0	1.5	—	**9a**	90	14:86
18	**7**	PhMgBr (1.6)	0	12	$AlMe_3$	**9a**	0	—
19	**7**	PhLi (2.6)	−78	12	—	**9a**	83	65:35
20	**7**	MeMgBr (2.6)	0	4	—	**9b**	90	21:79
21	**7**	MeMgBr (2)	0	2.5	$AlMe_3$	**9b**	84	10:90
22	**7**	*i*-PrMgCl (3)	0	0.75	—	**9c**	41	49:51
23	**7**	*i*-PrLi (3)	−78	1	—	**9c**	91	67:33
24	**7**	*i*-BuMgBr (1.1)	0	0.5	—	**9d**	36	30:70
25	**7**	BnMgCl (1.1)	0	1.5	—	**9e**	90	43:57
26	**7**	AllylMgBr (1.1)	0	0.75	—	**9f**	91	8:92
27	**7**	VinylMgBr (1.5)	0	0.75	—	**9g**	98	35:65

[a] Ratio determined by ^{19}F NMR of the crude reaction mixture.
[b] Conversion determined by ^{19}F NMR of the crude reaction mixture.



Scheme 3. Synthesis of Fmoc-Ala-Ψ[(Z)CF=CH]-Gly dipeptide analogue **10**.

diastereomer of **8b**, which was found to have the *S*-configuration.[8a] This meant that addition of Grignard reagent MeMgBr to sulfinimine **6** proceeded on Re-face of the imine function. By analogy, we assumed that all other Grignard reagents were added similarly to β-fluoroenimines **6** and **7**.

This methodology is quite general and should be amenable to the synthesis of a large variety of chiral fluorinated allyl amines. Indeed, the stereoselective addition of organometallic species served as the key step in the construction of dipeptide analogues as exemplified by the transformation of (S_S,*S*)-**9b** into Fmoc-Ala-Ψ[(Z)CF=CH]-Gly **10** (Scheme 3).

In summary, an efficient synthetic method has been developed whereby diastereoselective addition of Grignard and organolithium reagents to *N*-(*tert*-butanesulfinyl)-β-fluoroenimines provided chiral fluorinated sulfinamides in high yields with diastereomeric ratios of up to 96:4. Separation of diastereomers on silica gel chromatography provided enantiopure versatile intermediates for the synthesis of stable drug analogues. We have demonstrated that further simple chemical transformations afforded fluoroolefin dipeptide mimics.

Acknowledgment

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12. *Typical procedure for synthesis of N-((Z)-1-allyl-5-{[tert-butyl(diphenyl)silyl]oxy}-2-fluoro-2-pentenyl)-2-methyl-2-propanesulfinamide* **9f**: β-Fluoroenimine **7** (70 mg, 0.152 mmol) was placed in a flask under argon and dissolved in anhydrous toluene (1 mL). The solution was cooled to 0 °C and allylmagnesium bromide (168 μL of a 1 M solution in diethyl ether, 0.168 mmol) was slowly added. After stirring for 40 min, the solution was quenched with a saturated solution of NH_4Cl and extracted three times with EtOAc. The combined organic layers were then washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was checked by ^{19}F NMR for determination of diastereomeric ratio (dr = 8:92) and purified by chromatography on silica gel (eluent: cyclohexane/EtOAc 80/20 to 70/30) affording the expected compound **9f** as a colorless oil (70.2 mg, yield 91%). Diastereomer (S_S,*R*)-**9f**: ^1H NMR ($CDCl_3$, 300 MHz): δ 1.04 (s, 9H), 1.19 (s, 9H), 2.32–2.39 (m, 2H), 2.43–2.57 (m, 2H), 3.35 (d, ^3J = 4.35 Hz, 1H), 3.66 (t, ^3J = 6.42 Hz, 2H), 3.92 (ddd, ^3J = 4.35 Hz, ^3J = 6.75 Hz, ^3J = 17.50 Hz), 4.93 (dt, ^3J = 7.53 Hz, ^3J = 37.11 Hz, 1H), 5.15–5.20 (m, 2H), 5.73 (ddd, ^3J = 6.97 Hz, ^3J = 10.40 Hz, ^3J = 17.52 Hz, 1H), 7.35–7.45 (m, 6H), 7.64–7.67 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 19.3, 22.5, 26.9, 27.2, 38.0, 55.4, 55.9, 63.1, 105.4 (d, ^3J = 4.4 Hz), 119.8, 127.8, 128.9, 133.2, 133.8, 135.6, 157.7 (d, ^1J = 257 Hz); ^{19}F NMR ($CDCl_3$, 282.5 MHz): δ 123.9 (dd, ^3J = 17.5 Hz, ^3J = 37.1 Hz); MS (EI$^+$): [M+H$^+$] = 502.00; Anal. Calcd for $C_{28}H_{40}FNO_2SSi$: C, 67.02; H, 8.04; N, 2.79. Found: C, 66.99; H, 8.31; N, 2.75. Diastereomer (S_S,*S*)-**9f**: ^1H NMR ($CDCl_3$, 300 MHz): δ 1.04 (s, 9H), 1.20 (s, 9H), 2.33–2.52 (m, 4H), 3.41 (d, ^3J = 4.53 Hz, 1H), 3.43 (t, ^3J = 6.59 Hz, 2H), 3.79 (ddd, ^3J = 4.53 Hz, ^3J = 6.78 Hz, ^3J = 18.50 Hz,), 4.95 (dt, ^3J = 7.35 Hz, ^3J = 38.20 Hz, 1H), 5.07–5.14 (m, 2H), 5.72 (ddd, ^3J = 6.97 Hz, ^3J = 10.00 Hz, ^3J = 17.14 Hz, 1H), 7.34–7.45 (m, 6H), 7.65–7.67 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 19.3, 22.7, 26.9, 27.2 (d, ^3J = 4.4 Hz), 37.6, 56.4, 56.8 (d, ^2J = 28.5 Hz), 63.1, 105.0 (d, ^2J = 14.2 Hz), 118.6, 127.7, 129.7, 133.5, 133.9, 135.7, 158.5 (d, ^1J = 257 Hz); ^{19}F NMR ($CDCl_3$, 282.5 MHz): δ −122.8 (dd, ^3J = 18.5 Hz, ^3J = 38.2 Hz); MS (EI$^+$): [M+H$^+$] = 502.00; Anal. Calcd for $C_{28}H_{40}FNO_2SSi$: C, 67.02; H, 8.04; N, 2.79. Found: C, 67.25; H, 8.11; N, 2.77.