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SPANamine derivatives in the catalytic asymmetric α-fluorination of β-keto esters

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ABSTRACT

The use of C_2-symmetric enantiopure nitrogen ligands in the asymmetric catalytic α-fluorination of β-ketoesters is described. SPANamine **1** in the presence of nickel salts gives up to 63% ee in the fluorination of *tert*-butyl 2-oxocyclopentanecarboxylate with *N*-fluorosuccinimide (NFSI). The same enantioselectivity is obtained when SPANamine **1** is used as an organocatalyst, although the reaction is much slower.

1. Introduction

Direct asymmetric fluorination has recently become an important tool in organic chemistry. It is one of the most useful methods to obtain access to quaternary chiral centers bearing a fluorine atom. The general methods that lead to these molecules involve the use of a chiral fluorine donor, the application of a chiral organocatalyst, or the use of a chiral ligand coordinated to a metal.[1] The asymmetric α-fluorination of β-ketoesters is particularly interesting in view of the possibility of further derivatization of the chiral product. Nitrogen based molecules proved suitable compounds to convert β-ketoesters into their α-fluorinated products, either as organocatalysts[2] or chiral ligands.[3]

Recently our group described the synthesis of a new family of chiral, C_2-symmetric diamines,[4] SPANamines, and the first application of one of them in the palladium catalyzed asymmetric resolution of phenylethanol by an oxidation reaction. Previously these enantiopure ligands were obtained through derivatization of racemic SPANdiamine *rac*-**1** or SPANdialdehyde, respectively, with (−)-(1*R*,2*S*,5*R*)-menthyl chloroformate and (−)-*cis*-myrtanylamine and separation of the enantiopure diastereoisomers. The enantiopure SPAN derivatives used in our work were obtained by direct separation of the enantiomers of **1** and SPANdialdehyde with a semi-preparative HPLC column (vide infra Section 4). We now also report the synthesis of the chiral SPANbisoxazoline **10**,[5] and the application of these SPAN derivatives as chiral ligands in the asymmetric α-fluorination of β-ketoesters.

As the starting point of our studies, we set out to use our new enantiopure nitrogen ligands in the nickel-catalyzed asymmetric α-fluorination of β-ketoesters, beginning with the commonly used racemic substrate **2**.[2b,3b–d,g,i,6]

2. Results and discussion

2.1. Nickel catalysts

The first experiments were aimed at establishing the influence of the solvent on the catalytic performance of a mixture of nickel chloride, as metallic salt, and SPANamine **1** as the chiral ligand (Table 1).

The results show that the use of a coordinating solvent (THF, DMF, MeCN) gives a high conversion into the fluorinated product but no enantioselectivity was achieved. Dichloromethane was revealed to be the best solvent, giving both high conversion and good enantioselectivity.

Subsequently several nickel precursors were tested in the presence of (−)-**1** and the results are gathered in Table 2. Note that the commonly used nickel perchlorate[3a,d,e,i,7] was not tested here because of its potentially dangerous handling.

With each nickel precursor the conversion was over 80% and the best enantioselectivities were obtained with the nickel halide salts. These dissolved only partially in dichloromethane at room temperature and thus an excess of free ligand **1** is probably present in solution. The soluble nickel sources, such as $Ni(acac)_2$, $Ni(oct)_2{\cdot}x\text{-}H_2O$, and $Ni(cod)_2$ gave a faster reaction, but lower ee's.

Surprisingly, the reaction carried out without a nickel salt provided almost the same enantiomeric excess as the one with nickel chloride, but with a much lower conversion. A preliminary explanation might be that non-ligated nickel causes a fast catalytic

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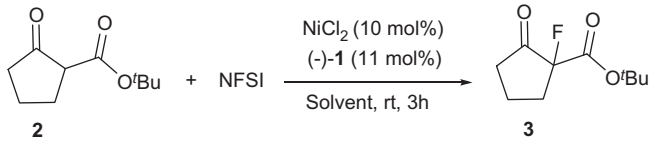
Table 1
Influence of the solvent

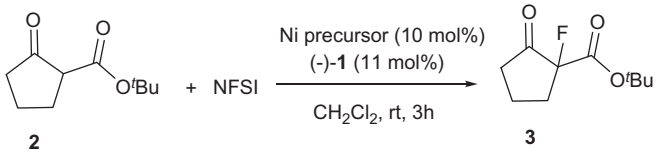


2 3

Solvent	Conv.[a] (%)	ee[b] (%)
CH_2Cl_2	87	63
THF	100	3
DMF	92	0
MeCN	100	0
Toluene	70	43

[a] Determined by GC analysis.
[b] Determined by chiral GC analysis with a β-Dex column.

Table 2
Influence of the nickel precursor



2 3

Ni precursor	Conv.[a] (%)	ee[b] (%)
$NiCl_2$	87	63
$NiCl_2$,DME	91	55
$Ni(OAc)_2{\cdot}4H_2O$	82	42
$NiSO_4$, $6H_2O$	87	53
$Ni(acac)_2$	97	6
NiF_2	93	61
$Ni(oct)_2{\cdot}xH_2O$	100	18
$Ni(cod)_2$	100	10
None	48	61

[a] Determined by GC analysis.
[b] Determined by chiral GC analysis with a β-Dex column.

fluorination giving racemic product, and that **1** acts independently as an organocatalyst giving enantioselectivity. Alternatively, the two entities might act together, nickel activating the substrate and the organocatalyst delivering chirality. In part the system may work via the route planned, namely with a chiral nickel complex as the catalyst.

The reaction was also tested with an equimolar amount of an aqueous solution of potassium carbonate but the conversion and enantioselectivity were very low (15%, racemic), proving that **1** does not act as a chiral phase transfer agent.

Table 3 shows the results obtained in a screen of diamines and diimines in the presence and absence of $NiCl_2$. Several SPANamine derivatives and commercially available ligands were tested. The best result for nickel chloride was obtained with bisoxazoline **15** with full conversion after three hours and an enantiomeric excess of 65%. In comparison with SPANamine **1** the enantiomeric excess is similar, although the conversion with **1** is slightly lower. Apart from the dibenzyl derivatives SPAN **6** and **7** that provided a significant ee (41% and 53%, respectively), the other SPAN derivatives only led to a racemic product. Ligands **8**, **9**, and **10** have an N···N distance different from that of **1**, while ligands **4** and **5** exert a steric hindrance that is larger than that of **1**.

SPANamine derivative **6**, SPANimine **7**, and *H8*-binaphthylamine **14** show the same behavior as **1**, in that the enantioselectivities are almost the same in the reactions with or without nickel.

The results obtained with protonated SPANamine **17** and **18** demonstrate the importance of the NH_2 unit both for the activity and the enantioselectivity (Table 4).

In conclusion, in the SPANamine/Ni catalytic systems, nickel only seems to activate the substrate but it does not appear necessary to induce enantioselectivity. In the case of bisoxazoline **15**, however, a chiral nickel complex must be involved, because compound **15** does not induce chirality when used as an organocatalyst.

2.2. Organocatalysts

In view of these results, we continued our study using the unique property of **1** to act as an organocatalyst, and further investigated the influence of the reaction conditions on the asymmetric organocatalyzed reaction on substrate **2** (Table 5).

Similar to the results given in Table 1, dichoromethane is the best solvent for the organocatalyzed reaction. The reaction is faster in a protic solvent such as ethanol but the enantioselectivity is lower.

The results displayed in Table 6, reveal a dramatic effect of the fluorinating agent both on the activity and on the enantioselectivity of the reaction. When Selectfluor was used the fluorination was slower than that with the two other fluorine donors and the enantioselectivity was lower than that of the reaction with NFSI. In the case of NFPY (*N*-fluoropyridinium trifluoromethanesulfonate) the activity obtained was the same as with NFSI, but the fluorinated product obtained was racemic.

The catalyzed asymmetric fluorination using SPANamine **1** was also tested using other substrates, **20**–**24**, under both metal-catalyzed and organocatalyzed conditions (Scheme 1). For **20**, the catalytic results are similar to those obtained for substrate **2**, although slightly lower ee's were obtained. This effect had already been reported in the literature; when changing a *tert*-butyl group for an ethyl group in the α-fluorination of 2-oxocyclopentanecarboxylate derivatives the ee dropped.[3f] For the ethyl and *tert*-butyl-2-oxocyclopentanecarboxylate-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylates **21** and **22** fluorination only occurs in the presence of nickel chloride. Moreover, the enantioselectivities are lower than the ones obtained with substrates **2** and **20**.

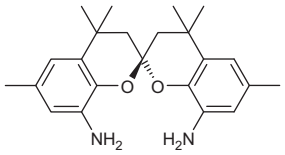
Finally, ethyl α-cyano-α-phenylacetate **23** and the unsymmetrical malonate **24** could not be converted into the expected fluorinated products by either method, and only the starting material was recovered.

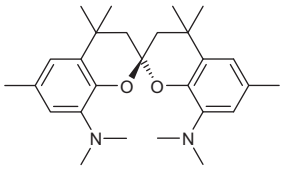
2.3. Mechanistic studies

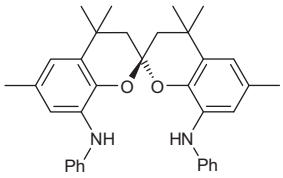
Three potential mechanisms for obtaining enantioselectivity in the organocatalyzed reaction with **1** are presented in Scheme 2. A first explanation for the enantioselectivity obtained with SPANamine **1** could be the formation of a chiral enamine via a reaction of the SPANamine and the ketone (Scheme 2). This mechanism was proposed for proline or pyrrolidine derivatives as organocatalysts.[8] Another possibility might be that first the fluorination of amine takes place, resulting in an intermediate that can act as a chiral fluorine donor (Scheme 2), similar to the examples involving alkaloids.[9] Finally, a hydrogen-bond interaction could occur between the enolic form of the substrate and SPANamine, leading to a chiral intermediate (Scheme 2).

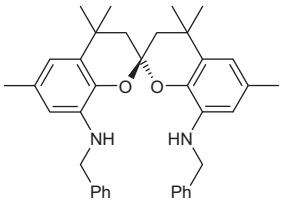
In order to obtain more insight into the possible mechanism of this reaction several NMR experiments were performed in deuterated chloroform at room temperature (note that the results are comparable with those obtained with dichloromethane). First, a ^{1}H NMR experiment of a 1:1 mixture of substrate/SPANamine did not show any formation of enamine or enolate. If there would be any interaction between the substrate and **1**, we expected to see a change in the chemical shift of the protons of the amine and/or

Table 3
Ligand screening[a]


(-)-**1**


(-)-**4**


(-)-**5**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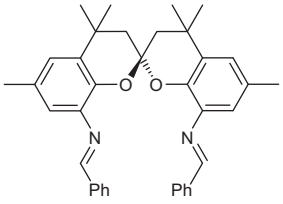
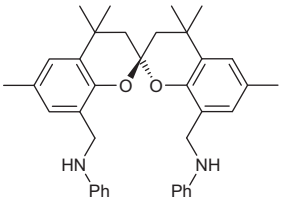
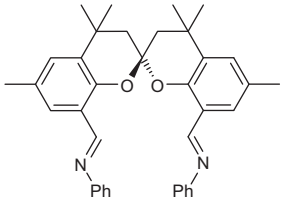
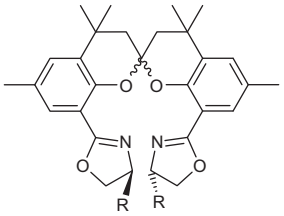
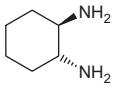
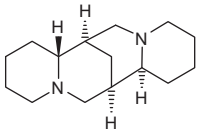

(-)-**7**

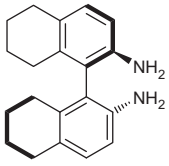

(-)-**8**

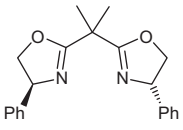

(-)-**9**

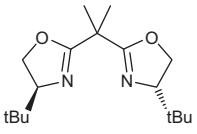

(-)-**10a,b**: R=Ph
(-)-**11a,b**: R=*i*Pr


(*R*,*R*)-**12**


(-)-**13**


(*R*)-**14**


(*S*,*S*)-**15**


(*S*,*S*)-**16**

Ligand	Conv. (%) (without $NiCl_2$)[b]	ee (%) (without $NiCl_2$)[c]
1	87 (81)	63 (62)
4	44 (9)	0 (0)
5	85	0
6	85 (55)	41 (40)
7	81 (53)	60 (53)
8	87 (13)	0 (0)
9	85	0
10	81 (10)	5 (0)
12	69 (61)	0 (2)
13	52	0
14	100 (91)	18 (17)
15	100 (58)	65 (0)
16	90	58

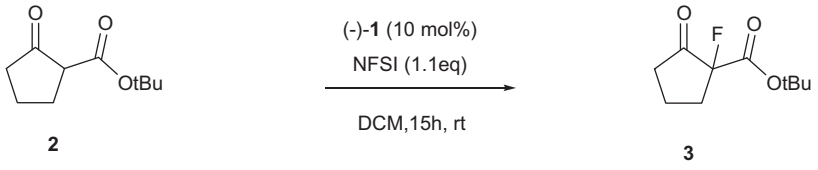
[a] Reaction conditions: NFSI (1.1 equiv), $NiCl_2$ (10 mol %), ligand (11 mol %), dichloromethane, rt, 3 h. In parentheses data without $NiCl_2$.
[b] Determined by GC analysis.
[c] Determined by chiral GC analysis with a β-Dex column.

a disappearance of the acidic proton of the substrate; however, in this case both reagents remained unchanged. It seems there is no interaction between **1** and **2** unless for some reason it cannot be detected by NMR.

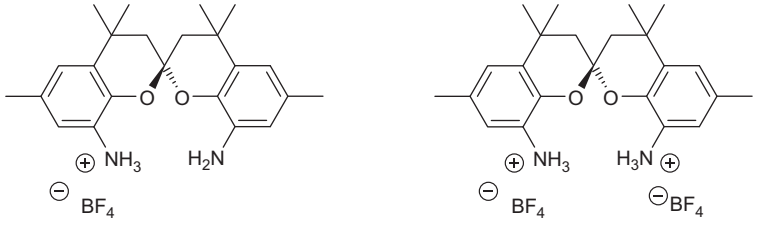
In Scheme 3 are presented the ^1H NMR spectrum of **1** and the ^1H and ^{19}F NMR spectra of NFSI. Then we mixed a 1/2 ratio of these compounds and recorded several ^1H and ^{19}F NMR spectra of the mixture after 2, 4, and 8 h. The ^{19}F NMR spectrum showed no fluorinated compound other than NFSI; we followed the conversion of the catalytic reaction by ^{19}F NMR which showed both the gradual consumption of NFSI and the formation of the fluorinated β-ketoester (vide infra in Section 4). In the ^1H NMR spectra (Scheme 3) the signals of **1** with 2 equiv of NFSI added became broad, indicating that paramagnetic species may be involved, and simultaneously a green color was observed. Interestingly though, when **1**, **5**, **6**, **7,** and **14** were employed a similar deep green coloration appeared during the catalytic reactions.

A possible explanation of these observations (coloration and broad peaks) could be the oxidation of amine by NFSI, leading to small amounts of radical (cation) species. However, this partial oxidation of SPANamine may not be relevant for the fluorination reaction. Next, EPR experiments were performed on several mixtures of **1**, NFSI, and **2** but no conclusive results occurred. In the presence of nickel chloride an enolate complex forms, but surprisingly for amines the chiral induction is the same for the nickel/amine catalyzed reactions and the organocatalyzed reactions. The NMR experiments did not lead to any conclusion concerning the mechanism and does not favor any of the previously proposed pathways. Thus, there still remains at least two possible mechanisms for SPANamine derivatives or bis-oxazolines such as **15**. When other

Table 4
Use of protonated SPANamine



2 3

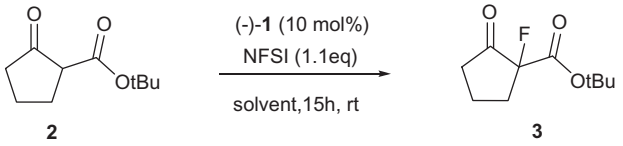


17 18

Ligand	Conv.[a] (%)	ee[b] (%)
17	78	10
18	30	5

[a] Determined by GC analysis.
[b] Determined by chiral GC analysis with a β-Dex column.

Table 5
Influence of the solvent in organocatalysis

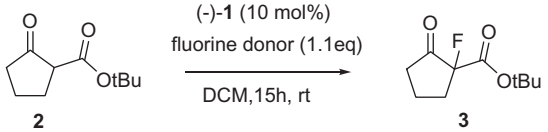


2 3

Solvent	Conv.[a] (%)	ee[b] (%)
CH_2Cl_2	81	62
THF	22	7
Et_2O	44	24
Toluene	59	39
MeCN	23	10
DMF	11	4
EtOH	100	30
Acetone	42	22

[a] Determined by GC analysis.
[b] Determined by chiral GC analysis with a β-Dex column.

Table 6
Influence of the fluorine donor



2 3

Fluorine donor	Conv.[a] (%)	ee[b] (%)
NFSI	81	62
Selectfluor	35	37
NFPY	82	2

[a] Determined by GC analysis.
[b] Determined by chiral GC analysis with a β-Dex column.

metallic salts were employed such as copper triflate or zinc acetate only racemic products were obtained, and thus, whatever the mechanism is, it cannot be generalized.

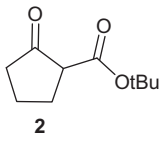
3. Conclusion

In conclusion, enantiopure SPANamine derivatives are active organocatalysts for the asymmetric α-fluorination of β-ketoesters and their behavior is different from those described previously. When using unreactive substrates, the use of nickel salts increases the reactivity without loss of enantioselectivity, except with oxazoline-based ligands. Moreover, these compounds are not air sensitive and most are not water sensitive. We are currently working on the synthesis of new SPAN-N derivatives in order to increase the enantioselectivities and to apply them in the fluorination of other substrates, as organocatalysts and as a chiral ligand on a transition metal.

4. Experimental

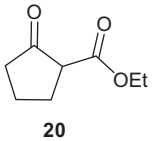
4.1. General

Unless otherwise specified, materials were obtained from commercial suppliers and were used without further purification. All reactions requiring anhydrous conditions were conducted in oven-dried glassware in a dry argon atmosphere. All solvents were dried using a Solvent Purification System (SPS) or using standard procedures. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance 400 Ultrashield NMR spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C). Chemical Shifts (δ) for ^1H and ^{13}C were referred to internal solvent references. Optical rotations were measured on a Jasco P-1030 polarimeter. HPLC analysis was performed on a Water apparatus, using a Daicel Chiralpak IC and IA column, 250 mm length, 4.6 mm diameter (10 mm for semi-preparative), 5 μm particle size. GC analyses were performed on a GC-FID equipped with a HP-5 (5% phenyl methyl siloxane; 30 m × 320 m × 0.25) capillary column or Daicel β-Dex 120 m. Substrates **2**,[10] **21**,[11] **22**,[12] **23**,[13] and **24**[14] were prepared by previously reported methods. NMR and chiral GC or HPLC data of fluorinated products data were identical to the reported ones.[3b,d,j,9c]



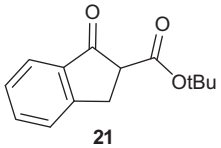
2

A: conv: 87%, ee: 63%
B: conv: 81%, ee: 62%



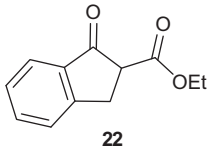
20

A: conv: 66%, ee: 51%
B: conv: 96%, ee: 43%



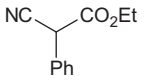
21

A: conv: 100%, ee: 27%
B: conv <5%



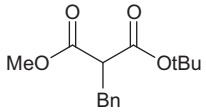
22

A: conv: 100%, ee: 9%
B: conv <5%



23

A: no conversion
B: no conversion



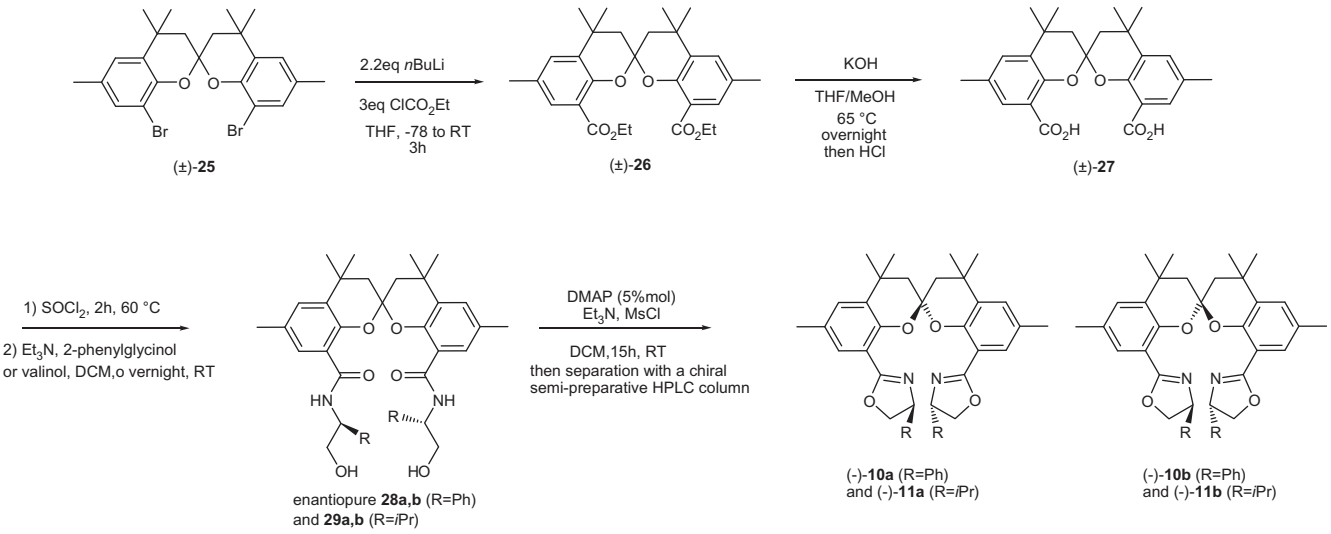
24

A: no conversion
B: no conversion

A: $NiCl_2$ (10 mol%), *(-)*-**1** (12 mol%), NFSI (1.1eq), CH_2Cl_2, rt, 3h
B: (-)-**1** (10 mol%), NFSI (1.1eq), CH_2Cl_2, rt, 15h

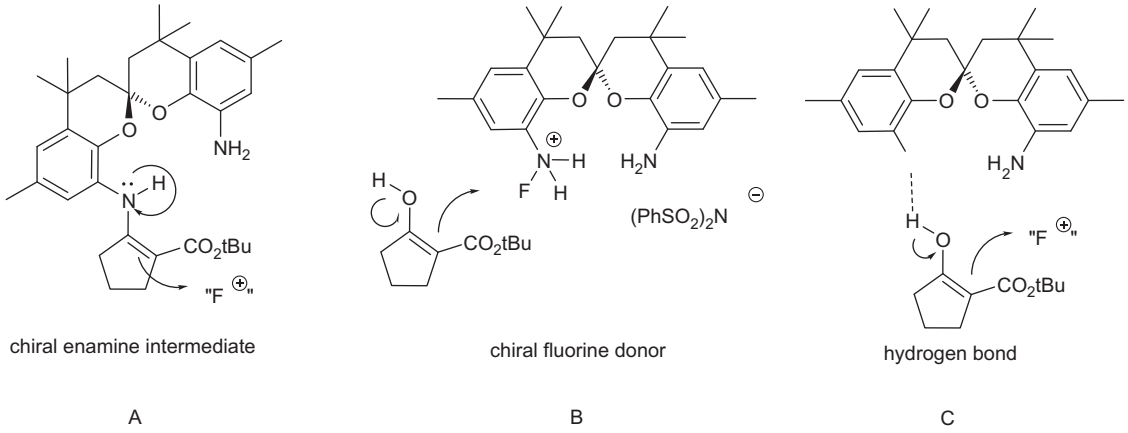
Scheme 1.

4.1.1. Synthesis of SPANoxazolines ('SPANbox') 10a,b, 11a,b



4.1.1.1. Compound 26. 8,8′-Dibromo-4,4,4′,4′,6,6′-hexamethyl-2,2′-spirobi[chroman] **25** (2 g, 4.05 mmol) was dissolved in 60 mL of dry THF and cooled to −78 °C. Then *n*BuLi 1.6 M in hexane (7.59 mL, 12.14 mmol) was added dropwise. After stirring 30 min at this temperature ethyl chloroformate (1.16 mL, 12.14 mmol) was syringed in the flask and the resulting mixture was stirred overnight while warming slowly to room temperature. Water and ethyl acetate were added and the aqueous layer was washed twice with ethyl acetate. The organic layers were mixed, dried over $MgSO_4$, and the solvent removed under vacuum. The residue was purified by flash chromatography over silica gel (hex 95/5 AcOEt then gradient) in order to render the pure product as a white solid (1.1 g, 57%yield). ^{1}H NMR: 1.03 (6H, t, J = 6.94 Hz); 1.35 (6H, s); 1.60 (6H, s); 2.11 (2H, d, J = 14.3 Hz); 2.22 (2H, d, J = 14.3 Hz); 2.28 (6H, s); 3.97 (4H, 2 dq, J = 7.05 and 10.58 Hz); 7.18 (2H, d, J = 2.05 Hz); 7.22 (2H, d, J = 2.05 Hz). ^{13}C NMR: 13.9; 20.6; 30.9; 31.6; 32.5; 47.3; 60.5; 98.7; 122; 128.3 ; 129.9 ; 130.1; 133.5; 147.2; 166.9. IR (cm^{-1}): 2955; 1728; 1710; 1449; 1194; 1100. HRMS (IE, m/z): experimental: 503.2389 (M+Na), calculated: 503.2410. Enantiomers were resolved on a IA column: 254 nm, heptane/isopropanol 95/5, 1 ml/min. (−)-enantiomer: 4.25 min, $[\alpha]_D^{24} = -49$ (c 0.1198, CH_2Cl_2); (+)-enantiomer: 6.05 min.

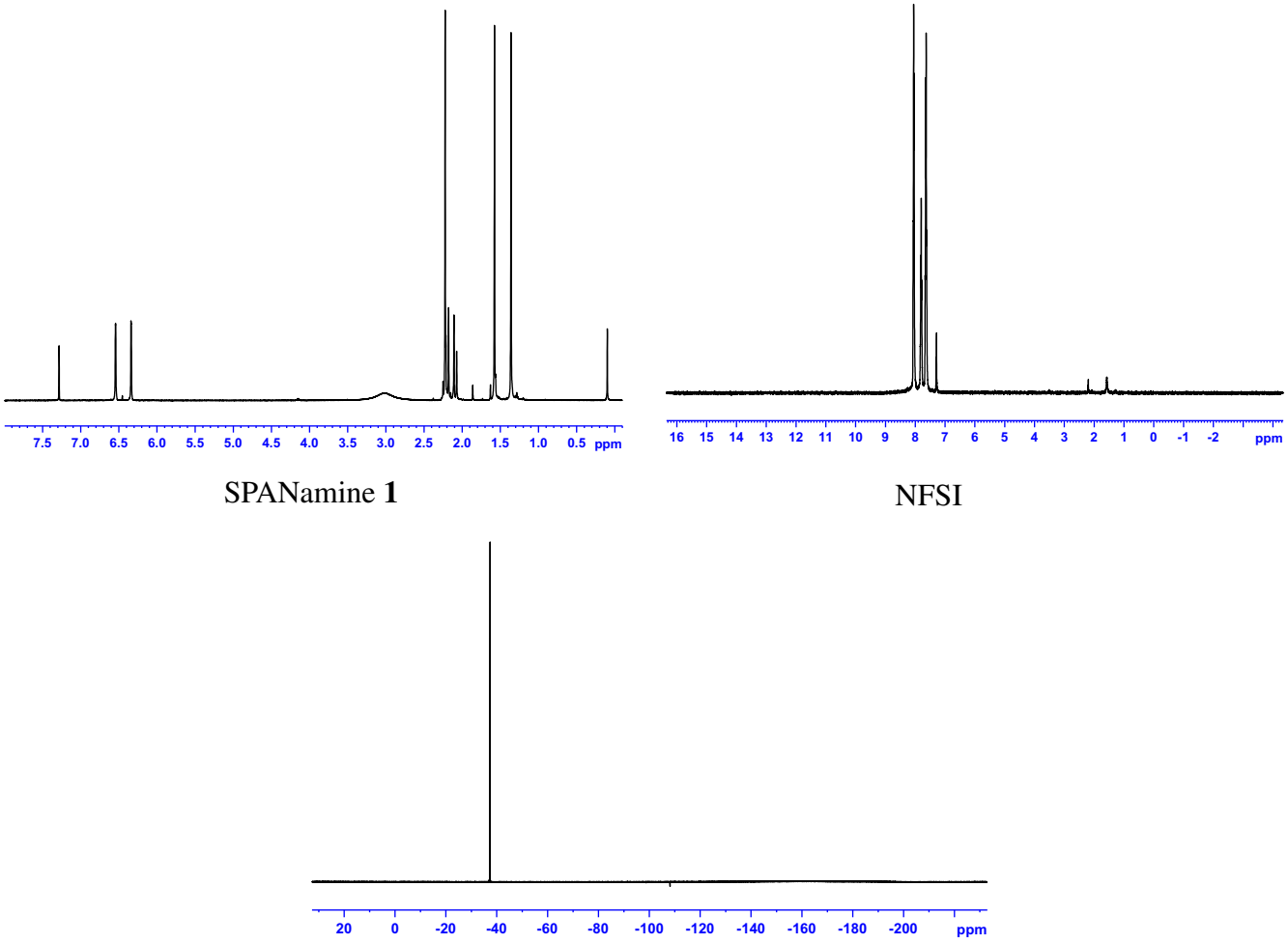
4.1.1.2. Compound 27. Diethyl 4,4,4′,4′,6,6′-hexamethyl-2,2′-spirobi[chroman]-8,8′-dicarboxylate **26** (1.1 g, 2.29 mmol) was dissolved in 20 mL of THF, then 20 mL of methanol was added followed by an aqueous solution of KOH (2 g of KOH in 10 mL of water, 35.6 mmol). The mixture was stirred 18 h at 65 °C. Then



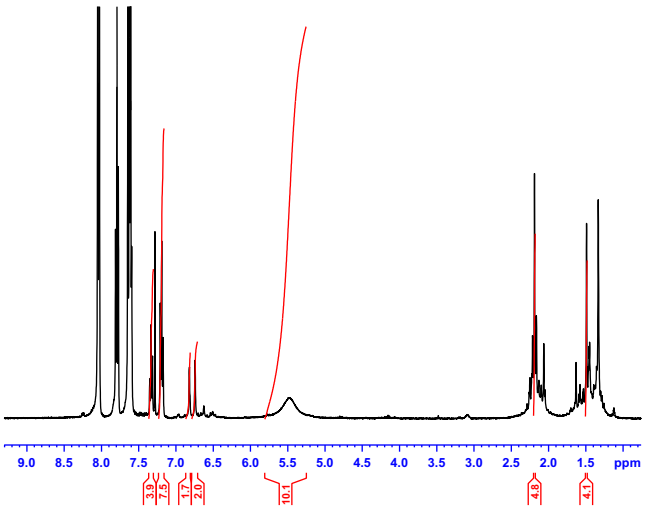
Scheme 2.

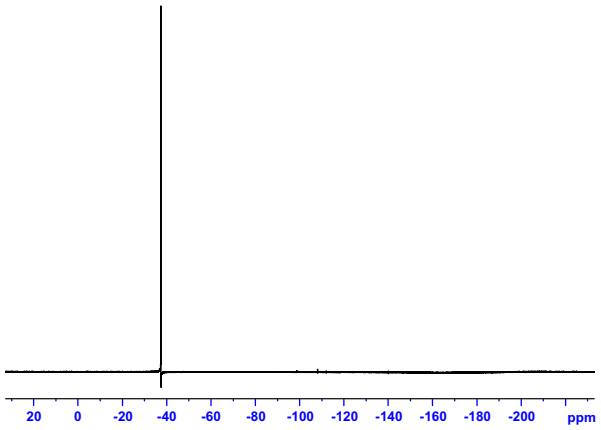
most of the THF and methanol were removed under vacuum with a rotavapor, the flask was put in an ice bath and concentrated hydrogen chloride was slowly added until acidic pH (<3). The diacid precipitated and was filtered off and washed with water. After being dried under vacuum the diacid was obtained as a white solid (965 mg, 99% yield). IR (cm^{-1}): 2958; 2616; 1696; 1445; 1224; 1165; 875. HRMS (IE, *m*/*z*): experimental: 447.1789 (M+Na), calculated: 447.1784.

4.1.1.3. Compounds 28a and 28b. In a first step SPANdiacid **27** (300 mg, 0.707 mmol) was placed in a Schlenk tube with 3 equiv of triethylamine (296 µl, 2.121 mmol) and 8 mL of thionyl chloride.

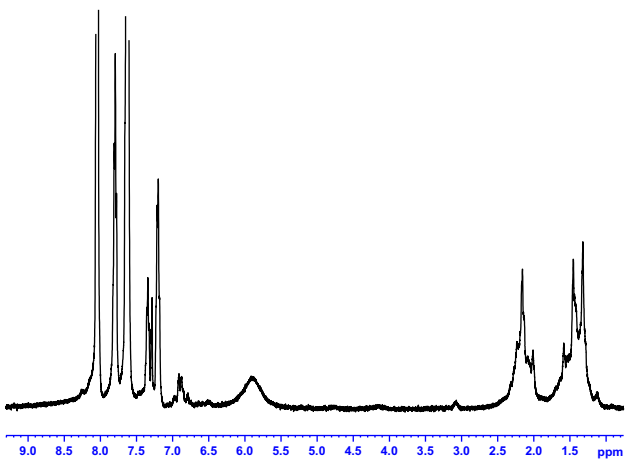


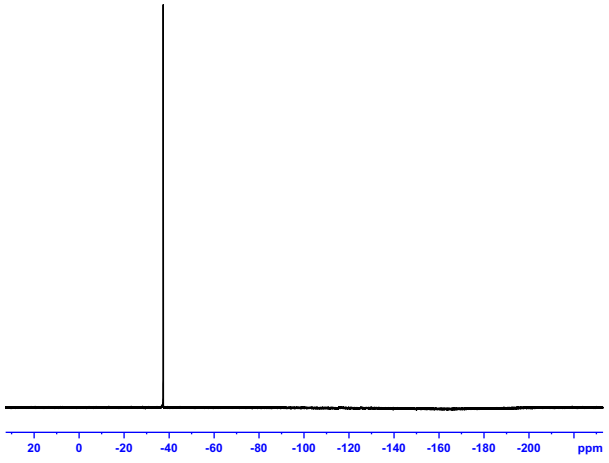
Scheme 3. ^{1}H and ^{19}F NMR study (in $CDCl_3$) of a 1/2 mixture of **1**/NFSI.



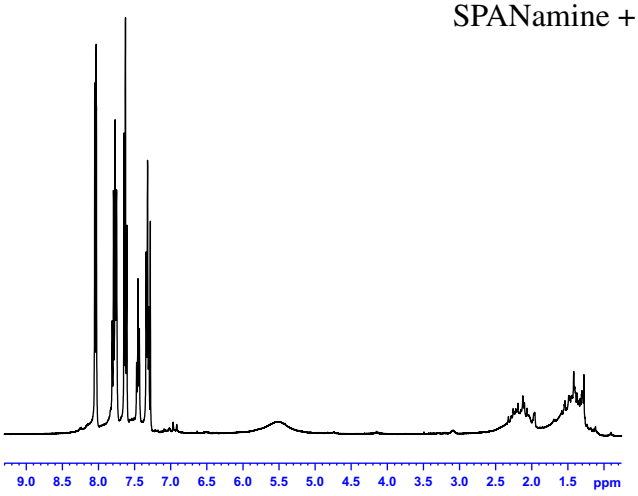


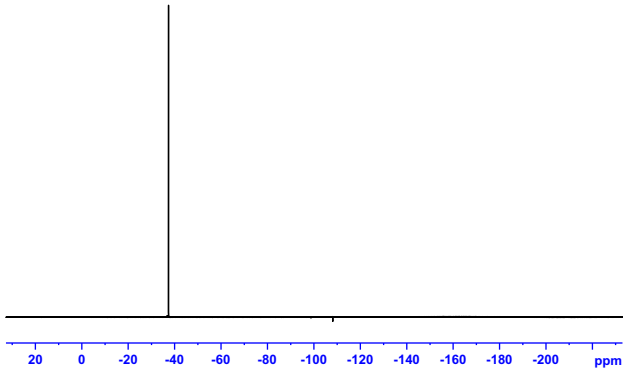
SPANamine + NFSI (2h)





SPANamine + NFSI (4h)





SPANamine + NFSI (8h)

Scheme 3 (*continued*)

The resulting dark mixture was stirred for 3 h at 60 °C, then the volatiles were removed under vacuum. The crude diacyl chloride was dissolved in 7 mL of DCM, then 3 equiv of triethylamine (296 µl, 2.121 mmol) and 3 equiv of (*S*)-(+)-phenylglycinol (291 mg, 2.121 mmol) (previously dissolved in 1 mL of DCM) were successively added.. The resulting brown solution was stirred for 15 h at rt. Then water was added, the aqueous layer was washed twice with DCM, the organic layers were mixed, dried over $MgSO_4$, and the volatiles were removed under reduced pressure. The crude product was pure by NMR and used without further purification for next step. ^{1}H NMR (400 MHz, $CDCl_3$): 1.32 (6H, s); 1.34 (6H, s); 1.36 (12H, s); 2.08 (2H, d, J = 14.3 Hz); 2.17 (2H, d,

J = 14.3 Hz); 2.23 (2H, d, J = 14.3 Hz); 2.24 (2H, d, J = 14.3 Hz); 2.33 (6H, s); 2.35 (6H, s); 3.48 (4H, m); 3.62 (4H, m); 4.87 (2H, ddd, J = 2.3, 3.9 and 6.2 Hz); 5.07 (2H, ddd, J = 3.2, 3.8 and 7 Hz); 6.89 (2H, d, J = 2 Hz); 6.91 (2H, d, J = 1.4 Hz); 7.04 (2H, d, J = 2 Hz); 7.06 (2H, d, J = 2.4 Hz); 7.19 (12H, m); 7.28 (2H, d, J = 2 Hz); 7.65 (2H, d, J = 2 Hz); 7.77 (2H, d, J = 7 Hz); 7.81 (2H, d, J = 1.9 Hz); 7.95 (2H, d, J = 6.9 Hz).

4.1.1.4. Compounds 10a and 10b. The latter was dissolved in 8 mL of dry dichloromethane, then *N*,*N*-dimethylaminopyridine, (3.6 mg, 0.029 mmol) and triethylamine (0.411 mL, 2.95 mmol) were added successively. The mixture was then cooled to 0 °C and methanesulfonyl chloride (0.114 mL, 1.47 mmol) was added. The mixture was stirred overnight while warming to room temperature.

Water was added and the aqueous layer was washed twice with dichloromethane. The organic layers were mixed, dried over $MgSO_4$, and the solvents were removed under vacuum. The crude NMR showed a small amount of unreacted substrate. Diastereoisomers were resolved on a Chiralpak IC column: 254 nm, hexane/isopropanol/diethylamine 60/40/0.1, 1 mL/min.

The pure product is obtained as a pale yellow solid (140 mg, 50% yield).

Compound **10a**: ^{1}H NMR: 1.34 (6H, s); 1.62 (6H, s); 2.13 (2H, d, J = 14.26 Hz); 2.23 (2H, d, J = 14.26 Hz); 2.28 (6H, s); 3.83 (2H, t, J = 8.59 Hz); 4.36 (2H, dd, J = 8.36 and 10.30 Hz); 5.08 (2H, dd, J = 8.36 and 10.30 Hz); 7.10 (2H, d, J = 1.46 Hz); 7.12 (2H, d, J = 1.46 Hz); 7.26 (10H, m).^{13}C NMR: 20.6; 25.4; 30.9; 31.7; 33.1; 47.1; 69.6; 74.5; 98.5; 117.9; 126.8; 127.3; 128.5; 129.2; 129.5; 130.1; 133.5; 142.5; 147.4; 164.7.IR (cm^{-1}): 2959; 1644; 1630; 1451; 1163; 886. HRMS (IE, m/z): experimental: 627.3198 (M+H), calculated: 627.3223. $[\alpha]_D^{24} = -20$ (c 0.11, CH_2Cl_2)

Compound **10b**: ^{1}H NMR: 1.33 (6H, s); 1.51 (6H, s); 2.15 (2H, d, J = 14.23 Hz); 2.26 (2H, d, J = 14.23 Hz); 2.30 (6H, s); 3.81 (2H, t, J = 8.31 Hz); 4.28 (2H, dd, J = 8.35 and 10.41 Hz); 5.07 (2H, dd, J = 8.36 and 10.40 Hz); 7.11 (2H, d, J = 2.06 Hz); 7.13 (2H, d, J = 2.06 Hz); 7.26 (10H, m).^{13}C NMR: 20.6; 31.1; 31.2, 32.2; 48.0; 69.6; 74.3; 99.5; 117.8; 126.8, 127.2; 128.4; 129.3; 129.4; 130.2; 134.0; 142.7; 148.0; 164.5. IR (cm^{-1}): 2960; 1642; 1604; 1452; 1261; 999; 698. HRMS (IE, m/z): experimental: 627.3215 (M+H), calculated: 627.3223. $[\alpha]_D^{24} = -61$ (c 0.1034, CH_2Cl_2).

4.1.1.5. Compounds 29a and 29b. In the first step SPANdiacid **27** (300 mg, 0.707 mmol) was placed in a Schlenk tube with 3 equiv of triethylamine (296 μl, 2.121 mmol) and 8 mL of thionyl chloride. The resulting dark mixture was stirred for 3 h at 60 °C, then the volatiles were removed under vacuum. The crude diacyl chloride was dissolved in 7 mL of DCM, then 3 equiv of triethylamine (296 μl, 2.121 mmol) and 3 equiv of L-valinol (219 mg, 2.121 mmol) (previously dissolved in 1 mL of DCM) were successively added. The resulting brown solution was stirred for 15 h at rt. Then water was added, the aqueous layer was washed twice with DCM, the organic layers were mixed, dried over $MgSO_4$ and the volatiles were removed under reduced pressure. The crude product was pure by NMR and is used without further purification for the next step.^{1}H NMR: 0.75 (6H, t, J = 6.5 Hz); 0.82 (6H, t, J = 6.9 Hz); 1.41 (12H, s); 1.45 (6H, s); 1.47 (6H, s); 1.6 (4H, m); 2.19 (2H, d, J = 14.4 Hz); 2.30 (2H, d, J = 14.3 Hz); 2.35 (6H, s); 2.36 (6H, s); 2.37 (2H, d, J = 14.4 Hz); 2.38 (2H, d, J = 14.3 Hz); 2.89 (2H, m); 3.11 (2H, m); 3.25 (2H, dd, J = 6.7 and 11 Hz); 3.47 (2H, m); 3.51 (2H, m); 3.66 (2H, m); 7.24 (2H, d, J = 1.9 Hz); 7.26 (2H, d, J = 1.9 Hz); 7.37 (4H, m); 7.66 (2H, d, J = 1.9 Hz); 7.72 (2H, d, J = 1.9 Hz).

4.1.1.6. Compounds 11a and 11b. At first, *N*8,*N*8′-bis((*S*)-1-hydroxy-3-methylbutan-2-yl)-4,4,4′,4′,6,6′-hexamethyl-2,2′-spirobi[chroman]-8,8′-dicarboxamide is dissolved in 8 mL of dry dichloromethane, to this are successively added *N*,*N*-dimethylaminopyridine (4.32 mg, 0.035 mmol) and triethylamine (0.592 mL, 4.242 mmol). The mixture is then cooled to 0 °C and methanesulfonyl chloride (0.164 mL, 2.121 mmol) is added. It is stirred overnight letting it slowly warm up to room temperature. Water is added and the aqueous layer is washed twice with dichloromethane. The organic layers are mixed, dried over $MgSO_4$, and the solvents are removed under vacuum. The crude NMR shows a small amount of unreacted substrate. Diastereoisomers are resolved on a Chiralpak IC column: 254 nm, hexane/isopropanol/diethylamine 90/10/0.1, 1 ml/min. Compound **11a** is obtained as a clear paste (80 mg, yield: 41%) and **11b** is obtained as a viscous solid (125 mg, yield: 63%). Overall yield: 52% starting from the diacid.

Compound **11a**: ^{1}H NMR: 0.75 (6H, d, J = 6.7 Hz); 0.85 (6H, d, J = 6.7 Hz); 1.31 (6H, s); 1.56 (6H, s); 1.62 (2H, m); 2.11 (2H, d, J = 14.2 Hz); 2.22 (2H, d, J = 14.2 Hz); 2.26 (6H, s); 3.7 (4H, m); 3.93 (2H, dd, J = 7.1 and 8.5 Hz); 7.15 (2H, d, J = 2.2 Hz); 7.21 (2H, d, J = 2.2 Hz).^{13}CNMR: 18.1; 18.9; 20.6; 31; 31.4; 32.4; 32.5; 47.8; 69.6; 72.1; 99.1; 118.2; 128.8; 129.2; 130.1; 133.7; 147.5; 163.1.IR (cm^{-1}): 2957; 1649; 1459; 1359; 1192; 981; 891.HRMS (IE, m/z): experimental: 559.3525 (M+H), calculated: 559.3536. $[\alpha]_D^{24} = -16$ (c 0.1048, CH_2Cl_2).

Compound **11b**: ^{1}H NMR: 0.73 (6H, d, J = 6.7 Hz); 0.85 (6H, d, J = 6.7 Hz); 1.31 (6H, s); 1.60 (6H, s); 1.62 (2H, m); 2.08 (2H, d, J = 14.2 Hz); 2.16 (2H, d, J = 14.2 Hz); 2.24 (6H, s); 3.74 (4H, m); 3.94 (2H, dd, J = 6.7 and 8.4 Hz); 7.09 (2H, d, J = 2.2 Hz); 7.13 (2H, d, J = 2.2 Hz).^{13}CNMR: 18.0; 19.0; 20.6; 30.7; 31.9; 32.4; 33.2; 46.8; 69.7; 72.2; 98.1; 118.5; 128.9; 129.1; 130.1; 133.1; 146.8; 163.0. IR (cm^{-1}): 2955; 1641; 1449; 1318; 1163; 1001; 888. HRMS (IE, m/z): experimental: 559.3549 (M+H), calculated: 559.3536. $[\alpha]_D^{24} = -31$ (c 0.1012, CH_2Cl_2).

Procedure A with substrate **2**: $NiCl_2$ (2.6 mg, 0.02 mmol) and (−)-**1** (8 mg, 0.022 mmol) were placed in a Schlenk tube and 1.5 mL of dry DCM was added. The resulting mixture was stirred for 1 h at rt. Then the substrate, **2** (37 mg, 0.2 mmol) previously dissolved in 1.5 ml of dry DCM was added , followed by NFSI (69 mg, 0.22 mmol) in one portion. After 3 h of stirring at rt the crude mixture was filtered over a pad of silica gel and DCM removed under reduced pressure. The conversion and enantioselectivity were determined by GC analysis.

Procedure B with substrate **2**: To SPAN amine (−)-**1** (7.3 mg, 0.02 mmol) dissolved in 1.5 mL of dry DCM in a Schlenk tube, were successively added substrate **2** (37 mg, 0.2 mmol), previously dissolved in 1.5 mL of dry DCM, and NFSI (69 mg, 0.22 mmol) in one portion. After 18 h of stirring at rt the crude mixture was filtered over a pad of silica gel and DCM was removed under reduced pressure. The conversion and enantioselectivity were determined by GC analysis. The NMR spectra of isolated fluorinated products were similar to previously reported compounds.

^{19}F NMR (in $CDCl_3$) profile of SPANamine **1** catalyzed fluorination of substrate **2**:

Acknowledgments

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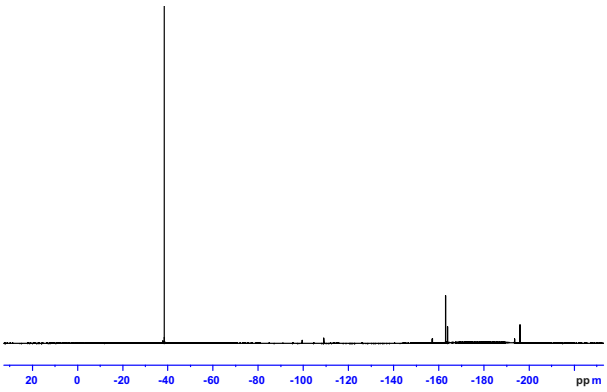
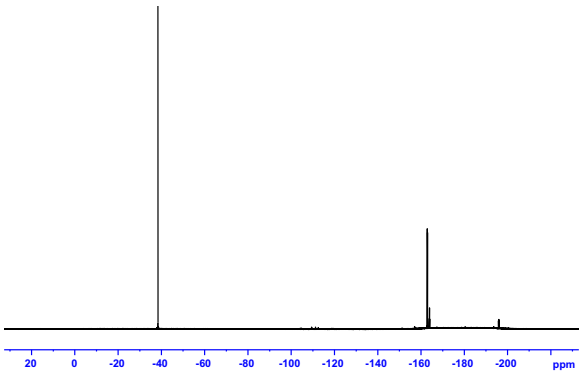
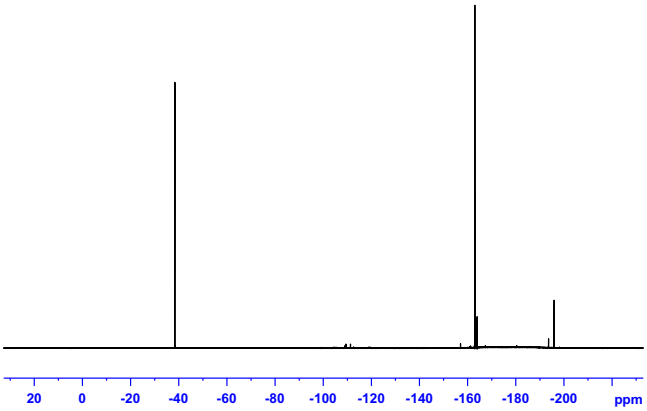


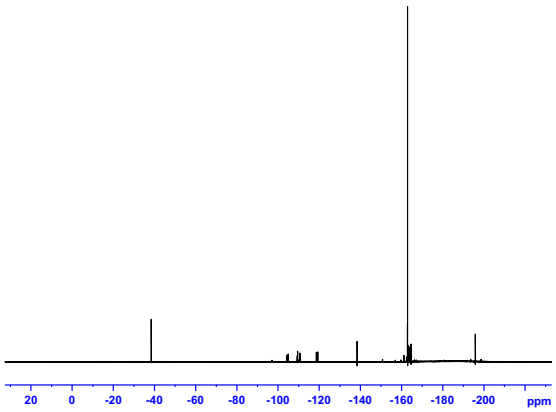
After 30min



After 2h



After 6h



After 12h

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