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# Enantioselective Synthesis of Fluorinated α-Amino Acids and Derivatives in Combination with Ring-Closing Metathesis: Intramolecular π-Stacking Interactions as a Source of Stereocontrol

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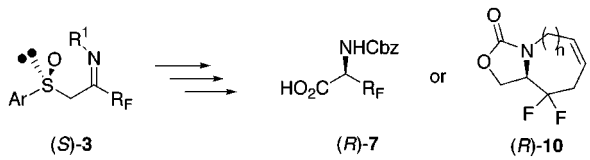
## ABSTRACT




(*S*)-**3** (*R*)-**7** (*R*)-**10**

**Hydride reduction of C═N bonds stereocontrolled by intramolecular π-stacking interactions of 1-naphthylsulfinyl and *N*-aryl groups, nonoxidative Pummerer rearrangement, and ring-closing metathesis are efficiently combined in a highly stereoselective entry to enantiomerically pure cyclic and acyclic fluorinated β-amino alcohols and α-amino acid derivatives, respectively.**

Attractive interactions between π-systems (π-stacking) play a key role in diverse phenomena, including stabilization of the helical structure of DNA, tertiary structures of proteins, and complexation in host−guest systems.[1] In asymmetric synthesis, π-stacking interactions are gaining increasing attention as a source of high stereoselectivity.[2] We now report a highly diastereoselective synthesis of cyclic and acyclic fluorinated α-amino acids and derivatives,[3] where intramolecular π-stacking interactions involving *N*-aryl and 1-naphthylsulfinyl groups were invoked to achieve stereocontrol with up to 98% de.

Fluorinated β-sulfinylamines **4**, available from enantiopure sulfinyl *N*-aryl imines (*S*)-*Z*-**3** (Scheme 1),[4] are suitable starting materials for the synthesis of fluorinated alaninols **6** and the corresponding alanines **7**.[5] The key issue allowing

(1) (a) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525−5534 and references therein. (b) Doyon, J. B.; Jain, A. *Org. Lett.* **1999**, *1*, 183−185. (c) Edge-to-face aromatic interactions have also been invoked in many examples of molecular recognition. See, for example: Paliwal, S.; Greib, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1994**, *116*, 4497−4498 and literature cited therein.

(2) Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475−497.

(3) For an overview of this field see: (a) *Fluorine-containing Amino Acids: Synthesis and Properties*; Kukhar, V. P., Soloshonok, V. A., Eds.; Wiley: Chichester, 1995. (b) *Enantiocontrolled Synthesis of Fluoro-organic Compounds*; Soloshonok, V. A., Ed.; Wiley: Chichester, 1999.

(4) (a) Fustero, S.; Navarro, A.; Pina, B.; Asensio, A.; Bravo, P.; Crucianelli, M.; Volonterio, A.; Zanda, M. *J. Org. Chem.* **1998**, *63*, 6210−6219. (b) Bravo, P.; Cavicchio, G.; Crucianelli, M.; Markovsky, A. L.; Volonterio, A.; Zanda, M. *Synlett* **1996**, 887−889.

(5) Crucianelli, M.; Bravo, P.; Arnone, A.; Corradi, E.; Meille, S. V.; Zanda, M. *J. Org. Chem.* **2000**, *65*, 2965−2971.

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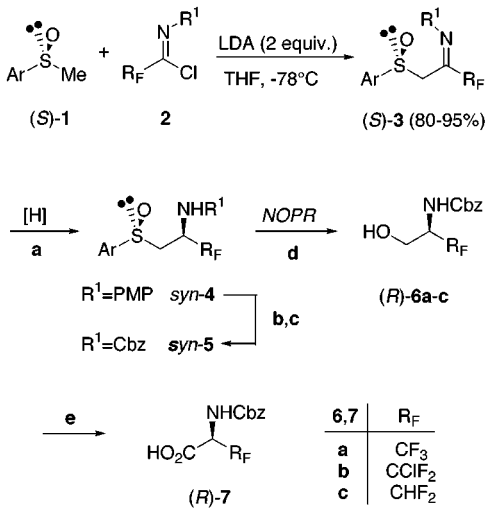
**Scheme 1**[a]




[a] (a) $Bu_4NBH_4$, MeOH, −70 °C. (b) CAN, $CH_3CN/H_2O$, rt, (> 90%). (c) $ClCO_2Bn$, dioxane/aq $K_2CO_3$ 50%, rt, (75−99%). (d) (i) TFAA, $CH_3CN$, *sym*-collidine, 0 °C; (ii) $K_2CO_3$ (10%); (iii) $NaBH_4$, $H_2O$, (three steps, 70−90%). (e) $RuO_2 \cdot xH_2O/NaIO_4$, acetone/$H_2O$, rt, (65−70%).

this protocol to become synthetically useful was the development of a highly efficient hydride reduction of the C=N bond of **3** to **4**. To this end, the influence of reaction conditions, sulfinyl residue Ar, and imine substituent $R^1$ on yields and diastereoselectivity was carefully investigated. Use of $Bu_4NBH_4$[6] as reducing agent, pure methanol or THF/methanol as solvent, and in general, low temperatures (−70 °C) provided the best diastereocontrol. In fact, nearly quantitative overall yields of **4a**−**j** were obtained from **3a**−**j**, with overwhelming predominance of the *syn*-diastereomers (dr ranging from 88:12 to 99:1) (Table 1). Apparently, the arylsulfinyl group exerts a significant influence on stereoselectivity, and the de follows the order: 1-naphthyl (entries 2 and 4) > 2-naphthyl (entry 3) > *p*-Tol (entry 1). To find some insights on the origin for the high *syn*-diastereoselectivity, ab initio molecular orbital (MO) and density functional theory (DFT) calculations were carried out on representative *β*-iminosulfoxides (*R*)-**3b**,**c**, all of them in both *Z* and *E* imino configuration. This study brought two interesting features to light (Table 2). First, *Z* imino tautomers are predicted to be more stable than those of the *E* configuration, regardless of the computational method used. Second, and most interestingly, calculations showed an almost parallel (face-to-face)[1c] geometry between PMP and the 1-naphthyl rings of (*R*)-*Z*-**3b** with an interplanar separation of 3.9−4.2 Å (Figure 1), which strongly suggests the presence of an attractive $\pi-\pi$ interaction.

**Table 2.** Energy Differences[a] between the *E* and *Z* Imino Tautomers of Optimized Structures of (*R*)-**3b,c**

| method | Δ*E* (*E*-*Z*)-**3b** | Δ*E* (*E*-*Z*)-**3c** |
|---|---|---|
| HF/6-31G* | 1.73 | 1.66 |
| B3LYP/6-31G*//HF/6-31G* | 1.26[b] | 1.80[b] |
| B3LYP/6-31G* | 1.56 | 2.20 |

[a] Energies in kcal $mol^{-1}$. [b] Single-point calculations using the HF/6-31G* geometry.

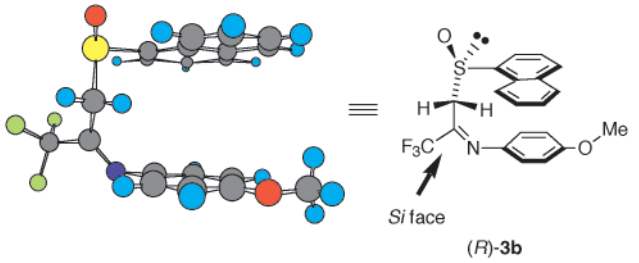



**Figure 1.**

Theoretical predictions regarding the first point (geometry of **3**) are in full agreement with the spectroscopic data.[4a] Satisfactorily, also the $\pi$-stacking predictions found support

**Table 1.** Synthesis of *N*-Aryl-*β*-sulfinylamines **4a**−**j**[a]

| entry | (*S*)-**3** | $R_F$ | Ar | R′ | 4 | yield (%)[b] | *syn*:*anti*[c] |
|---|---|---|---|---|---|---|---|
| 1[d] | **3a** | $CF_3$ | *p*-$MeC_6H_4$ | *p*-$MeOC_6H_4$ | **4a** | >98 | 88:12 |
| 2[d] | **3b** | $CF_3$ | 1-naphthyl | *p*-$MeOC_6H_4$ | **4b** | >98 | 99:1 |
| 3[d] | **3c** | $CF_3$ | 2-naphthyl | *p*-$MeOC_6H_4$ | **4c** | >98 | 94:6 |
| 4 | **3d** | $CClF_2$ | 1-naphthyl | *p*-$MeOC_6H_4$ | **4d** | >98 | 99:1 |
| 5 | **3e** | $CHF_2$ | 1-naphthyl | *p*-$MeOC_6H_4$ | **4e** | >98 | 91:9 |
| 6[e] | **3f** | $CF_3$ | 1-naphthyl | *o*-$MeOC_6H_4$ | **4f** | >98 | 97:3 |
| 7[e] | **3g** | $CF_3$ | 1-naphthyl | *p*-$FC_6H_4$ | **4g** | >98 | 98:2 |
| 8[e] | **3h** | $CF_3$ | 1-naphthyl | 1-naphthyl | **4h** | >98 | 99:1 |
| 9[e] | **3i** | $CF_3$ | 1-naphthyl | *c*-$C_6H_{11}$ | **4i** | 33 | 66:34 |
| 10[e,f] | **3j** | $CH_2$=$CHCH_2CF_2$ | 1-naphthyl | *p*-$MeOC_6H_4$ | **4j** | >98 | 99:1 |

[a] Reaction time 30 min except for entries 9 (168 h) and 10 (5 h); $Bu_4NBH_4$ as reducing agent and methanol as solvent. [b] Isolated overall yields. [c] Determined by $^{19}F$ NMR of the crude reaction mixture. [d] Similar results have been obtained starting from (*R*)-**3a** (entry 1), (*R*)-**3b** (entry 2), or (*R*)-**3c** (entry 3). [e] THF/MeOH as solvent. [f] See Scheme 2.

by NMR studies (ROESY) performed on (*S*)-*Z*-**3b** at 195 K in $CD_3OD$, which are the optimized reaction conditions. NOE contacts among the four hydrogens of the PMP having nearly the same chemical shift in $CD_3OD$ and all seven hydrogens of the 1-naphthyl ring were clearly detected. Moreover, the *p*-$CH_3O$ group showed selective NOE with the H-5,6,7 of the naphthalene ring. Finally, the pro-*S* diastereotopic methylene hydrogen showed preferential contact with H-8 (*peri* to the substituent) of the 1-naphthyl, while the pro-*R* showed preferential contact with H-2 (*ortho*). These observations suggest that the molecule is arranged in a preferred conformation with the PMP and naphthyl rings close in the space. The face-to-face $\pi$-stacking model predicted by the calculations is in good agreement with the experimental NOE data. However, those data cannot exclude the occurrence of a different interaction, such as edge-to-face stacking, which would also bring at short distance some protons of the aromatic rings.

The stacking is likely to have a decisive influence on the stereochemical outcome of the C=N bond reduction, because the *si* face for $R_F = CF_3$, $CHF_2$ and the *re* face for $R_F = CClF_2$ are exposed to the hydride attack, whereas the other diastereoface is efficiently shielded (Figure 1).

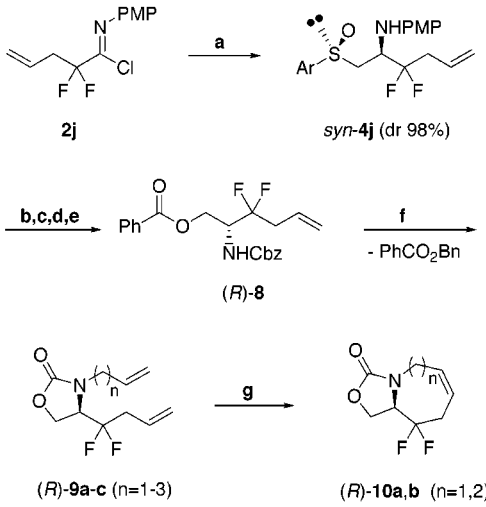
The calculated geometry for the 2-naphthyl derivative (*R*)-*Z*-**3c** predicts a less effective $\pi-\pi$ interaction;[7,8] in fact, formation of *syn*-**4c** occurred with lower diastereoselectivity (entry 3).

The influence of *N*-substituent $R^1$ was also investigated. A high degree of stereoselectivity was always obtained by replacing PMP with aromatic groups having different electron density, such as *o*-methoxyphenyl (**3f**, entry 6), *p*-fluorophenyl (**3g**, entry 7), and 1-naphthyl (**3h**, entry 8). This minor effect on diastereoselectivity and therefore on the stacking stability suggests that either van der Waals or electrostatic quadrupolar interactions[7b] involving 1-naphthylsulfinyl and Ar rings could be responsible for the stacking, rather than a charge-transfer that should be very sensitive to the ring electron density. In addition, substitution of the *N*-aryl with a *N*-cyclohexyl group, which cannot give stacking, featured a dramatic drop of stereoselectivity (**3i**, entry 9).

With the enantiopure precursors *syn*-**4** in hand, we completed the synthesis of the target alaninols (*R*)-**6a**−**c** and alanines (*R*)-**7a**−**c**[9] (Scheme 1). Replacement of the 1-naphthylsulfinyl auxiliary by a hydroxyl was accomplished by means of the "nonoxidative" Pummerer reaction (NOPR).[5] To this end, the PMP groups of *syn*-**4b,d,e** were cleaved oxidatively (CAN, 5 equiv), and then the amino groups were reprotected with $ClCO_2Bn$ to afford *syn*-**5b,d,e**.[10] Satisfactorily, the NOPR protocol afforded (*R*)-**6a**−**c** in good to excellent yields. The final oxidation with $RuO_2 \cdot xH_2O/NaIO_4$ provided (*R*)-**7a**−**c** in fair yields.

This methodology has remarkable potential for the synthesis of enantiomerically pure fluorinated amino-derivatives. A new application combined with the ring-closing metathesis (RCM)[11,12] is demonstrated for the synthesis of the first enantiomerically pure fluorinated cyclic $\beta$-amino alcohol derivatives (**10**) featuring seven- and eight-membered rings (Scheme 2).[13]

**Scheme 2**[a]




[a] (a) (i) (*S*)-**1a**, LDA (2.0 equiv), THF, −78 °C to rt, 6 h, (80%); (ii) $Bu_4NBH_4$, THF/MeOH, −70 °C to rt, 5 h, (>98%). (b), (c), and (d) As in Scheme 1 [(*R*)-**6d**]. (e) $PhCO_2H$, DCC, DMAP, $CH_2Cl_2$, rt, 7 h (95%). (f) $Br(CH_2)_nCH{=}CH_2$, NaH, DMF, 0 °C [**9a** ($n$ = 1), 84%; **9b** ($n$ = 2), 45%; **9c** ($n$ = 3), 90%]. (g) $Cl_2(PCy_3)_2Ru{=}CHPh$ (3−10 mol %), $CH_2Cl_2$ (0.01−0.005 M), rt, [(*R*)-**10a** ($n$ = 1),75%; (*R*)-**10b** ($n$ = 2),87%].

The strategy consists of the diastereoselective reduction of $\beta$-iminosulfoxide (*S*)-**3j** obtained by condensation reaction of the hitherto unknown imidoyl chloride **2j**[14b] and sulfoxide (*S*)-**1a**[14a] to afford *N*-PMP $\beta$-aminosulfoxide *syn*-**4j** (entry 10, Table 1 and Scheme 2).

(6) (a) Taniguchi, M.; Fujii, H.; Oshima, K.; Utimoto, K. *Tetrahedron* **1993**, *49*, 11169−11182. (b) *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A. Ed.; Wiley: Chichester 1995; Vol. 7, pp 4722−4724.

(7) For related examples, see: (a) Sakuraba, H.; Ushiki, S. *Tetrahedron Lett.* **1990**, *31*, 5349−5352. (b) Heaton, N. J.; Bello, P.; Herradón, B.; del Campo, A.; Jiménez-Barbero, J. *J. Am. Chem. Soc.* **1998**, *120*, 9632−9645.

(8) $\pi$-Stacking between aromatic rings in protic solvents have been described in the literature: (a) Kool, E. T.; Breslow, R. K. *J. Am. Chem. Soc.* **1988**, *110*, 1596−1597. (b) Schumacher, D. P.; Clark, J. E.; Murphy, B. L.; Fisher, P. A. *J. Org. Chem.* **1990**, *55*, 5291−5294.

(9) An efficient catalytic asymmetric synthesis of α-amino acids has been very recently described. See: Abe, H.; Amii, H.; Uneyama, K. *Org. Lett.* **2001**, *3*, 313−315 and references therein.

(10) The correct configuration assignments for these derivatives (*syn*-**4** or *syn*-**5**) was unambiguously obtained by X-ray crystallographic analyses. Because we were unable to obtain adequate single crystals for the major diastereoisomer of **4** or **5**, the relative stereochemistry of the new chiral created center was determined by comparison with the X-ray structure of the minor diastereoisomer *anti*-**5e** ($R_F = CHF_2$, Ar = 1-naphthyl, and $R^1 = p$-$MeOC_6H_4$), which turns our to be (2*R*,*S*$_S$)-**5e**. Full details of the X-ray structure of (2*R*,*S*$_S$)-**5e** will be published in a full account of this work.

(11) RCM has emerged as a prominent reaction for the synthesis of medium- and large-sized rings from acyclic diene precursors. See, for example: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (c) Morgan, J. P.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 3153−3155.

(12) RCM has been used to prepare a variety of nitrogen-containing natural products including peptidomimetics: Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75−89.

(13) For related systems, see: (a) Osipov, S. N.; Bruneau, Ch.; Picquet, M.; Kolomiets, A. F.; Dixneuf, P. H. *Chem. Commun.* **1998**, 2053−2054. (b) Osipov, S. N.; Artyushin, O. I.; Kolomiets, A. F.; Bruneau, Ch.; Dixneuf, P. H. *Synlett* **2000**, 1031−1033.

Conversion into the *N*-Cbz derivative, followed by NOPR, and *O*-protection furnished compound (*R*)-**8**. *N*-Alkylation of (*R*)-**8** with different alkenyl bromides gave oxazolidinones (*R*)-**9a**−**c**,[15] which in the presence of Grubb's catalyst $(PCy_3)_2Cl_2Ru{=}CHPh$ under high dilution conditions in dry dichloromethane gave the cyclized derivatives (*R*)-**10a,b** with good yields and high ee (>98%). The process works well for seven- ($n = 1$) and eight- ($n = 2$) membered rings, yet for nine-membered rings ($n = 3$) dimerization and oligomerization products have been obtained instead.

Experiments are now underway to further exploit this strategy.

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**Supporting Information Available:** Experimental procedures and analytical and spectroscopic data for compounds **2j** and **4**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For the preparation of enantiopure sulfoxides **1** and imidoyl halides **2**, see: (a) Fernández, I.; Khiar, N.; Llera, J. M.; Alcudia, F. *J. Org. Chem.* **1992**, *57*, 6789−6796. (b) Uneyama, K.; Tamura, K.; Mizukami, H.; Maeda, K. *J. Org. Chem.* **1993**, *58*, 32−36.

(15) Alternatively, (*R*)-**9a**−**c** can be directly obtained with slightly lower yields by treatment of *β*-amino alcohol (*R*)-**6d** ($R_F = CF_2CH_2CH{=}CH_2$) with NaH followed by *N*-alkylation of the previously isolated *N*-unsubstituted oxazolidinone.