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BINOL modification *via* S_NAr reactions with pentafluoropyridine

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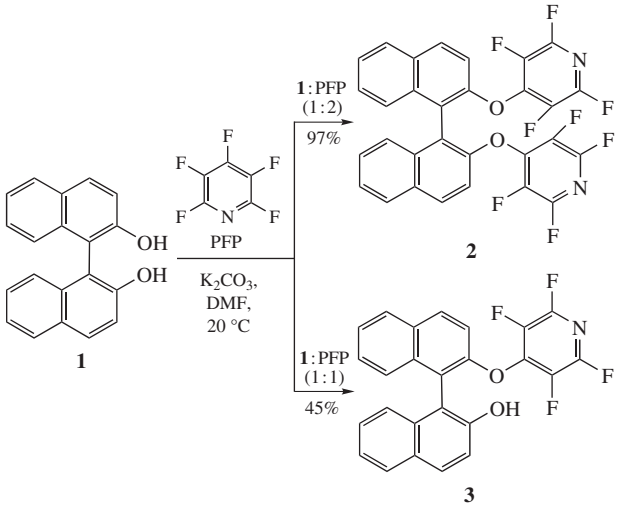
(*R*)- and (*S*)-binaphthyl-2,2′-diols (BINOLs) smoothly react with pentafluoropyridine without racemization to give (*R*)- and (*S*)-2,2′-bis(tetrafluoropyridin-4-yloxy)-1,1′-binaphthyls. The 2(6)-positioned pyridine fluorine atoms can be replaced with amino moieties by reactions with amines.

1,1′-Binaphthyl-2,2′-diol (BINOL) **1** and its derivatives are currently among the most versatile chiral reagents.[1,2] However, reports[3] on using aromatic nucleophilic substitution (S_NAr) as a means to modify BINOL are scarce, although its hydroxyl groups are easily deprotonated in basic media to form strong O-nucleophiles. On the other hand, the resulting anionic intermediates can undergo rotation about the C^1–$C^{1'}$ bond due to diminished steric hindrance, leading to partial racemization.[4] This possibility may reduce the interest to such type of chemical modification of compound **1**.

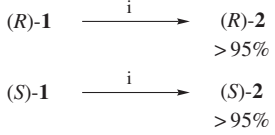
Taking into account the possible racemization of compound **1** under basic conditions, the objective of the present work was to examine its reaction with pentafluoropyridine (PFP) which is known to be very active towards nucleophilic attack thus providing access to a wide variety of 4-, 2,4- and 2,4,6-substituted PFP derivatives.[5] The aim of the study was also to evaluate sensitivity of this reaction to racemization.

For the purpose of an initial screening, the reactivity of racemic **1** toward PFP was investigated. In order to avoid strong basic conditions, K_2CO_3 was used as a mild base to induce the reaction. As appeared, PFP reacted readily with compound **1** at room temperature to give the corresponding diether **2** in quantitative yield within 20 min (Scheme 1).† Moreover, it was found possible to obtain monoether **3** in preparative yield 45% when 1:1 molar ratio of **1** to PFP was used.



Scheme 1

When enantiopure (*R*)-**1** and (*S*)-**1** reacted with PFP, the corresponding (*R*)-**2** and (*S*)-**2** were obtained in quantitative yields (Scheme 2). No racemization with these enantiomers was observed according to chiral GC-MS data. This is in agreement with reactions of (*R*)-**1** and (*S*)-**1** with less reactive haloarenes.[3]



Scheme 2 *Reagents and conditions*: i, 2 PFP, K_2CO_3, DMF, 20 °C.

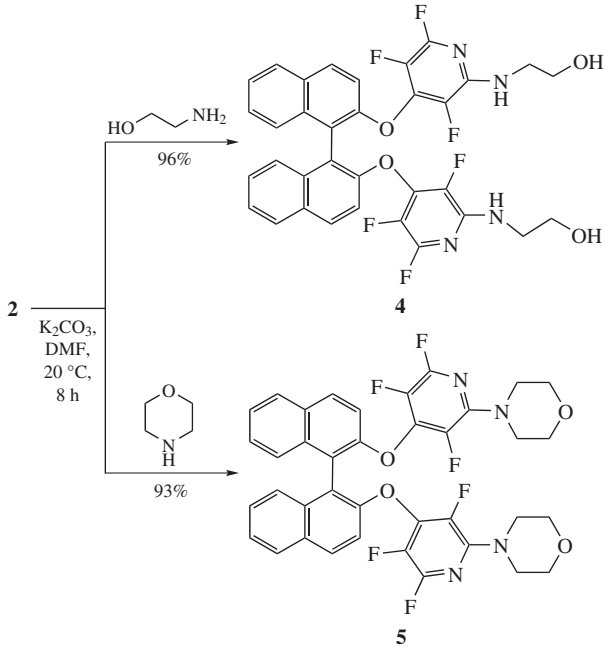
† The ^{1}H and ^{19}F NMR spectra were recorded on a Bruker AVANCE III 500 spectrometer at 500.13 and 470.59 MHz, respectively. The chemical shifts were measured relative to residual protio-solvent signals in ^{1}H NMR and internal C_6F_6 in ^{19}F NMR spectra. GC-MS data were acquired on an Agilent 6890N/5973N EI/PCI instrument using a Cyclosil-B column with a chiral sorbent. (*R*)- and (*S*)-**1** (*ee* > 99.6%) were obtained from chemical suppliers. Mass and accurate mass (HRMS) spectra were measured using a high resolution DFS Thermo Scientific mass-spectrometer.

*(*R,S*)-2,2′-bis(tetrafluoropyridin-4-yloxy)-1,1′-binaphthyl* **2** *(typical procedure)*. PFP (2.48 g, 14.7 mmol) was added dropwise to a stirred mixture of racemic **1** (2 g, 7 mmol) and powdered K_2CO_3 (1.93 g, 14 mmol) in 15 ml of DMF. The progress of the reaction was followed by TLC (eluent: benzene–acetone, 10:1) and when traces of **1** and intermediate **3** were disappeared (in 15–20 min), the resulting mixture was poured into water (100 ml). The precipitate (white crystals) was filtered off, washed with water and dried to obtain racemic **2** (3.97 g, 97%), mp 201–202 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 7.21 (d, 2H, *J* 8.5 Hz), 7.35 (ddd, 2H, *J* 8, 6.5, 1 Hz), 7.45 (d, 2H, *J* 9 Hz), 7,49 (ddd, 2H, *J* 8, 6.5, 1 Hz), 7.91 (d, 2H, *J* 8 Hz), 8.0 (d, 2H, *J* 9 Hz). ^{19}F NMR ($CDCl_3$) δ: 7.89 (m, 4F), 72.20 (m, 4F). HRMS, *m/z*: 584.0769 (calc., *m/z*: 584.0766). Found (%): C, 61.10; H, 2.05; F, 26.72; N, 4.92. Calc. for $C_{30}H_{12}F_8N_2O_2$ (%): C, 61.65; H, 2.07; F, 26.01; N, 4.79.

*(*R*)-2,2′-bis(tetrafluoropyridin-4-yloxy)-1,1′-binaphthyl (R)-***2**: *ee* > 99.6%, mp 204–205 °C.

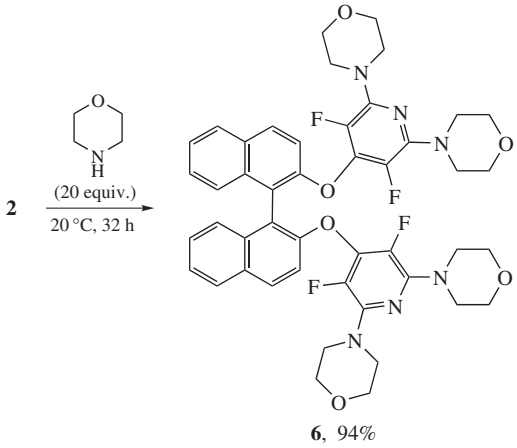
*(*S*)-2,2′-bis(tetrafluoropyridin-4-yloxy)-1,1′-binaphthyl (S)-***2**: *ee* > 99.6%, mp 206–207 °C.

*(*R,S*)-2-(tetrafluoropyridin-4-yloxy)-1,1′-binaphthalen-2′-ol* **3** was obtained analogously on using one equivalent of PFP and a longer reaction time (1 h). Pure **3** was isolated by column chromatography (SiO_2, eluent: hexane–benzene, 1:1), mp 139–140 °C. ^{1}H NMR ($CDCl_3$) δ: 6.98 (d, 1H, *J* 10 Hz), 7.19 (d, 1H, *J* 9 Hz), 7.21–7.25 (m, 1H), 7.27–7.32 (m, 1H), 7.33 (d, 1H, *J* 10 Hz), 7.36–7.41 (m, 1H), 7.51–7.55 (m, 1H), 7.57 (d, 1H, *J* 10 Hz), 7.76 (d, 1H, *J* 8.5 Hz), 7.81 (d, 1H, *J* 8.5 Hz), 7.99 (d, 1H, *J* 10 Hz), 8.1 (d, 1H, *J* 10 Hz). ^{19}F NMR ($CDCl_3$) δ: 7.72 (m, 4F), 72.91 (m, 4F). HRMS, *m/z*: 435.0869 (calc. for $C_{25}H_{13}F_4NO_2$, *m/z*: 435.0876).



Scheme 3

Notably, compound **2** can be further easily functionalized by reactions with various nucleophiles under mild conditions. It was involved in model reactions with 2-aminoethanol and morpholine to give derivatives **4** and **5**, respectively (Scheme 3).



Scheme 4

Moreover, the disubstituted derivative **6** was obtained smoothly on using excess of morpholine in the absence of solvent (Scheme 4).

In conclusion, we have introduced a promising approach to a new variety of functionalized BINOLs. Enantiopure (*R*)- and (*S*)-**2** and their derivatives can be used as new BINOL ligands and as starting materials for the synthesis of novel chiral catalysts, dendrimers and polymers. In addition, PFP has potential as a reagent for protecting hydroxyl groups in BINOL, since tetrafluoropyridyl-oxygen moiety can be cleaved with CsF or sodium methoxide to regenerate the phenolic function.[5(*d*),6]

(R,S)-**4** *(typical procedure)*. Solution of 2-aminoethanol (0.08 g, 1.3 mmol) in 5 ml DMF was added to a stirred mixture of racemic **2** (0.37 g, 0.63 mmol) and powdered K_2CO_3 (0.18 g, 1.3 mmol) in 10 ml of DMF and the mixture was stirred for 8 h. Then water (100 ml) was added dropwise to the resulting mixture. The precipitate (beige crystals) was filtered off, washed with water and dried to obtain racemic **4** (0.4 g, 96%). ^{1}H NMR (acetone-d_6) δ: 3.31–3.41 (m, 4H), 3.60–3.67 (m, 4H), 3.88 (br. s, 2H), 5.85 (br. s, 2H), 7.18 (d, 2H, *J* 8 Hz), 7.36 (t, 2H, *J* 7.5 Hz), 7.47 (t, 2H, *J* 7.5 Hz), 7.54 (d, 2H, *J* 9 Hz), 7.99 (d, 2H, *J* 8 Hz), 8.09 (d, 2H, *J* 8.5 Hz). ^{19}F NMR ($CDCl_3$) δ: 5.24 (m, 2F), 18.85 (m, 2F), 69.15 (m, 2F). Found (%): C, 59.92; H, 4.01; F, 16.19; N, 9.42. Calc. for $C_{34}H_{24}F_6N_4O_4$ (%): C, 61.26; H, 3.63; F, 17.10; N, 8.41.

(R,S)-**5** was obtained as described above. White crystals. mp 210–211 °C (Et_2O). ^{1}H NMR (acetone-d_6) δ: 3.16–3.24 (m, 8H), 3.63–3.67 (m, 8H), 7.16 (d, 2H, *J* 8.5 Hz), 7.38 (ddd, 2H, *J* 8.5, 5, 1.5 Hz), 7.48 (ddd, 2H, *J* 8, 7, 1 Hz), 7.58 (d, 2H, *J* 9 Hz), 8.0 (d, 2H, *J* 8 Hz), 8.12 (d, 2H, *J* 8.5 Hz). ^{19}F NMR ($CDCl_3$) δ: 3.34 (m, 2F), 16.62 (m, 2F), 67.11 (m, 2F). HRMS, *m/z*: 718.2000 (calc. for $C_{38}H_{28}F_6N_4O_4$, *m/z*: 718.2009).

(R,S)-**6**. Mixture of racemic **2** (2 g, 3.4 mmol), powdered K_2CO_3 (0.99 g, 7.2 mmol) and morpholine (6 g, 68 mmol) was stirred during 32 h. After usual workup, white crystals were obtained (2.7 g, 94%), mp 291–292 °C (decomp.). ^{1}H NMR (CD_3OD) δ: 3.14–3.20 (m, 16H), 3.65–3.71 (m, 16H), 7.11 (d, 2H, *J* 8.5 Hz), 7.32 (ddd, 2H, *J* 8, 6.5, 1 Hz), 7.46 (ddd, 2H, *J* 8, 6.5, 1 Hz), 7.52 (d, 2H, *J* 9 Hz), 7.94 (d, 2H, *J* 8 Hz), 8.06 (d, 2H, *J* 9 Hz). ^{19}F NMR ($CDCl_3$) δ: 8.42 (s, 4F). HRMS, *m/z*: 852.3247 (calc. for $C_{46}H_{44}F_4N_6O_6$, *m/z*: 852.3253).

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