Supporting Information

A Broad Substrate Scope of aza-Friedel−Crafts Alkylation for the Synthesis of Quaternary α-Amino Esters.

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Table of Content

I. General Information

Reagents are commercially available (from Alfa Aesar or Sigma Aldrich) and used without further purification. All reactions were carried out in flame-dried vessels under an atmosphere of argon and in anhydrous solvents unless stated otherwise. Toluene was distilled over sodium in the presence of benzophenone before use; CH_2Cl_2 and $CHCl_3$ were distilled over calcium hydride. Dry solvents were transferred under argon to a dark glass bottle containing activated 3Å molecular sieves for storage. Reactions were monitored by analytical TLC on Silicycle silica gel 60-F254 glass backed (ref. TLG-R10011B-323) via UV absorption followed by vanillin-H_2SO_4 (1% vanillin in ethanol + 2% H_2SO_4), ceric ammonium molybdate (CAM), or ninhydrin (0.25% ninhydrin in ethanol + 3% ACOH) as staining system. The products were purified over silica gel column chromatography (Silicycle silica gel, 40-63 µm, ref. R10030B). NMR spectra were recorded on a Bruker 400 MHz Avance III spectrometer. ^{1}H-decoupled and APT (attached proton test) ^{13}C NMR spectra must be recorded with an adjustment of relaxation delay (d1) to larger values (d1 ≥ 4s) to observed optimal signal for both quaternary perfluorinated-geminal and vicinal carbons. Chemical shifts (δ) are quoted in ppm with internal calibration from residual solvent peak with $CDCl_3$: 7.26, 77.0 ppm; DMSO-d_6: 2.50, 39.5 ppm; CD_3CN: 1.94, 1.32 ppm for ^{1}H and ^{13}C NMR, respectively, and C_6F_6: -161.64 ppm for ^{19}F NMR. All coupling constants (*J*) are quoted in Hertz. The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Mass spectra (*m/z*) and High-resolution spectra (HRMS) were obtained from the University of Florida using an Agilent 6210 TOF instrument, using electrospray ionization (ESI) or direct analysis in real time (DART). Infrared spectra were recorded on a Nicolet IS5 FT-IR spectrophotometer. Melting points were measured on a MPA 160 digital apparatus.

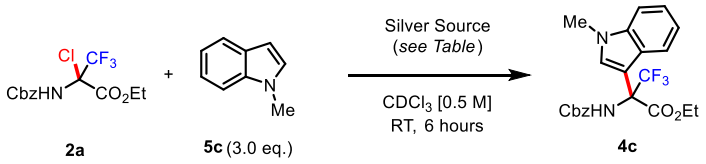
II. Reaction Optimization for Chloride Abstraction with Silver Salts

Fluorinated amino acids have recently attracted considerable attention due to their outstanding physicochemical and medicinal properties (*e.g.* high stability to metabolic degradation, increased lipophilicity and hydrogen-bond acceptor ability).[SI-1] For these reasons, we initiated a collaborative project for the synthesis α-perfluorinated α,α-disubstituted amino esters at the Automated Synthesis Laboratory (ASL) at Eli Lilly. The ASL program operated by Eli Lilly from 2013 to 2018 [SI-2] was developed to initiate industry-academic collaborations for the synthesis of compound libraries to identify new medicinally promising building blocks that are currently not available in the company repository.

a. Silver salt screening:

Given that reaction monitoring on the fully automated and remotely-controlled robotic system was achieved by syringing out aliquots for LC-MS analysis, the instability of the chloroaminal starting material **2a** became a major drawback for automated reaction optimization (chloroaminal to hemiaminal transformation upon work-up). Therefore, we turned our attention to optimizing the reaction conditions with the selected most reactive *N*-methyl indole **5c** nucleophile (3.0 eq.) by *in situ* ^{1}H NMR, which can be accomplished at higher concentrations (0.5 M) to shorten reaction times (Table SI-1). Some common silver (I) salts were tested such as AgOAc or the more ionizing $AgBF_4$ and $AgSbF_6$ but, in each case, the desired Friedel-Crafts reactions did not occur. $AgBF_4$ and $AgSbF_6$ promoted extended decomposition, while AgOAc (entry 1) favored the formation of the acetylated hemiaminal product. Reactions carried out with AgOTs (entry 2), or the relatively insoluble $AgNO_3$ (entry 3) afforded the desired α-amino ester **4c** in 80 and 72% yield respectively.

Table SI-1. Selected key reaction conditions from a screening of experiments at the ASL



2a **5c** (3.0 eq.) **4c**

Entry	Silver source (Ag^+ eq.)	% Conversion[a]		% Yield[a]
		3 h	6 h	
1	AgOAc (2.0 eq.)	65	90	--[d]
2	AgOTs (2.0 eq.)	66	100	80
3	$AgNO_3$ (2.0 eq.)	85	100	72
4[b]	Ag_2CO_3 (2.0 eq.)	72	82	74
5[b,c]	Ag_2CO_3 (2.0 eq.)	58	100	68
6[b]	Ag_2CO_3 (1.5 eq.)	62	100	95

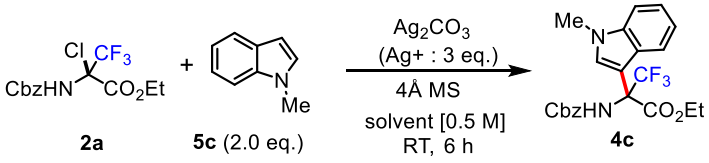
[a] conversions and yields were determined by ^{1}H NMR of the crude reaction mixtures; [b] 4 Å MS was added to the reaction mixture; [c] Triflic acid (20 mol%) was added. [d] The major prodcut was acetoxy-aminal which was generated via displacement of chloride by acetate

To avoid the counteranion effect and the stoichiometric formation of strong Brønsted acids (HNO_3, TsOH), silver carbonate (Ag_2CO_3) was also evaluated for the halogen abstraction in this reaction (Entries 4-6). Indeed, as shown in entry 4, the reaction with Ag_2CO_3 led to 82% conversion and a 74% yield after six hours. To test our hypothesis about the potential role of Brønsted acid in the reaction, 20 mol% of triflic acid was added to the reaction. The results from entries 4 *vs* 5 were very comparable, but the reaction with acid underwent full conversion with somehow a lower NMR yield. Finally, the equivalents of Ag_2CO_3 and of nucleophile **5c** were lowered to 1.5 eq. and 2.0 eq. respectively, and the reaction proceeded smoothly as shown by the 95% NMR yield in product **4c** (entry 6).

b. Solvent Screening:

The choice of solvent might play a crucial role in the reaction due to the initial solubility of the silver salts reagents and the silver chloride byproduct; therefore, a solvent screen was achieved at (0.5 M) concentration (Table SI-2). Upon exposure of chloroaminal **2a** to Ag_2CO_3 (1.5 eq., 3.0 eq. in Ag+) and nucleophile **5c** (2.0 eq.), reactions in various solvents were monitored over the course of six hours. When polar protic and aprotic solvents were used (*e.g.* DMF, DMSO, CH_3CN, acetone), full conversions were observed, along with large amounts of decomposition leading to ~25% yield of the desired product **4c** (Entries 1-2). For comparison, reactions in aprotic apolar solvents (Entries 3-5), reactions proceeded smoothly with a reaction in dichloromethane being the most efficient with a full conversion observed after 6 hours, and an NMR yield of 85% (Entry 5). Having identified optimal reaction conditions, we were then able to reevaluate the reaction performance on the automated chemical synthesis platform. To our delight, both reactions in hexane and dichloromethane (Entries 4-5) were highly reproducible and product **4c** was isolated on the automatized system in 52% and 50% yields respectively.

Table SI-2. Solvents tested for the Friedel–Crafts mediated by silver carbonate



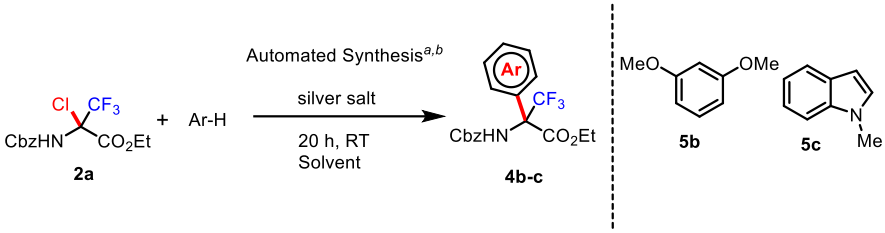
2a **5c** (2.0 eq.) **4c**

Entry	Solvent	% Conversion[a]		% Yield[a,b]
		3 h	6 h	
1	DMF	20	100	25
2	CH_3CN	20	100	25
3	toluene	58	100	74
4	hexane	44	85	76 (52)[b]
5	CH_2Cl_2	78	100	85 (50)[b]

[a] Conversions and yields were determined by ^1H NMR of the crude reaction mixtures;
[b] Isolated yields, for reactions conducted on the automatized robot for 20 hours.

Having an initial set of optimized conditions for the synthesis of the α-prefluorinated α,α-disubstituted amino esters **2a**, produced by *N*-methyl indole **5c** in the Friedel−Crafts functionalization, we turned our attention to the less reactive 1,3-dimethoxy benzene nucleophile **5b** (Table SI-3). The evaluation of novel reaction conditions was achieved using the two aromatic nucleophiles and some common silver(I) salts for halogen abstraction. The reaction **5c** as nucleophile was tested using AgOTf and AgOTs as shown in entries 1-2. The milder reaction conditions using silver tosylate, which was thought to generate a stoichiometric amount of *p*-toluenesulfonic acid, afforded the desired amino ester **4c** in 31% yield. Using similar reaction

Table SI-3. Reaction optimization for the Friedel–Crafts alkylation with weaker π-nucleophile **5b**



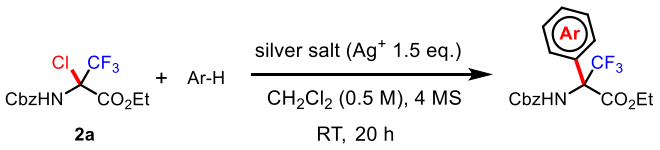
2a **4b-c** **5b** **5c**

Entry	Solvent [Conc.]	Silver source (Ag^+ eq.)	Arene (eq.)	Product (% Yield)[d]
1	CH_2Cl_2 [0.1 M]	AgOTf (2.0 eq.)	**5c** (2.0 eq.)	**4c** (<10%)
2	CH_2Cl_2 [0.1 M]	AgOTs (1.0 eq.)	**5c** (1.5 eq.)	**4c** (31%)
3	CH_2Cl_2 [0.1 M]	AgOTs (1.0 eq.)	**5b** (1.5 eq.)	NR
4	THF [0.1 M]	AgOTf (2.0 eq.)	**5b** (2.0 eq.)	**4b** (<10%)
5	CH_2Cl_2 [0.1 M]	AgOTf (2.0 eq.)	**5b** (2.0 eq.)	**4b** (29%)
6[b]	CH_2Cl_2 [0.3 M]	AgOTf (3.0 eq.)	**5b** (2.0 eq.)	**4b** (25%)[d]
7[b,c]	Et_2O [0.3 M]	AgOTf (2.0 eq.)	**5b** (2.0 eq.)	**4b** (71%)[d]

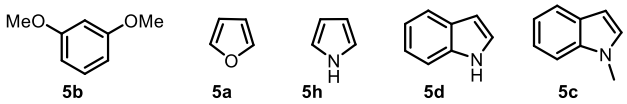
[a] Reactions carried on a robot at the automated synthesis laboratory facility @ Lilly; [b] Reaction carried at the bench for control and optimization; [c] Reaction carried for 48 hours; [d] NMR yield obtained on crude reaction mixture.

conditions with **5b** as nucleophile was unsuccessful to deliver the desired product (Entry 3). Switching to silver triflate was required for the reaction to proceed (Entries 4-7). While the reaction was poorly efficient in THF (Entry 4), substantially more desired product **4b** was obtained in dichloromethane with efficacy between 25-29% yields as shown in entries 5-6. To further optimize the AgOTf-mediated conditions, reactions were performed at the bench where we increased both concentration of starting material [0.3 M] and the equivalents of silver source as shown in entries 6-7. It was found that the reaction was highly efficient in diethyl ether (Et_2O) leading to a full conversion and 71% yield of the desired α-amino ester **4b** as judged by ^1H NMR. Given the low flashpoint of Et_2O, such solvents are strictly prohibited on an automated synthesis system, therefore an alternative for Et_2O was investigated but unfortunately reactions carried under similar conditions to entry 7, in other ethereal solvents (THF, 1,4-dioxane or TBDME) afforded the desired product **5b** only with low conversion and poor yields (< 10% yield).

Table SI-4. Initial reaction discovery screen at the ASL



arenes tested:



5b **5a** **5h** **5d** **5c**

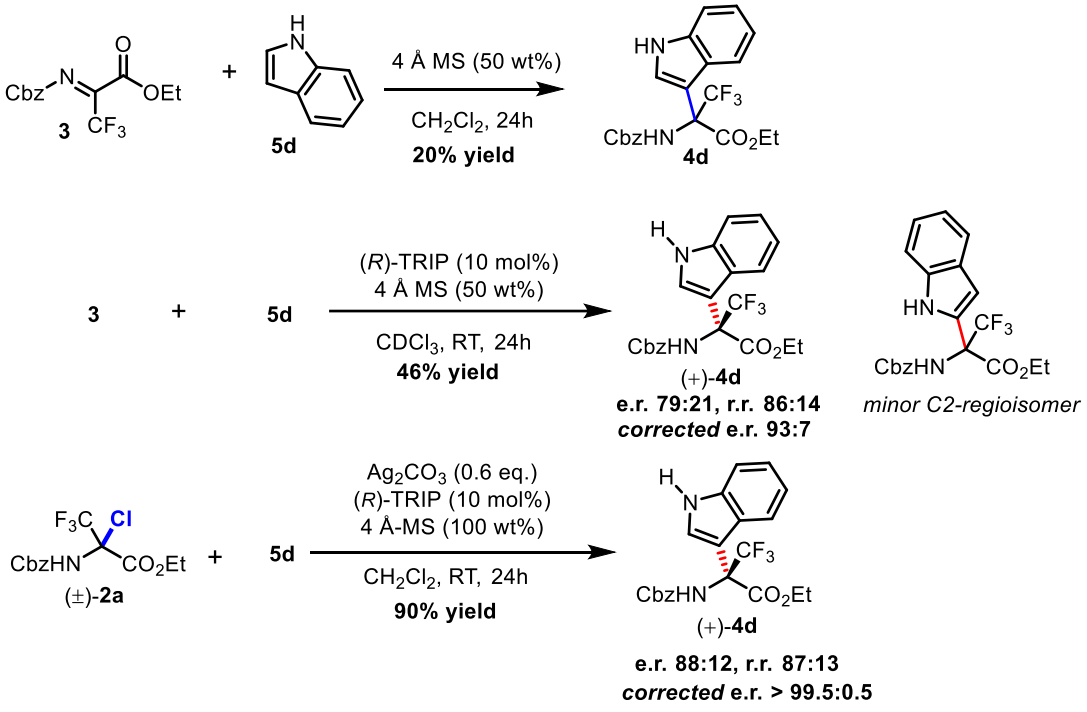
Entry	Nucleophilicity (N)[a]	Silver source	Arene	Product (% Yield)
1	1.33	AgOTf	**5a**	**4a** (9)[b,c]
		Ag_2CO_3	**5a**	*NR*
2	2.48	AgOTf	**5b**	**4b** (31)[b,c]
		Ag_2CO_3	**5b**	*NR*
3	4.63	Ag_2CO_3	**5h**	**4h** (71)
4	5.55	Ag_2CO_3	**5d**	**4d** (55)
5	5.75	Ag_2CO_3	**5c**	**4c** (61)

[a] The nucleophilicity values adapted from the Mayr's scale; [b] Impurities still present after purification (possible regioisomer); [c] Reactions performed without 4Å MS.

The overall results of reaction discovery obtained at the ASL are summarized in Table SI-4. When reactions of chloroaminal **2** were attempted with arenes of low nucleophilicity **5b** and **5a** (entries 1-2), the halogen abstraction mediated by Ag_2CO_3 was inefficient thus the Friedel–Crafts reaction did not take place in an efficient manner. In this case, the corresponding imine was formed, but the low Lewis basicity and electrophilicity of this intermediate does not allow for weak arene nucleophiles to add and achieve the Friedel–Crafts reaction. Therefore, the use of AgOTf was required; this reagent likely generates triflic acid, which might protonate the imine to facilitate the arylation and deliver **4b** and **4c** albeit in low yields (31% and 9% yields respectively). Finally, for electron-rich arenes **5h, 5d** and **5c**, the optimum reaction conditions developed with Ag_2CO_3 were applied and the corresponding products **4h**, **4d** and **4c** were isolated in reasonable yields of 71%, 55% and 61%, respectively (Entries 3-5). In this case, the postulated imine intermediate was not observed by ^{1}H or ^{19}F NMR (at 1, 6, 20 hours), thus suggesting that AgOTf, or the TfOH byproduct might enhance the Friedel–Crafts arylation rate. This hypothesis was later confirmed by several control experiments of imine reactivity.

III. Reaction Optimization for a catalytic enantioselective aza-Friedel−Crafts Alkylation with indole

Imine **3** was prepared and quickly isolated (filtration under argon) to be further reacted with indole **5d** which proceeded with low conversions at room temperature in 24 hours with complete regioselectivity. Phosphoric acid at room temperature with indole **5d** as nucleophile was relatively efficient and delivered **4d** in 46% yield with a 86:14 regioisomer ratio as determined by ^{19}F NMR. To our surprise the major C3-regioisomer product was found to be contaminated with the C2-regiosiomer. The enantiomeric ratio measured for this mixture of isomers by chiral HPLC was e.r. = 79:21. As the C2-regioisomer coelutes with the minor enantiomer (–)-**4d**, a corrected enantiomeric ratio was estimated, based on the fact that the HPLC peak at 8.088 min, (minor enantiomer) contains 67% of regioisomers (corresponding to 14% overall). Thus a corrected e.r. = 93:07 was calculated (86% e.e.). This results suggests that a Brønsted catalysis might be operating in the second step after halide abstraction. Also, under similar conditions, reaction of chloroaminal (±)-**2a** delivered the same product (+)-**4d** in a much higher enantiomeric ratio (corrected e.r. >99.5:0.5). Taken together, these results suggest that the (*R*)-TRIP catalyst –which has been often been proposed to bind to both imine electrophile and indole nucleophile– might affect the indole C2/C3 partial charges resulting in the formation of the minor C2-regioisomer.



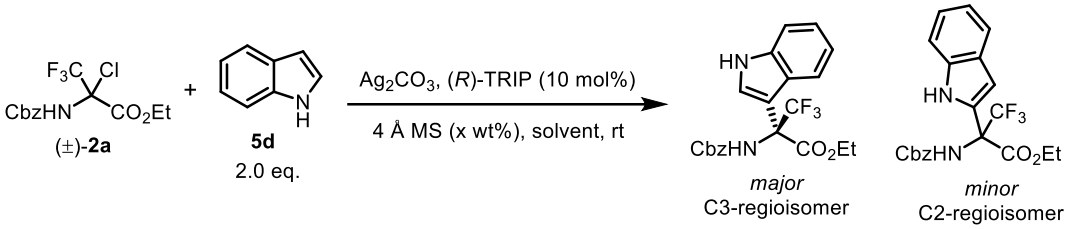
Synthesis of enantioenriched (+)-**4d** (Entry 6): Ag_2CO_3 (16.5 mg, 0.06 mmol, 0.60 eq.), activated 4 Å molecular sieves (17.0 mg, 50 wt % rel. to chloroaminal **2a**) in a reaction tube were heated under vacuum with a heat gun. After the tube was cooled down under argon, it was charged with indole (23.5 mg, 0.2 mmol, 2.0 eq) and chloroaminal **2a** (34.0 mg, 0.10 mmol, 1.0 eq.) followed

by anhydrous toluene (0.5 mL). The mixture was stirred at room temperature for 24 hours. The crude solution was filtered through a pad of celite which was then washed using EtOAc. Solvent was removed under reduced pressure and the crude material was purified on silica plate by preparative thin-layer chromatography (*n*-hexane: ethyl acetate, 50:50) to give enantioenriched **4d** ($[\alpha]_D^{21}$ = 19.8 (*c* = 1.16, $CHCl_3$), 35.6 mg, 0.085 mmol, 85% yield). The chromatographically pure sample of **4d** was solubilized in isopropanol (1 mg/mL) and analyzed on NP-HPLC (CHIRALCEL OD-H, isocratic 10% IPA/ 90% hexanes, 1.0 mL/min, detection at 254 nm). Racemic sample, retention times: T_r = 7.061, 8.292 mins (e.r. = 51:49). Enantioenriched sample, retention times: T_R = 6.929, 8.161 mins (e.r. = 91:09).

1 mmol Scale experiment (Entry 9): Ag_2CO_3 (165 mg, 0.6 mmol, 0.60 eq.), activated 4 Å molecular sieves (170 mg, 50 wt % rel. to chloroaminal **2a**) in a reaction flask were heated under vacuum with a heat gun. The reaction flask was cooled down under argon and it was charged with indole (235 mg, 2.0 mmol, 2.0 eq) and chloroaminal **2a** (340 mg, 1.0 mmol, 1.0 eq.) followed by anhydrous toluene (5 mL). The reaction mixture was stirred at room temperature for 24 hours. The crude solution was filtered through a pad of celite which was then washed using ethyl acetate (3 X 5 mL). Solvent was removed under reduced pressure, and the crude material was purified by silica gel column chromatography using ethyl acetate and cyclohexane (gradient elution from 0:100 to 30:70). The desired enantioenriched product **4d** was obtained as a white solid (294 mg, 0.70 mmol, 70% yield, e.r. = 88:12, r.r. = 87:13).

We noted that in all reactions catalyzed by (*R*)-TRIP, the C2-regioisomer was formed and contaminated the major reaction product (+)-**4d**. This isomer has not been observed in any uncatalyzed reactions and seems to be formed when a combination of (*R*)-TRIP and molecular sieves is used. In our hands, the C2-regioisomer could not be removed neither by silica gel chromatography nor by reverse-phase HPLC as it coelutes with the C3-regioisomer. As shown in the Table SI-5 below, C2/C3 regioisomer ratios (r.r.) determined by ^{19}F NMR appear to be closely related to the e.r. values measured by chiral HPLC in each reaction.

Table SI-5. Application to an enantioselective catalytic *aza*-Friedel-Crafts transformation.[a-g]

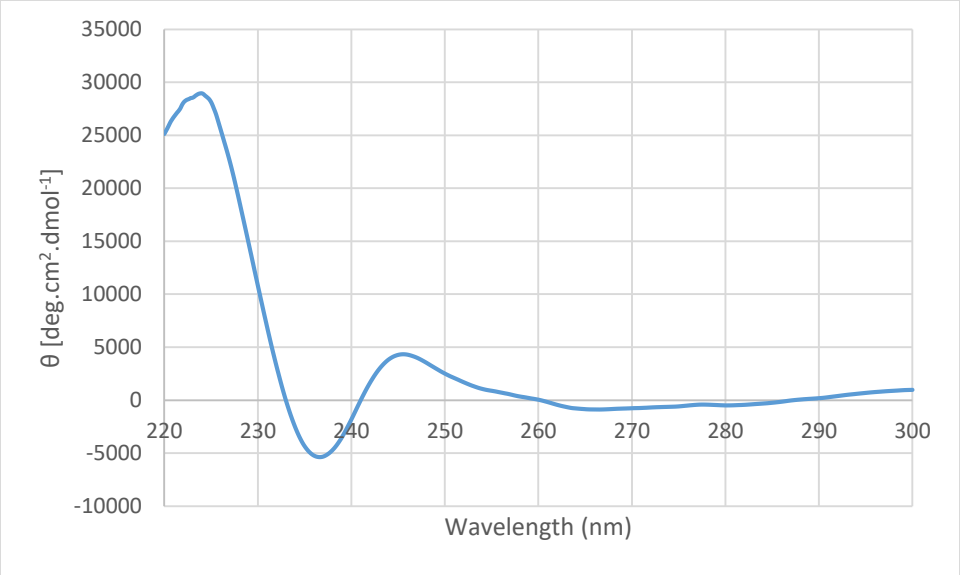


Entry	Ag^{+}(I) eq.	4 Å-MS (x wt%)	solvent	Yield (%)	e.r.[b]	r.r.[c]
1[d]	2.4	300	CH_2Cl_2	87	49:51	100:0
2	2.4	300	CH_2Cl_2	87	82:18	83:17
3	1.2	300	CH_2Cl_2	75	80:20	77:23
4	1.2	100	CH_2Cl_2	96	88:12	88:12
5	1.2	300	toluene	97	88:12	87:13
6	1.2	50	toluene	85	90:10	91:09
7[e]	1.2	50	toluene	85	90:10	86:14
8[f]	1.2	50	toluene	83	88:12	87:13
9[g]	1.2	30	toluene	70	88:12	87:13

[a] Standard reactions carried out on 0.1-0.2 mmol scale of (±)-**2a** in various solvents (0.2 M) at rt for 24 h. [b] Determined by NP-HPLC on an enantiodiscriminating Chiralcel OD-H stationary phase. [c] The ratio of C2/C3 regioisomers was determined by integration of peaks area of ^{19}F NMR. [d] Reaction achieved without (*R*)-TRIP. [e] Reaction at -20 °C. [f] Reaction at -78 °C for 30 h. [g] Reaction scale-up with 1.0 mmol of (±)-**2a** and 5 mol% of (*R*)-TRIP catalyst.

Since the two regioisomers weren't separable through chromatography, crystallization experiments were carried out to separate them. A slow evaporation crystallization was successful in ethyl acetate and ethanol mixture. Separated mother liquor and solid were analyzed by NMR and chiral HPLC.

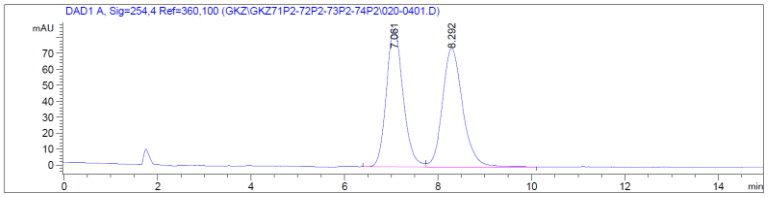
Product **4d** (Entry 6: 44.1 mg, 91:09 r.r., 90:10 e.r.) was purified by crystallization from a solution of ethyl acetate and ethanol (0.4 mL, 1:1). The solvent was slowly evaporated until solid precipitated out. The mother liquor (containing 24.6 mg of solute) and the precipitated solid (19.5 mg) were separated for NMR and HPLC analysis. Analytical results showed that the concentrated mother liquor contains the C3-regioisomer (+)-**4d** as enantiomeric pure (> 99% e.e.), and that the solid contains an increased ratio in C2-regioisomer (80:20 r.r., 78:22 e.r.). These results suggest that the initial reaction is highly enantioselective, but contaminated with the product **4d** C2-regioisomer, therefore enantiomeric ratio can be corrected based on r.r. measured by ^{19}F NMR.



CD spectrum of enantioenriched (+)-**4d** (Entry 6).

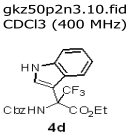
The CD spectrum was recorded at room temperature using a solution of enantioenriched (+)-**4d** (>99% e.e., Entry 6) in CH_3CN (1.08×10^{-3} mol L^{-1}) on a JASCO J-810 Spectropolarimeter (path length 0.1 cm). The CD spectrum of (+)-**4d** presented above is highly similar to the experimental ECD spectrum for (*R*) enantiomers predicted by Bolm and coworkers (*Org. Lett.* **2011**, *13*, 1044).[SI-4]

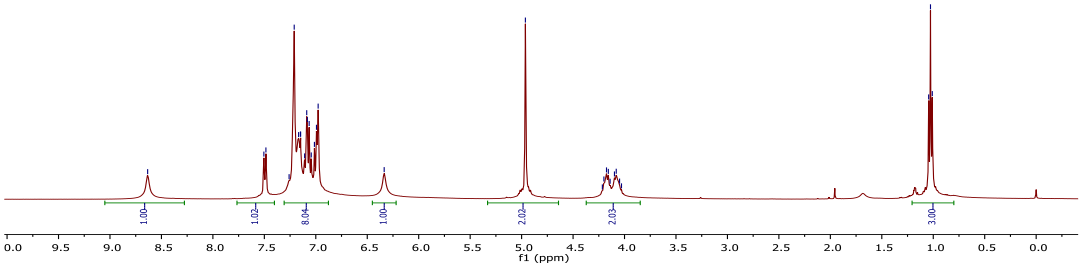
The chromatographically pure sample of (±)-**4d** (Entry 1) was solubilized in isopropanol (1 mg/mL) and analyzed on NP-HPLC (CHIRALCEL OD-H, isocratic 10% IPA/ 90% hexanes, 1.0 mL/min, detection at 254 nm). Retention times: T_r = 7.061, 8.292 mins (**e.r. = 49:51**).

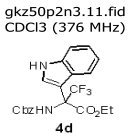


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.061	BV	0.3858	2156.96069	86.22986	49.0953
2	8.292	VB	0.4599	2236.45459	74.57313	50.9047

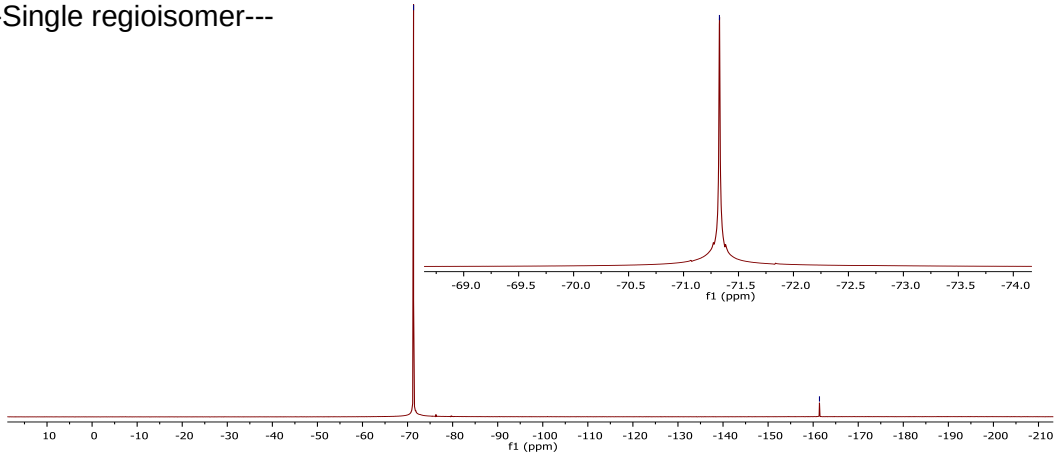
^{1}H NMR of Racemic sample (±)-**4d** (Entry 1)



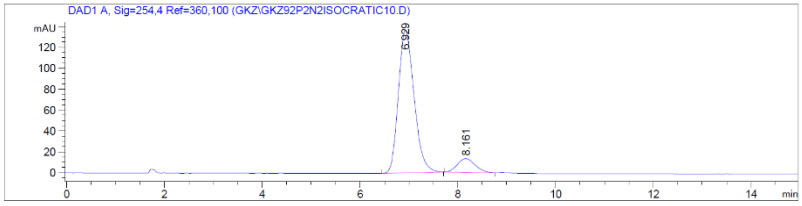




^{19}F NMR of Racemic sample (±)-**4d** (Entry 1)
---Single regioisomer---

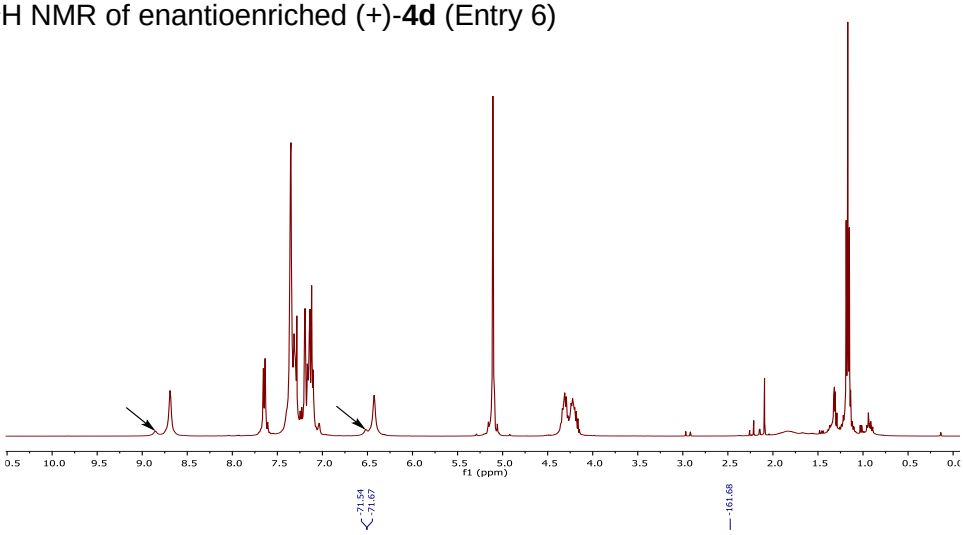


The chromatographically pure sample of (+)-**4d** (Entry 6) was solubilized in isopropanol (1 mg/mL) and analyzed by NP-HPLC (CHIRALCEL OD-H, isocratic 10% IPA/ 90% hexanes, 1.0 mL/min, detection at 254 nm). Retention times: T_R = 6.929, 8.161 mins (**e.r. = 90:10**).

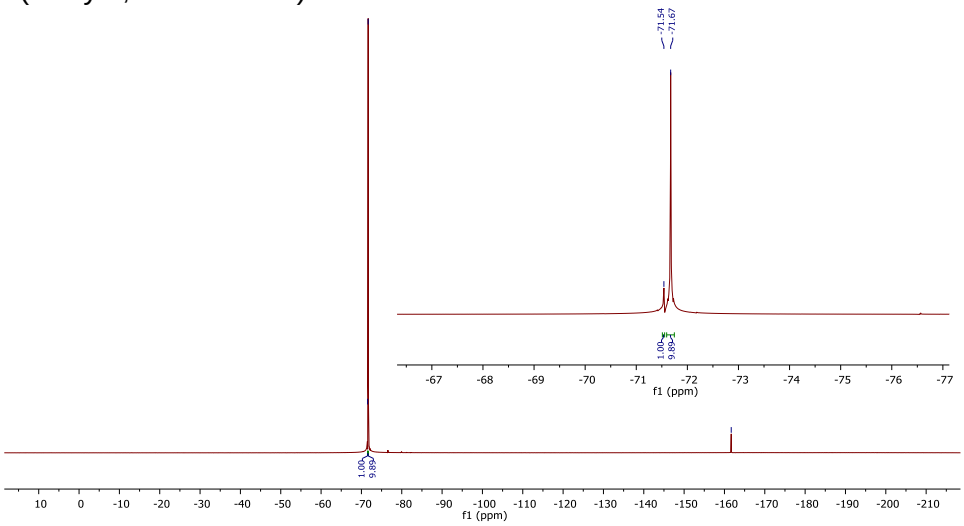


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.929	BB	0.3439	3054.63428	137.10504	90.3966
2	8.161	BB	0.3882	324.51172	12.95807	9.6034

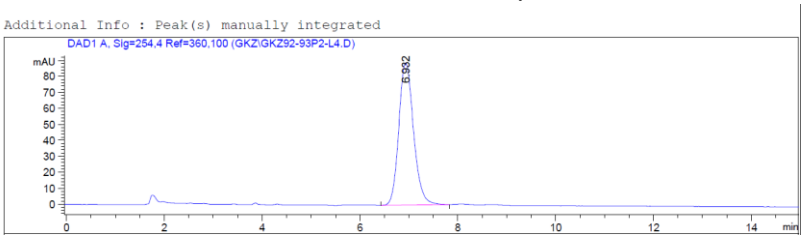
^{1}H NMR of enantioenriched (+)-**4d** (Entry 6)



^{19}F NMR of enantioenriched sample (+)-**4d** (Entry 6, **r.r. of 91:09**)



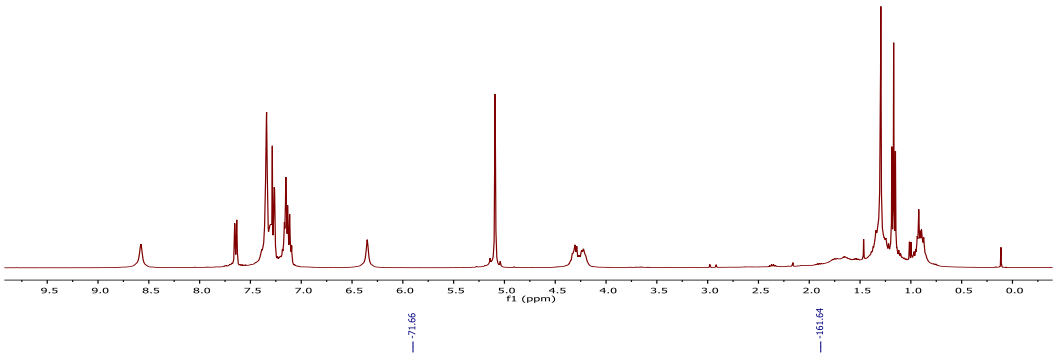
Sample of the concentrated mother liquor from the crystallization of **4d** was solubilized in isopropanol (1 mg/mL) and analyzed on NP-HPLC (CHIRALCEL OD-H, isocratic 10% IPA/ 90% hexanes, 1.0 mL/min, detection at 254 nm). Retention times: T_R = 6.932 mins (**e.r. >99.5:0.5**).



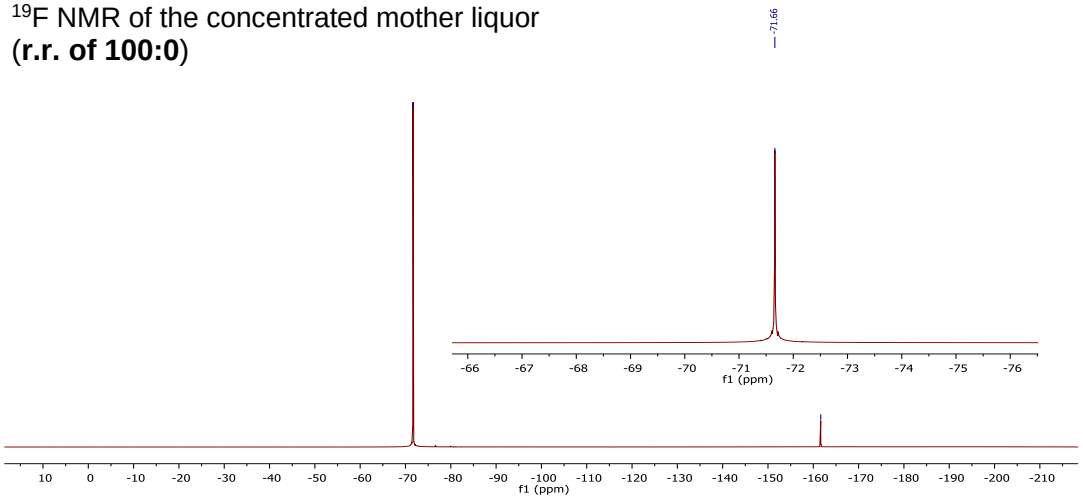
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.932	BB	0.3238	1861.33679	89.05700	100.0000
Totals :				1861.33679	89.05700	

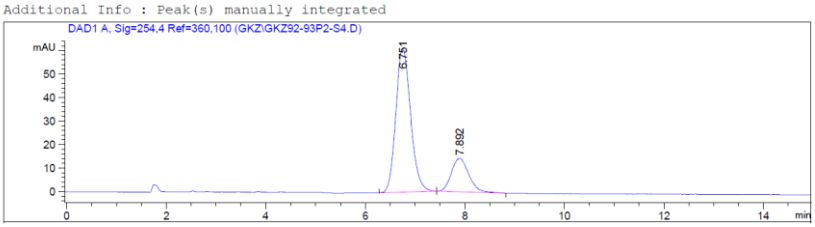
^{1}H NMR of the concentrated mother liquor



^{19}F NMR of the concentrated mother liquor
(**r.r. of 100:0**)



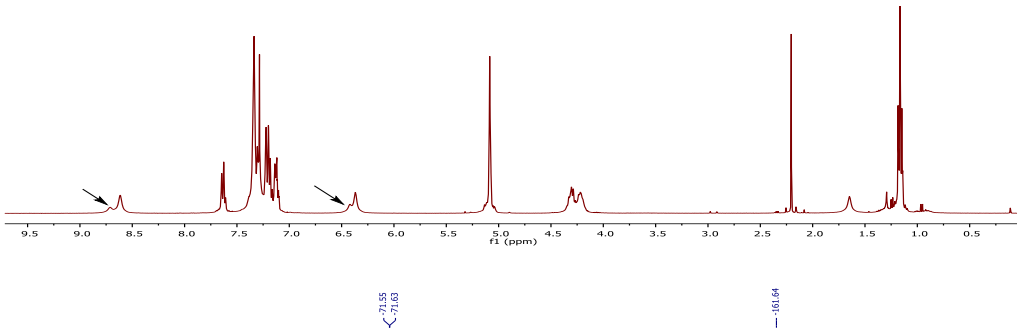
Sample of the precipitated solid from the crystallization of **4d** was solubilized in isopropanol (1 mg/mL) and analyzed on NP-HPLC (CHIRALCEL OD-H, isocratic 10% IPA/ 90% hexanes, 1.0 mL/min, detection at 254 nm). Retention times: T_r = 6.751, 7.892 mins (**e.r. = 78:22**).



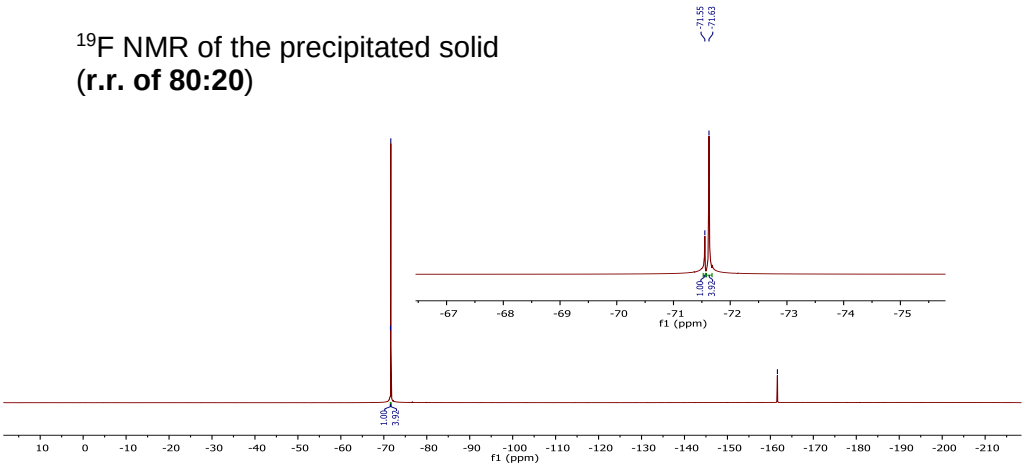
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.751	BB	0.3185	1262.06140	61.21057	78.4419
2	7.892	BB	0.3740	346.85107	14.24871	21.5581
Totals :				1608.91248	75.45928	

^{1}H NMR of the precipitated solid

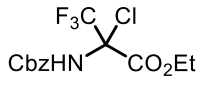


^{19}F NMR of the precipitated solid
(**r.r. of 80:20**)



IV. Synthetic Procedures and Compounds Characterization

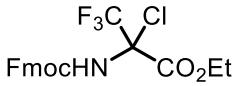
Ethyl 2-(((benzyloxy)carbonyl)amino)-2-chloro-3,3,3-trifluoropropanoate (**2a**)



$C_{13}H_{13}ClF_3NO_4$
MW: 339.70 g/mol

Synthesis of chloroaminal **2a**: $SOCl_2$ (2.9 mL, 40 mmol, 2.0 eq.) was added neat and dropwise to a mixture of ethyl 3,3,3-trifluoropyruvate (3.4 mL, 26 mmol, 1.0 eq.) and benzyl carbamate (3.0 g, 20 mmol, 1.0 eq.). The reaction mixture was stirred neat at 60°C heated with oil bath in a sealed vessel for 3 days. $SOCl_2$ was then evaporated and the residue washed with *n*-hexane (3 X 6.0 mL) to obtain the crude chloroaminal **2** as a white solid (6.1 g, 36.4 mmol, 91% yield). The product was used into the next step without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) = 7.44 – 7.30 (m, 5H_{Ph}), 5.95 (br, NH), 5.17 (s, 2H, O-CH_2-Ph), 4.33 (q, *J* = 7.1 Hz, 2H, O-CH_2-CH_3), 1.29 (t, *J* = 7.1 Hz, 3H, O-CH_2-CH_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm) = 161.1 (C-1), 153.2 (C(O)O-CH_2-Ph), 135.0 (*i*-H_{Ph}), 128.9 (p-H_{Ph}), 128.8 (H_{Ph}), 128.8 (H_{Ph}), 121.32 (q, *J* = 285.2 Hz, CF_3), 78.0 (q, *J* = 33.3 Hz, C-CF_3), 68.6 (C(O)O-CH_2-Ph), 64.9 (O-CH_2-CH_3), 13.7 (O-CH_2-CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -76.26 (referred to -161.64 ppm of C_6F_6). **IR** (film): 3315, 2987, 1742, 1523, 1266, 1237, 1194, 1063 cm^{-1}. Note: The compound is not stable under infusion conditions and the hydrolized adduct mass was obtained. **HRMS** (ESI) m/z: $[M-(Cl+OH)+H]^+$ calcd. for $C_{13}H_{15}F_3NO_5$ 322.0897; Found 322.0919 (+6.8 ppm). **SMILES**: ClC(C(OCC)=O)(C(F)(F)F)NC(OCC1=CC=CC=C1)=O

Ethyl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-2-chloro-3,3,3-trifluoropropanoate (**2b**)

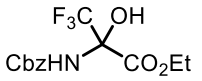


$C_{20}H_{17}ClF_3NO_4$
MW: 427.80 g/mol

Synthesis of chloroaminal **2b**: $SOCl_2$ (4.4 mL, 60 mmol, 3.0 eq.) was added neat and dropwise to a mixture of ethyl 3,3,3-trifluoropyruvate (3.4 mL, 26 mmol, 1.0 eq.) and (9*H*-fluoren-9-yl)methyl carbamate (4.8 g, 20 mmol, 1.0 eq.). The reaction mixture was stirred neat at 80 °C heated with oil bath in a sealed vessel for 36 hours. $SOCl_2$ was then evaporated and the gummy residue was kept under vacuum for one day to obtain the crude chloroaminal **2b** as a white solid (8.5 g, 20 mmol, 100% yield). Product **2b** was used into the next step without further purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) = 7.81 (d, *J* = 7.5 Hz, 2H), 7.61 (dd, *J* = 7.5 Hz, 3.0 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 6.24 (br, 1H), 4.63 – 4.49 (m, 2H), 4.41 (q, *J* = 7.1 Hz, 6.6 Hz, 2H), 4.27 (t, *J* = 6.7 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm) = 160.9 (Cq), 153.1 (Cq), 143.1 (Cq), 141.3 (Cq), 127.9 (2 CH), 127.1 (2 CH), 124.8 (2 CH), 121.1 (q, *J* = 285.8 Hz, Cq), 120.0 (2 CH), 77.8 (q, *J* = 34.3 Hz, Cq), 68.3 (CH_2), 64.8 (CH_2), 46.7 (CH), 13.6 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -75.90 (referred to -161.64 ppm of C_6F_6). **IR** (film): 3314, 2986, 1739, 1518, 1478, 1232, 1060 cm^{-1}. Note: The compound is not stable and the exact mass of the corresponding methoxyaminal was obtained in presence of methanol. **HRMS** (ESI) m/z: $[M+H]^+$ calcd. for $C_{21}H_{21}F_3NO_5$ 424.1366; Found 424.1365 (-0.2 ppm).

SMILES: ClC(C(OCC)=O)(C(F)(F)F)NC(OCC1C(C=CC=C2)=C2C3=C1C=CC=C3)=O

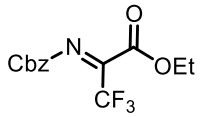
Ethyl 2-(((benzyloxy)carbonyl)amino)-3,3,3-trifluoro-2-hydroxypropanoate (**1**) [SI-3]



$C_{13}H_{14}F_3NO_5$
MW: 321.25 g/mol

White solid, **m. p.** 116.8 – 117.0 °C. **R_f** (*n*-hexane:CH_2Cl_2, 1:1) = 0.15. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) = 7.67 – 7.26 (m, 5H), 6.04 (br, 1H), 5.39 (br, 1H), 5.13 (s, 2H), 4.62 – 4.17 (m, 2H), 1.30 (t, *J* = 8.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm) = 165.7 (Cq), 154.6 (Cq), 135.1 (Cq), 128.6 (2 CH), 128.5 (CH), 128.3 (2 CH), 121.4 (q, *J* = 288.8 Hz, Cq), 80.4 (q, *J* = 33.3 Hz, Cq), 67.9 (CH_2), 64.6 (CH_2), 13.7 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -80.63 (referred to -161.64 ppm of C_6F_6). **IR** (film): 3288, 1748, 1692, 1540, 1322, 1270, 1239, 1156 cm^{-1}. **HRMS** (ESI) m/z: $[M+H]^+$ calcd. for $C_{13}H_{15}F_3NO_5$ 322.0897; Found 322.0910 (+4.0 ppm).
SMILES: OC(C(OCC)=O)(C(F)(F)F)NC(OCC1=CC=CC=C1)=O

Ethyl (*Z*)-2-(((benzyloxy)carbonyl)imino)-3,3,3-trifluoropropanoate (**3**)



$C_{13}H_{12}F_3NO_4$
MW: 303.24 g/mol

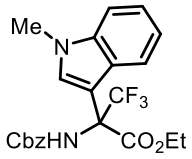
Synthesis of imine **3**: Ag_2CO_3 (83 mg, 0.30 mmol, 1.5 eq.), activated 4 Å molecular sieves (300 wt % rel. to chloroaminal **2a**) in a reaction tube were heated under vacuum with a heat gun. After the tube was cooled down under argon, chloroaminal **2a** (68 mg, 0.20 mmol, 1.0 eq.) was added to the tube, then $CDCl_3$ (1 mL, dehydrated passing through aluminum oxide, neutral, 60 Å) was injected into the tube. The reaction was monitored by ^{1}H and ^{19}F NMR, and after 7-hour stirring, chloroaminal **2a** was fully transformed into imine **3** (60 mg, 0.20 mmol, 100% yield). Imine **3** is highly hygroscopic and unstable at room temperature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) = 7.43 – 7.37 (m, 5H), 5.34 (s, 2H), 4.32 (q, *J* = 8.0 Hz, 2H), 1.32 (t, *J* = 8.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm) = 158.5 (Cq), 139.2 (Cq), 136.7 (Cq), 134.2 (Cq), 128.9 (CH), 128.8 (2 CH), 128.7 (2 CH), 117.8 (q, *J* = 280.8Hz, Cq), 69.6 (CH_2), 64.3 (CH_2), 13.7 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -70.05 (referred to -161.64 ppm of C_6F_6). **HRMS** (ESI) m/z: $[M+NH_4]^+$ calcd. for $C_{13}H_{16}F_3N_2O_4$ 321.1062; Found 321.1051 (-3.4 ppm). Spectral data for compound **3** are consistent with the data previously reported in the literature. [SI-4]
SMILES: O=C(OCC)/C(C(F)(F)F)=N/C(OCC1=CC=CC=C1)=O

General Protocol A: Friedel–Crafts Functionalization with Strongly Reactive π-Nucleophiles.

All reactions were performed in flamed dry scintillation vials (2 mL) equipped with stir bars and placed under an inert atmosphere of argon. A vial was initially charged with chloroaminal **2** (0.20 mmol, 1.0 eq.) dissolved in anhydrous dichloromethane (1.0 mL, 0.20 M) before adding 4Å MS (30 mg), silver carbonate (82 mg, 0.30 mmol, 1.5 eq.) and arene nucleophiles (0.40 mmol, 2.0 eq.). The resulting reaction mixture was stirred at RT. The progress of the reaction was monitored via ^{1}H, ^{19}F NMR, and TLC, until reaction completion (different reaction time in each case) as shown by the total disappearance of chloroaminal **2** by TLC (Note: the R_f of **2** is actually the same as hemiaminal **1**, so moisture or water work-up can be misleading). The crude reaction mixture was then taken back in anhydrous dichloromethane (10 mL) and filtered over Celite® to remove residual silver salts and the filtrate was quenched with a sat. solution of $NaHCO_3$ (20 mL). The aqueous phase was extracted with dichloromethane (3 X 10 mL) and the combined organic layers

were dried over Na_2SO_4 and evaporated *in vacuo*. The crude reaction mixture was finally purified by silica gel column chromatography under the appropriate eluent conditions.

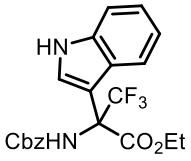
Ethyl 2-(((benzyloxy)carbonyl)amino)-3,3,3-trifluoro-2-(1-methyl-1H-indol-3- yl)propanoate (**4c)**



$C_{22}H_{21}F_3N_2O_4$
MW: 434.42 g/mol

18 hours at RT. The crude reaction mixture was purified by precipitation with ethyl acetate and petroleum ether. The mother liquor was then evaporated and purified by silica gel chromatography using an isocratic solvent system of *n*-hexane and ethyl acetate (85:15) to deliver **4c** as a white solid (58.2 mg, 0.134 mmol, 67% yield). **m. p.** 124.9 – 125.1 °C. $\mathbf{R_f}$ (*n*-hexane:ethyl acetate, 85:15) = 0.38. **^{1}H NMR** (400 MHz, CD_3CN): δ (ppm) = 7.66 (d, *J* = 8.2 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.39 – 7.31 (m, 5H), 7.25 (td, *J* = 8.0 Hz, 1.0 Hz, 1H), 7.12 (td, *J* = 8.0 Hz, 1.0 Hz, 1H), 6.81 (br, 1H), 5.13 (d, *J* = 12.4 Hz, 1H), 5.08 (d, *J* = 12.4 Hz, 1H), 4.23 – 4.03 (m, 2H), 3.79 (s, 3H), 1.10 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, CD_3CN): δ (ppm) = 166.7, 155.6, 138.0, 130.2, 129.0, 126.1, 125.5 (q, *J* = 286.4 Hz), 123.1, 120.9, 118.3, 111.0, 106.0, 67.6, 65.8 (q, *J* = 29.5 Hz), 63.3, 33.5, 14.1. **^{19}F NMR** (376 MHz, $CDCl_3$) δ = -71.74. **IR** (film): 1732, 1549, 1525, 1435, 1404, 1372, 1339, 1258, 1228, 1184, 1069 cm^{-1}. **HRMS** (ESI) m/z: $[M+H]^+$ calcd. for $C_{22}H_{22}F_3N_2O_4$ 435.1532; Found 435.1518 (-3.2 ppm).
SMILES: O=C(NC(C(OCC)=O)(C(F)(F)F)C1=CN(C)C2=C1C=CC=C2)OCC3=CC=CC=C3

Ethyl 2-(((benzyloxy)carbonyl)amino)-3,3,3-trifluoro-2-(1H-indol-3-yl)propanoate (**4d**) [SI-5]

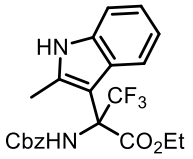


$C_{21}H_{19}F_3N_2O_4$
MW: 420.39 g/mol

24 hours at RT. Purified by preparative TLC (*n*-hexane: ethyl acetate, 50:50). White solid (73.0 mg, 0.174 mmol, 87% yield). **m. p.** 130.3 – 130.6 °C. $\mathbf{R_f}$ (*n*-hexane: ethyl acetate, 85:15) = 0.33. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) = 8.63 (br, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.31 – 6.88 (m, 8H), 6.34 (br, 1H), 4.96 (s, 2H), 4.23 – 4.02 (m, 2H), 1.03 (t, *J* = 8.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm) = 166.4 (Cq), 153.9 (Cq), 136.1 (Cq), 135.9 (Cq), 128.5 (2 CH), 128.1 (CH), 127.8 (2 CH), 124.8 (CH), 124.4 (Cq), 124.1 (q, *J* = 287.8 Hz, Cq),122.4 (CH), 120.3 (CH), 119.0 (CH), 111.9 (CH), 105.7 (Cq), 67.1 (CH_2), 65.2 (q, *J* = 30.3 Hz, Cq), 63.4 (CH_2), 13.6 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -71.57 (referred to -161.64 ppm of C_6F_6). **IR** (film): 3393, 2963, 1729, 1496, 1460, 1255, 1187, 1025 cm^{-1}. **HRMS** (ESI) m/z: $[M+H]^+$ calcd. for $C_{21}H_{20}F_3N_2O_4$: 421.1375; Found 421.1400 (+5.9 ppm).
SMILES: O=C(OCC1=CC=CC=C1)NC(C2=CNC3=C2C=CC=C3)(C(F)(F)F)C(OCC)=O.

Ethyl 2-(((benzyloxy)carbonyl)amino)-3,3,3-trifluoro-2-(2-methyl-1H-indol-3-yl)propanoate (**4e**)

24 hours at RT. The crude material was purified by silica gel chromatography using *n*-hexane and ethyl acetate (gradient elution from 90:10 to 70:30) yielding **4e** as a white solid (60.8 mg, 0.14 mmol, 70% yield). **m. p.** 115.0 – 115.3 °C. $\mathbf{R_f}$ (*n*-hexane: ethyl acetate, 70:30) = 0.36. **^{1}H NMR** (400 MHz, CD_3CN) δ (ppm) = 9.51 (br, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.44 – 7.28 (m, 6H), 7.19 – 7.07 (m, 2H), 6.55 (br, 1H), 5.18 (d, *J* = 12.5 Hz, 1H), 5.06 (d, *J* = 12.5 Hz, 1H), 4.31 – 4.20 (m, 2H), 2.40 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, CD_3CN) δ (ppm) = 167.5, 155.9, 137.5, 136.0, 135.7, 129.4, 129.1, 128.8, 126.91, 126.1 (q, *J* = 287.3 Hz), 122.5, 121.2, 119.7, 112.1, 102.8, 67.9, 66.0 (q, *J* = 29.7 Hz), 63.4, 14.1, 13.4. **^{19}F NMR** (376 MHz, CD_3CN) δ (ppm) = -72.55. **IR** (film): 3300, 1746.9, 1691, 1536, 1498, 1456, 1456, 1407, 1374, 1320, 1271, 1233, 1202, 1180, 1134 cm^{-1}. **HRMS** (ESI) m/z: $[M+H]^+$ calcd. for $C_{22}H_{22}F_3N_2O_4$ 435.1532; Found 435.1518 (-3.2 ppm).



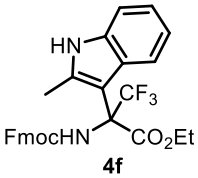
4e

$C_{22}H_{21}F_3N_2O_4$
MW: 434.41 g/mol

SMILES: CC1=C(C(C(OCC)=O)(C(F)(F)F)NC(OCC2=CC=CC=C2)=O)C(C=CC=C3)=C3N1.

Ethyl 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3,3,3-trifluoro-2-(2-methyl-1H-indol-3-yl)propanoate (**4f**)

24 hours at RT. Colorless oil (92.9 mg, 0.178 mmol, 89% yield). $\mathbf{R_f}$ (*n*-hexane: ethyl acetate, 1:1) = 0.40. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) = 8.23 (br, 1H), 7.78 (d, *J* = 7.6 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.45 – 7.29 (m, 2H), 7.37 – 7.29 (m, 3H), 7.24 – 7.17 (m, 2H), 6.46 (br, 1H), 4.47 – 4.32 (m, 4H), 4.26 (t, *J* = 7.2 Hz, 1H), 2.42 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm) = 166.8 (Cq), 154.4 (Cq), 143.7 (Cq), 143.6 (Cq), 141.3 (2 Cq), 134.5 (Cq), 134.1 (Cq), 127.8 (CH), 127.7 (CH), 127.1 (2 CH), 126.3 (Cq), 125.1 (2 CH), 124.6 (q, *J* = 288.8 Hz, Cq), 122.0 (CH), 120.8 (CH), 120.0 (2 CH), 118.9 (CH), 118.8 (CH), 111.0 (CH), 103.0 (Cq), 67.7 (CH_2), 65.2 (q, *J* = 30.3 Hz, Cq), 62.9 (CH_2), 47.1 (CH), 13.8 (CH_3), 13.3 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -71.58 (referred to -161.64 ppm of C_6F_6). **IR** (film): 3390, 2928, 1750, 1488, 1282, 1190, 1031 cm^{-1}. HRMS (ESI) m/z: $[M+H]^+$ calcd. for $C_{29}H_{26}F_3N_2O_4$ 523.1839; Found 523.1837 (-0.3 ppm).



4f

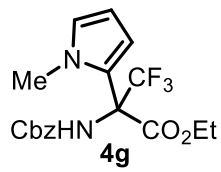
$C_{29}H_{25}F_3N_2O_4$
MW: 522.52 g/mol

SMILES:CC1=C(C(C(OCC)=O)(C(F)(F)F)NC(OCC2C(C=CC=C3)=C3C4=C2C=CC=C4)=O)C(C=CC=C5)=C5N1

When *N*-methyl pyrrole was used as nucleophile, two regioisomers **4g** and **4g'** formed (2:3 ratio) after 25 hours at RT, and were separated during purification by silica gel column chromatography using *n*-hexane and ethyl acetate (gradient elution from 95:15 to 70:30).

Ethyl 2-(((benzyloxy)carbonyl)amino)-3,3,3-trifluoro-2-(1-methyl-1H-pyrrol-2-yl)propanoate (**4g**)

Minor isomer, colorless oil (27.7 mg, 0.07 mmol, 36% yield). $\mathbf{R_f}$ (*n*-hexane: ethyl acetate, 85:15) = 0.24. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) = 7.36 – 7.26 (m, 5H), 6.61 – 6.57 (m, 1H), 6.47 – 6.42 (m, 1H), 6.22 (br, 1H), 6.15 (t, *J* = 3.2 Hz, 1H), 5.12 – 4.98 (m, 2H), 4.44 – 3.22 (m, 2H), 3.40 (s, 3H), 1.25 (t, *J* = 8.0 Hz, 3H). **^{13}C NMR** (101 MHz, CD_3CN) δ (ppm) = 165.2, 153.8, 136.6, 128.2, 126.2,123.4 (q, *J* = 289.8 Hz), 121.1, 111.4, 106.8, 66.7, 64.8 (q, *J* = 30.5 Hz), 35.1, 13.1.**^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -67.34. **IR** (film):

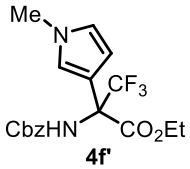


4g

$C_{18}H_{19}F_3N_2O_4$
MW: 384.35 g/mol

3405, 2926, 1756, 1738, 1497, 1455, 1417, 1369, 1259, 1238, 1221, 1170, 1098 cm^{-1}. **HRMS** (ESI) m/z: $[M+H]^+$ calcd. for $C_{18}H_{20}F_3N_2O_4$ 385.1375; Found 385.1386 (+2.9 ppm).
SMILES: CN1C=CC=C1C(C(OCC)=O)(C(F)(F)F)NC(OCC2=CC=CC=C2)=O

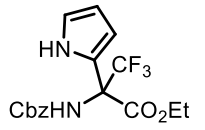
Ethyl 2-(((benzyloxy)carbonyl)amino)-3,3,3-trifluoro-2-(1-methyl-1H-pyrrol-3-yl)propanoate (**4g'**)



4f'

Major isomer, white solid (39.5 mg, 0.10 mmol, 51% yield). **m. p.** 99.6 – 99.9 °C. **Rf** (n-hexane:ethyl acetate, 85:15) = 0.10. **^{1}H NMR** (400 MHz, CD_3CN) δ (ppm) = 7.44 – 7.30 (m, 5H), 6.78 (t, *J* = 1.9 Hz, 1H), 6.63 (t, *J* = 2.6 Hz, 1H), 6.48 (br, 1H), 6.18 – 6.12 (m, 1H), 5.13 (d, *J* = 12.6 Hz, 1H), 5.07 (d, *J* = 12.6 Hz, 1H), 4.16 (q, *J* = 7.0 Hz, 2H), 3.61 (s, 3H), 1.15 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, CD_3CN) δ (ppm) = 166.4 (Cq), 155.2 (Cq), 137.4 (Cq), 129.1 (2 CH), 128.7 (2 CH), 128.4 (CH), 125.0 (q, *J* = 289.8 Hz, Cq), 122.9 (CH), 121.8 (CH), 107.7 (CH), 104.9 (Cq), 67.2 (CH_2), 64.5 (CH_2), 36.3 (CH_3), 13.7 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -73.33. **IR** (film): 3357, 2926, 1750, 1498, 1455, 1369, 1346, 1265, 1217, 1175, 1151, 1061 cm^{-1}. **HRMS** (ESI) m/z: $[M+H]^+$ calcd. for $C_{18}H_{20}F_3N_2O_4$ 385.1375; Found 385.1381 (+1.6 ppm).
SMILES: CN1C=CC(C(C(OCC)=O)(C(F)(F)F)NC(OCC2=CC=CC=C2)=O)=C1

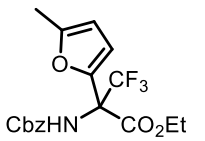
Ethyl 2-(((benzyloxy)carbonyl)amino)-3,3,3-trifluoro-2-(1H-pyrrol-2-yl)propanoate (**4h**)



$C_{17}H_{17}F_3N_2O_4$
MW: 370.33 g/mol

20 hours at RT. The crude material was purified by silica gel chromatography using an isocratic solvent system of *n*-hexane and ethyl acetate (85:15). Colorless oil (52.6 mg, 0.14 mmol, 71% yield). **R_f** (*n*-hexane: ethyl acetate, 85:15) = 0.20. **^{1}H NMR** (400 MHz, CD_3CN): δ (ppm) = 9.60 (br, 1H), 7.54 – 7.29 (m, 5H), 6.90 (br, 1H), 6.86 (td, *J* = 2.8 Hz, 1.6 Hz, 1H), 6.39 – 6.28 (m, 1H), 6.18 – 6.11 (m, 1H), 5.22 – 5.05 (m, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, CD_3CN): δ (ppm) = 165.9, 155.8, 137.6, 129.5, 129.2, 128.8, 124.5 (q, *J* = 241.7 Hz), 121.9, 121.1, 110.3, 109.1, 65.31 (q, *J* = 29.1 Hz), 67.9, 63.8, 14.2. **^{19}F NMR** (376 MHz, CD_3CN) δ (ppm) = -73.33. **IR** (film): 3386, 1727, 1499, 1455, 1405, 1370, 1254, 1220, 1192, 1098 cm^{-1}. **HRMS** (ESI) m/z: $[M+H]^+$ calcd. for $C_{17}H_{18}F_3N_2O_4$, 371.1219; Found 371.1223 (+1.1 ppm).
SMILES: [H]N1C=CC(C(C(OCC)=O)(C(F)(F)F)NC(OCC2=CC=CC=C2)=O)=C1

Ethyl 2-(((benzyloxy)carbonyl)amino)-3,3,3-trifluoro-2-(5-methylfuran-2-yl)propanoate (**4i**)

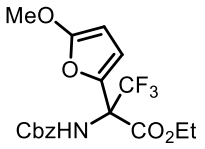


$C_{18}H_{18}F_3NO_5$
MW: 385.34 g/mol

48 hours at RT. The crude material was purified by silica gel chromatography using an isocratic solvent system of *n*-hexane and ethyl acetate (90:10). Colorless oil (56.2 mg, 0.15 mmol, 73% yield). **R_f** (*n*-hexane: ethyl acetate, 85:15) = 0.32. **^{1}H NMR** (400 MHz, CD_3CN) δ (ppm) = 7.52 – 7.26 (m, 5H), 6.88 (br, 1H), 6.49 (d, *J* = 3.3 Hz, 1H), 6.09 (d, *J* = 3.3 Hz, 1H), 5.14 (d, *J* = 12.4 Hz, 1H), 5.08 (d, *J* = 12.4 Hz, 1H), 4.25 – 4.18 (m, 2H), 2.26 (s, 3H),1.16 (t, *J* = 7.1 Hz, 3H)**. ^{13}C NMR** (101 MHz, CD_3CN) δ (ppm) = 164.2 (Cq), 155.0 (Cq), 154.5 (Cq), 142.8 (Cq), 137.1 (Cq), 129.1 (2 CH), 128.7 (2 CH), 128.5 (CH), 123.9 (q, *J* = 287.8 Hz, Cq), 112.3 (CH), 107.6 (CH), 67.5 (CH_2), 65.0 (q, *J* = 30.3 Hz, Cq), 63.4 (CH_2), 13.7 (CH_3), 13.1 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -73.18 (referred to -161.64 ppm of C_6F_6). **IR** (film): 3291, 1755, 1735,

1508, 1457, 1384, 1369, 1296, 1242, 1190, 1154, 1061 cm^{-1}. **HRMS** (ESI) m/z: $[M+H]^+$ calcd. for $C_{18}H_{19}F_3NO_5$ 386.1215; Found 386.1212 (+0.8 ppm).
SMILES: CC(O1)=CC=C1C(C(OCC)=O)(C(F)(F)F)NC(OCC2=CC=CC=C2)=O.

Ehyl 2-(((benzyloxy)carbonyl)amino)-3,3,3-trifluoro-2-(5-methoxyfuran-2-yl)propanoate (**4j**)



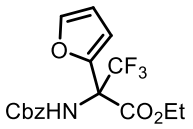
$C_{18}H_{18}F_3NO_6$
MW: 401.34 g/mol

72 hours at RT. The crude material was purified by silica gel chromatography using *n*-hexane and DCM (gradient elution from 55:45 to 40:60) yielding **4i** as a colorless oil (45.0 mg, 0.11 mmol, 56% yield). $\mathbf{R_f}$ (*n*-hexane:CH_2Cl_2, 1:1) = 0.22. **^{1}H NMR** (400 MHz, CD_3CN) δ (ppm) = 7.34 (m, 5H), 6.84 (br, 1H), 6.52 (d, *J* = 3.5 Hz, 1H), 5.30 (d, *J* = 3.5 Hz, 1H), 5.13 (d, *J* = 12.4 Hz, 1H), 5.08 (d, *J* = 12.4 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.84 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, CD_3CN) δ (ppm) = 164.4, 163.2, 155.4, 137.5, 134.5, 129.5, 129.1, 128.8, 124.2 (q, *J* = 286.7 Hz), 118.3, 113.9, 81.7, 67.8, 65.1 (q, *J* = 28.9 Hz), 63.8, 58.9, 14.0. **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -73.09. **IR** (film): 1737, 1616, 1574, 1500, 1455, 1439, 1734, 1257, 1193, 1163, 1066 cm^{-1}. **HRMS** (ESI): m/z $[M+H]^+$ calcd. for $C_{18}H_{19}F_3NO_6$ 402.1164; Found 402.1174 (+2.5 ppm).
SMILES: O=C(OCC1=CC=CC=C1)NC(C(OCC)=O)(C(F)(F)F)C2=CC=C(OC)O2.

General Protocol B: Friedel–Crafts Functionalization with Weak π-Nucleophiles

AgOTf (103 mg, 0.40 mmol, 2.0 eq.) and activated 4 Å molecular sieves (300 wt % rel. to chloroaminal **2a**) in a reaction tube were heated under vacuum with a heat gun. After the tube was cooled down under argon, the appropriate arene nucleophile (0.40 mmol, 2.0 eq) and chloroaminal **2a** (68 mg, 0.20 mmol, 1.0 eq.) were successively added followed by CH_2Cl_2 (1 mL). The reaction mixture was stirred at the room temperature for 3 hours, then the crude solution was filtered through a pad of celite and washed using EtOAc. Solvent was removed under reduced pressure and the crude material was purified on silica plate by preparative thin-layer chromatography (*n*-hexane: ethyl acetate).

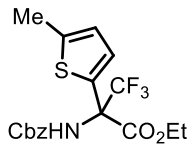
Ethyl 2-(((benzyloxy)carbonyl)amino)-3,3,3-trifluoro-2-(furan-2-yl)propanoate (**4a**)



$C_{17}H_{16}F_3NO_5$
MW: 371.31 g/mol

Colorless oil (53.2 mg, 0.14 mmol, 72% yield). $\mathbf{R_f}$ (*n*-hexane:CH_2Cl_2, 1:1) = 0.17. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) = 7.46 – 7.30 (m, 6H), 6.58 (d, *J* = 3.2 Hz, 1H), 6.44 (dd, *J* = 3.2 Hz, 3.2 Hz, 1H), 6.14 (br, 1H), 5.15 (d, *J* = 12.4 Hz, 1H), 5.08 (d, *J* = 12.4 Hz, 1H),4.44 – 4.22 (m, 2H), 1.23 (t, *J* = 8.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm) = 163.8 (Cq), 153.7 (Cq), 143.9 (Cq), 143.2 (CH), 135.6 (Cq), 128.5 (2 CH), 128.3 (CH), 128.2 (2 CH), 122.8 (q, *J* = 287.8 Hz, Cq), 111.1 (CH), 110.7 (CH), 67.5 (CH_2), 64.3 (q, *J* = 30.3 Hz, Cq), 63.5 (CH_2), 13.6 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -73.04 (referred to -161.64 ppm of C_6F_6). **IR** (film): 3352, 2985, 1739, 1495, 1253, 1167, 1021 cm^{-1}. **HRMS** (ESI): m/z $[M+H]^+$ calcd. for $C_{17}H_{17}F_3NO_5$ 372.1059; Found 372.1050 (-2.5 ppm).
SMILES: O=C(OCC1=CC=CC=C1)NC(C(OCC)=O)(C(F)(F)F)C2=CC=CO2.

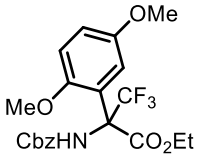
Ethyl 2-(((benzyloxy)carbonyl)amino)-3,3,3-trifluoro-2-(5-methylthiophen-2-yl)propanoate (**4k**)



$C_{18}H_{18}F_3NO_4S$
MW: 401.40 g/mol

Colorless oil (65.8 mg, 0.16 mmol, 82% yield). $\mathbf{R_f}$ (*n*-hexane:CH_2Cl_2, 1:1) = 0.17. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) = 7.40 – 7.30 (m, 5H), 7.08 (d, *J* = 3.6 Hz, 1H), 6.70 (dd, *J* = 3.6 Hz, 1.0 Hz, 1H), 5.86 (br, 1H), 5.13 (s, 2H), 4.37 – 4.23 (m, 2H), 2.47 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm) = 164.6 (Cq), 153.9 (Cq), 141.9 (Cq), 135.6 (Cq), 131.5 (Cq), 128.5 (2 CH), 128.3 (CH), 128.2 (3 CH), 125.1 (CH), 123.1 (q, *J* = 287.8 Hz, Cq), 67.5 (CH_2), 66.0 (q, *J* = 30.3 Hz, Cq), 63.3 (CH_2), 15.0 (CH_3), 13.6 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -72.81 (referred to -161.64 ppm of C_6F_6). **IR** (film): 3349, 2983, 1739, 1497, 1220, 1173, 1025 cm^{-1}. **HRMS** (ESI): m/z $[M+H]^+$ calcd. for $C_{18}H_{19}F_3NO_4S$ 402.0987; Found 402.0981 (+1.7 ppm). **SMILES**: CC(S1)=CC=C1C(C(OCC)=O)(C(F)(F)F)NC(OCC2=CC=CC=C2)=O.

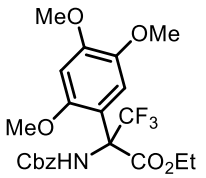
Ethyl 2-(((benzyloxy)carbonyl)amino)-2-(2,5-dimethoxyphenyl)-3,3,3-trifluoropropanoate (**4l**)



$C_{21}H_{22}F_3NO_6$
MW: 441.40 g/mol

White solid, **m. p.** 111.1 – 111.3 °C (74.1 mg, 0.17 mmol, 84% yield). $\mathbf{R_f}$ (*n*-hexane:CH_2Cl_2, 1:1) = 0.10. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) = 7.50 – 7.25 (m, 5H), 7.25 – 7.00 (m, 2H), 6.97 – 6.76 (m, 2H), 5.07 – 4.95 (m, 2H), 4.28 (q, *J* = 8.0 Hz, 2H), 3.76 (s, 3H), 3.72 (s, 3H), 1.19 (t, *J* = 8.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm) = 166.5 (Cq), 153.7 (Cq), 153.2 (Cq), 151.0 (Cq), 136.2 (Cq), 128.4 (2 CH), 128.1 (3 CH), 123.8 (q, *J* = 279.8 Hz, Cq), 121.4 (Cq), 116.6 (CH), 114.9 (CH), 112.7 (CH), 66.8 (CH_2), 66.5 (q, *J* = 28.3 Hz, Cq), 63.2 (CH_2), 56.2 (CH_3), 55.6 (CH_3), 13.7 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -71.41 (referred to -161.64 ppm of C_6F_6). **IR** (film): 3388, 2837, 1742, 1488, 1465, 1234, 1184, 1026 cm^{-1}. **HRMS** (ESI): m/z $[M+H]^+$ calcd. for $C_{21}H_{23}F_3NO_6$ 442.1477; Found 442.1462 (-3.4 ppm).
SMILES: O=C(OCC1=CC=CC=C1)NC(C2=CC(OC)=CC=C2OC)(C(F)(F)F)C(OCC)=O.

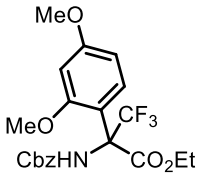
Ethyl 2-(((benzyloxy)carbonyl)amino)-3,3,3-trifluoro-2-(2,4,5-trimethoxyphenyl)propanoate (**4m**)



$C_{22}H_{24}F_3NO_7$
MW: 471.43 g/mol

Colorless oil (66.9 mg, 0.14 mmol, 71% yield). $\mathbf{R_f}$ (*n*-hexane:CH_2Cl_2, 1:1) = 0.20. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) = 7.40 – 7.20 (m, 6H), 6.93 (br, 1H), 6.49 (s, 1H), 5.16 – 4.92 (m, 2H), 4.40 – 4.14 (m, 2H), 3.89 (s, 3H), 3.80 (s, 3H), 3.75 (s, 3H), 1.20 (t, *J* = 8.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm) = 166.7 (Cq), 153.7 (Cq), 151.6 (Cq), 150.5 (Cq), 142.7 (Cq), 136.1 (Cq), 128.3 (2 CH), 128.0 (3 CH), 123.9 (q, *J* = 289.9 Hz, Cq), 113.7 (CH), 111.5 (Cq), 97.8 (CH), 66.8 (CH_2), 66.5 (q, *J* = 29.3 Hz, Cq), 63.0 (CH_2), 56.6 (CH_3), 56.4 (CH_3), 55.8 (CH_3), 13.7 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -71.76 (referred to -161.64 ppm of C_6F_6). **IR** (film): 3389, 2939, 1740, 1615, 1494, 1454, 1393, 1217, 1121, 1000 cm^{-1}. **HRMS** (ESI): m/z $[M+Na]^+$ calcd. for $C_{22}H_{24}F_3NO_7Na$ 494.1403; Found 494.1392 (-2.2 ppm).
SMILES: O=C(OCC1=CC=CC=C1)NC(C2=CC(OC)=C(OC)C=C2OC)(C(F)(F)F)C(OCC)=O.

Ethyl 2-(((benzyloxy)carbonyl)amino)-2-(2,4-dimethoxyphenyl)-3,3,3-trifluoropropanoate (**4b**)



$C_{21}H_{22}F_3NO_6$
MW: 441.40 g/mol

Colorless oil (63.2 mg, 0.14 mmol, 72%). $\mathbf{R_f}$ (*n*-hexane:CH_2Cl_2, 7:3) = 0.19. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) = 7.50 – 7.21 (m, 6H), 6.94 (br, 1H), 6.53 (d, *J* = 4.0 Hz, 1H), 6.44 (d, *J* = 4.0 Hz, 1H), 5.15 – 4.85 (m, 2H), 4.31 – 4.23 (m, 2H), 3.82 (s, 3H), 3.72 (s, 3H), 1.20 (t, *J* = 8.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm) = 167.0 (Cq), 161.3 (Cq), 157.8 (Cq), 153.6 (Cq), 136.2 (Cq), 130.9 (CH), 130.8 (CH), 128.4 (CH), 128.1 (2 CH), 128.0 (CH), 124.0 (q, *J* = 289.9 Hz, Cq), 113.0 (Cq), 104.3 (CH), 99.3 (CH), 66.7 (CH_2), 66.3 (q, *J* = 28.3 Hz, Cq), 63.2 (CH_2), 55.6 (CH_3), 55.3 (CH_3), 13.7 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -71.20 (referred to -161.64 ppm of C_6F_6). **IR** (film): 3400, 2942, 2842, 1742, 1615, 1496, 1305, 1243, 1211, 1027 cm^{-1}. **HRMS** (ESI): m/z $[M+Na]^+$ calcd. for $C_{21}H_{22}F_3NO_6Na$ 464.1297; Found 464.1283 (-3.0 ppm).

SMILES: O=C(OCC1=CC=CC=C1)NC(C2=CC=C(OC)C=C2OC)(C(F)(F)F)C(OCC)=O.

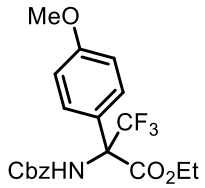
When 1,3-dimethoxy-5-methylbenzene was used as nucleophile, regioisomers **4n** and **4n'** formed (5:1 ratio) and were separated by preparative thin-layer chromatography. The ^{1}H NMR and ^{19}F spectra of compound **4n'** (13.8 mg, 0.03 mmol, 15% yield) are presented in the following section without further analysis.

Ethyl 2-(((benzyloxy)carbonyl)amino)-2-(2,4-dimethoxy-6-methylphenyl)-3,3,3-trifluoropropanoate (**4n**): Major isomer; Colorless oil (67.4 mg, 0.15 mmol, 74% yield). $\mathbf{R_f}$ (*n*-hexane:CH_2Cl_2, 1:1) = 0.12. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) = 7.92 (br, 1H), 7.39 – 7.13 (m, 5H), 6.31 (s,1H), 6.30 (s, 1H), 5.06 (d, *J* = 12.4 Hz, 1H), 4.95 (d, *J* = 12.4 Hz, 1H), 4.26 – 4.16 (m, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 2.33 (s, 3H), 1.15 (t, *J* = 8.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm) = 166.9 (Cq), 160.1 (Cq), 160.0 (Cq), 154.1 (Cq), 140.9 (Cq), 136.3 (Cq), 128.4 (2 CH), 128.1 (CH), 128.0 (CH), 124.6 (q, *J* = 288.8 Hz, Cq), 112.9 (Cq), 110.8 (CH), 98.5 (CH), 67.1 (q, *J* = 29.3 Hz, Cq), 66.9 (CH_2), 62.6 (CH_2), 56.4 (CH_3), 55.1 (CH_3), 22.4 (CH_3), 13.6 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -73.19 (referred to -161.64 ppm of C_6F_6). **IR** (film): 3369, 2943, 1763, 1741, 1607, 1498, 1454, 1322, 1228, 1202, 1034 cm^{-1}. **HRMS** (ESI): m/z $[M+Na]^+$ calcd. for $C_{22}H_{24}F_3NO_6Na$ 478.1453; Found 478.1440 (-2.7 ppm). **SMILES**: CC1=C(C(C(OCC)=O)(C(F)(F)F)NC(OCC2=CC=CC=C2)=O)C(OC)=CC(OC)=C1.

4n

$C_{22}H_{24}F_3NO_6$
MW: 455.43 g/mol

Ethyl 2-(((benzyloxy)carbonyl)amino)-3,3,3-trifluoro-2-(4-methoxyphenyl)propanoate (**4o**)

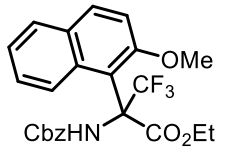


$C_{20}H_{20}F_3NO_5$
MW: 411.13 g/mol

Colorless oil (68.4 mg, 0.17 mmol, 83% yield). $\mathbf{R_f}$ (*n*-hexane:CH_2Cl_2, 1:1) = 0.15. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) = 7.71 – 7.10 (m, 7H), 6.91 (d, *J* = 8.0 Hz, 2H), 5.95 (br, 1H), 5.15 – 5.04 (m, 2H), 4.54 – 4.07 (m, 2H), 3.81 (s, 3H), 1.20 (t, *J* = 8.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm) = 166.1 (Cq), 160.1 (Cq), 154.1 (Cq), 135.7 (Cq), 128.5 (2 CH), 128.3 (CH), 128.2 (2 CH), 128.1 (CH), 128.0 (CH), 124.3 (Cq), 123.7 (q, *J* = 287.8 Hz, Cq), 114.1 (2 CH), 67.5 (q, *J* = 28.3 Hz, Cq), 67.4 (CH_2), 63.1 (CH_2), 55.3 (CH_3), 13.7 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -71.17 (referred to -161.64 ppm of C_6F_6). **IR** (film): 2982, 1750, 1497,

1253, 1178, 1152, 1027 cm^{-1}. **HRMS** (ESI): m/z $[M+Na]^+$ calcd. for $C_{20}H_{20}F_3NO_5Na$ 434.1191; Found 434.1177 (-3.2 ppm).
SMILES: O=C(OCC1=CC=CC=C1)NC(C2=CC=C(OC)C=C2)(C(F)(F)F)C(OCC)=O.

Ethyl 2-(((benzyloxy)carbonyl)amino)-3,3,3-trifluoro-2-(2-methoxynaphthalen-1-yl)propanoate (**4p**) Colorless oil (65.7 mg, 0.14 mmol, 72% yield). $\mathbf{R_f}$ (*n*-hexane:CH_2Cl_2, 1:1) = 0.10. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm) = 8.26 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.51 – 7.44 (m, 1H), 7.41 – 7.27 (m, 7H), 5.12 (d, *J* = 12.3 Hz, 1H), 5.02 (d, *J* = 12.3 Hz, 1H), 4.27 – 4.17 (m, 2H), 3.96 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ (ppm) = 167.3 (Cq), 157.0 (Cq), 154.2 (Cq), 136.0 (Cq), 132.9 (CH), 132.3 (Cq), 130.1 (Cq), 129.4 (CH), 128.4 (2 CH), 128.2 (2 CH), 128.1 (CH), 127.5 (CH), 124.6 (q, *J* = 288.9 Hz, Cq), 123.9 (CH), 123.6 (CH), 115.0 (CH), 114.4 (Cq), 67.4 (q, *J* = 30.3 Hz, Cq), 67.1 (CH_2), 62.7 (CH_2), 57.4 (CH_3), 13.6 (CH_3). **^{19}F NMR** (376 MHz, $CDCl_3$) δ (ppm) = -71.51 (referred to -161.64 ppm of C_6F_6). **IR** (film): 3368, 1759, 1499, 1219, 1194, 1027 cm^{-1}. **HRMS** (ESI): m/z $[M+Na]^+$ calcd. for $C_{24}H_{22}F_3NO_5Na$ 484.1348; Found 484.1334 (-2.9 ppm).
SMILES: O=C(OCC1=CC=CC=C1)NC(C2=C(OC)C=CC3=C2C=CC=C3)(C(F)(F)F)C(OCC)=O.



$C_{24}H_{22}F_3NO_5$
MW: 461.44 g/mol

V. References

[SI-1] (a) Salwiczek, M.; Nyakatura, E. K.; Gerling, U. I. M.; Ye, S.; Koksch, B. Fluorinated amino acids: compatibility with native protein structures and effects on protein–protein interactions. *Chem. Soc. Rev.* **2012**, *41*, 2135. (b) Marsh, E. N. G. Fluorinated proteins: from design and synthesis to structure and stability. *Acc. Chem. Res.* **2014**, *47*, 2878. (c) Berger, A. A.; Völler, J. S.; Budisa, N.; Koksch, B. Deciphering the fluorine code-the many hats fluorine wears in a protein environment. *Acc. Chem. Res.* **2017**, *50*, 2093.

[SI-2] Godfrey, A. G.; Masquelin, T.; Hemmerle, H. A remote-controlled adaptive medchem lab: an innovative approach to enable drug discovery in the 21st Century. *Drug Discovery Today* **2013**, *18*, 795.

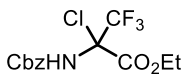
[SI-3] Burger, K.; Karl Gaa, E.; Sewald, N.; Schierlinger, C. New synthetic pathways to 3,3,3-trifluoroalanine, 2-deutero-3,3,3-trifluoroalanineand their derivatives. *Chem. Sci.* **1991**, *46*, 361.

[SI-4] (a) Burger, K.; Höß, E.; Gaa, K.; Sewald, N.; Schierlinger, C. New Synthetic Pathways to 3,3,3-Trifluoroalanine, 2-Deutero-3,3,3-trifluoroalanine and their Derivatives. *Zeitschrift für Naturforschung B* **1990,** *46*, 361. (b) Bravo, P.; Fustero, S.; Guidetti, M.; Volonterio, A.; Zanda, M. Stereoselective Mannich-Type Reaction of an Acyclic Ketimine with a Substituted Chlorotitanium Enolate: Efficient Approach to D-erythro-α-Trifluoromethyl-β-hydroxyaspartic Units. *J. Org. Chem.* **1999**, *64*, 8731.

[SI-5] Husmann, R.; Sugiono, E.; Mersmann, S.; Raabe, G.; Rueping, M.; Bolm, C. Enantioselective organocatalytic synthesis of quaternary α-amino acids bearing a CF_3 moiety. *Org. Lett.* **2011**, *13*, 1044.

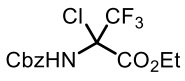
VI. NMR Spectra

$CDCl_3$ (400 MHz)



2a

$CDCl_3$ (101 MHz)



2a

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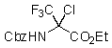
F19-2.11.fid
CDCl3 (376 MHz)



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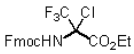
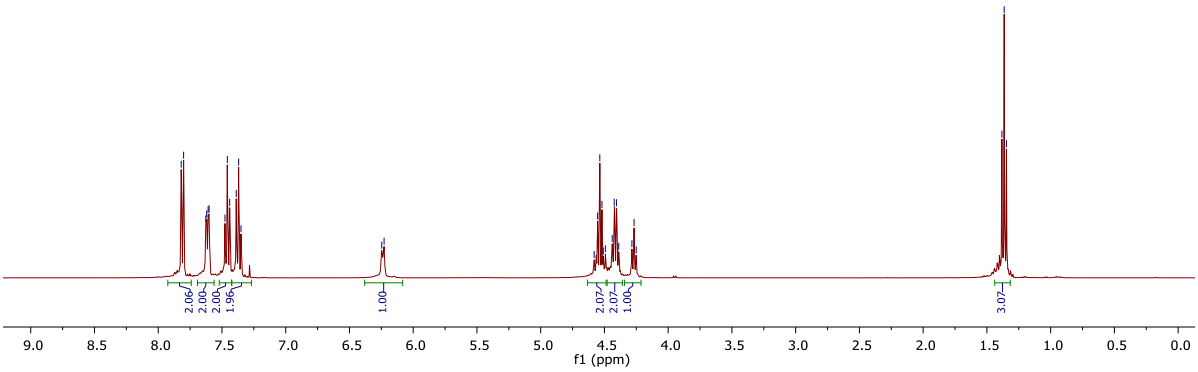
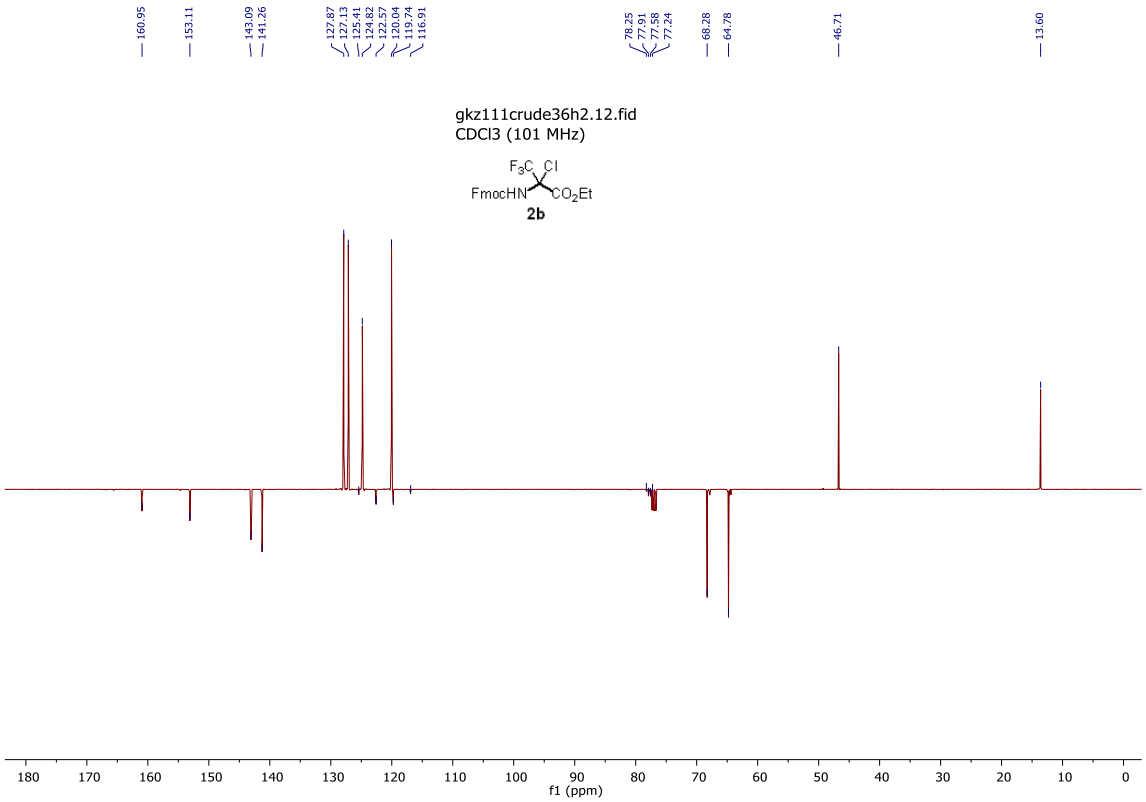
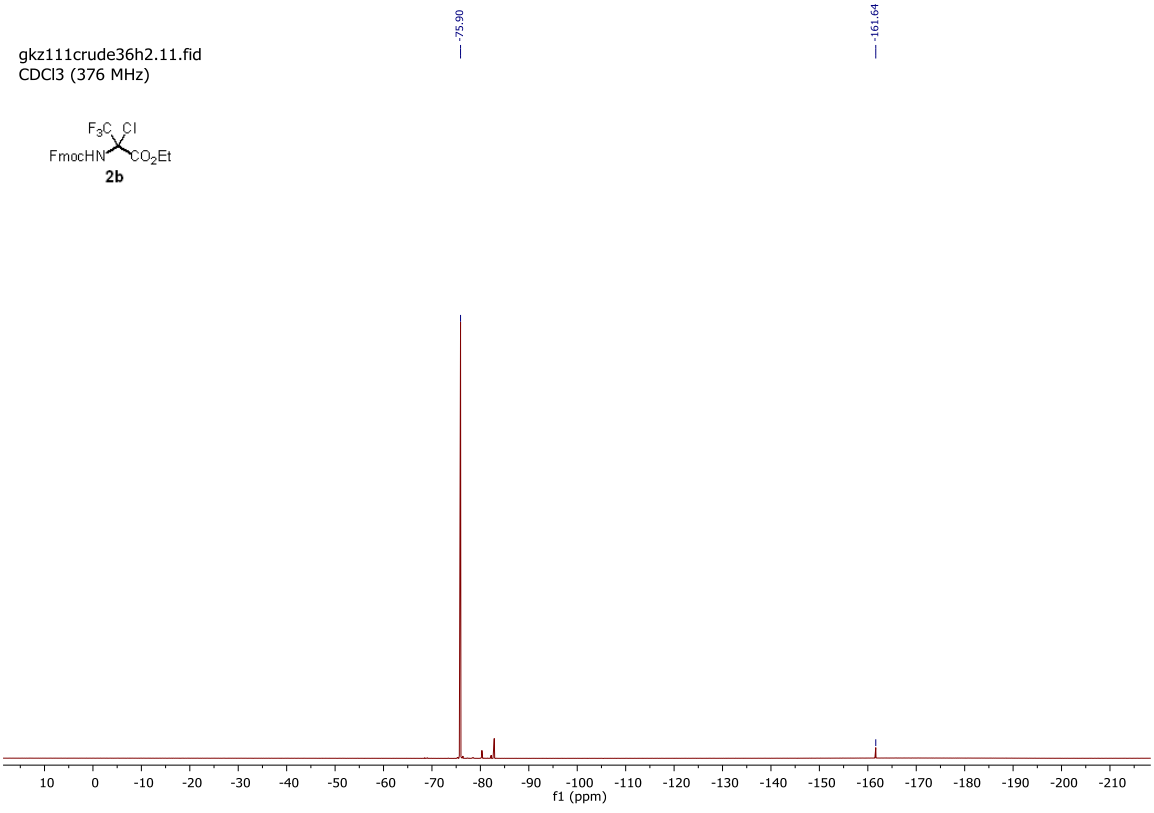


2b




160.95
153.11
143.09
141.26
127.87
127.13
125.41
124.82
122.57
120.04
119.74
116.91
78.25
77.91
77.58
77.24
68.28
64.78
46.71
13.60
gkz111crude36h2.12.fid
CDCl3 (101 MHz)
F3C Cl
FmocHN CO2Et
2b
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


-75.90
-161.64
gkz111crude36h2.11.fid
CDCl3 (376 MHz)
F3C Cl
FmocHN CO2Et
2b
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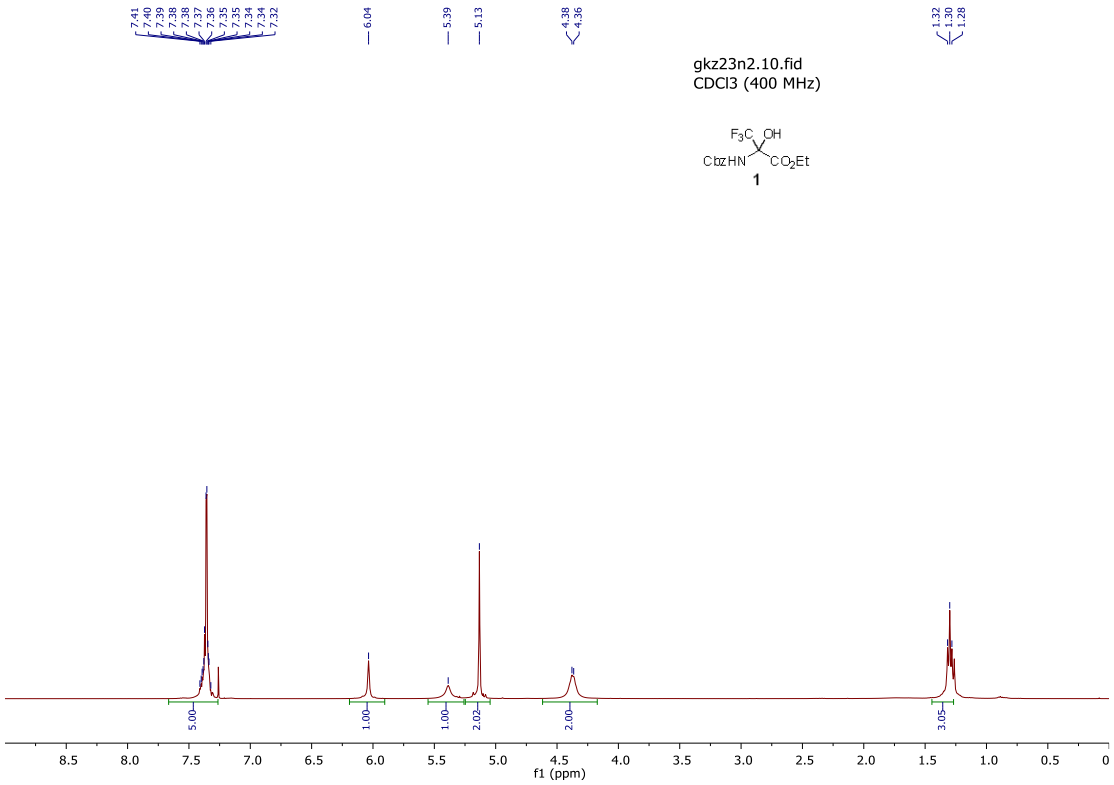
f1 (ppm)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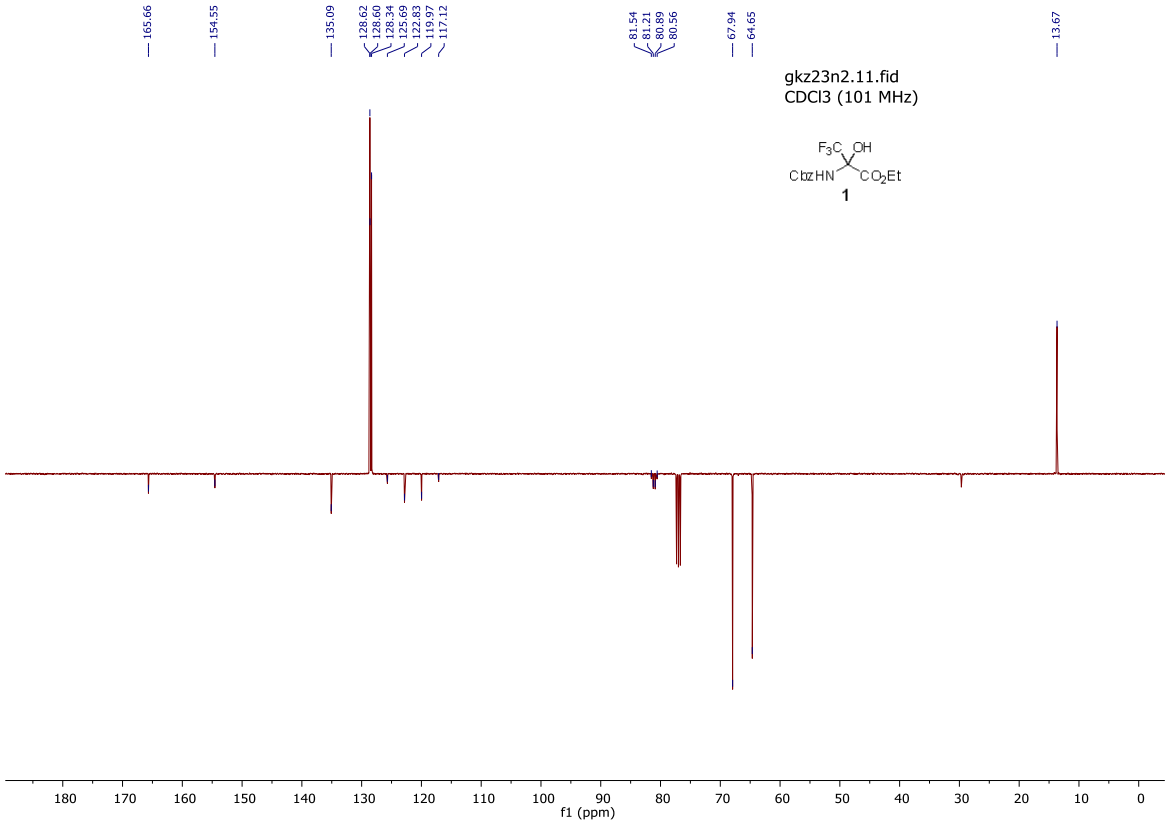
7.40
7.39
7.38
7.38
7.37
7.36
7.35
7.35
7.34
7.34
7.32
6.04
5.39
5.13
4.38
4.36
1.32
1.30
1.28
gkz23n2.10.fid
CDCl3 (400 MHz)
F3C OH
CbzHN CO2Et
1
5.00
1.00
1.00
2.02
2.00
3.05
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)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128.34
125.69
122.83
119.97
117.12
81.54
81.21
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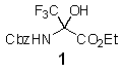
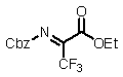
80.56
67.94
64.65
13.67
gkz23n2.11.fid
CDCl3 (101 MHz)
F3C OH
CbzHN CO2Et
1
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

gkz23test24h.11.fid
CDCl3 (376 MHz)

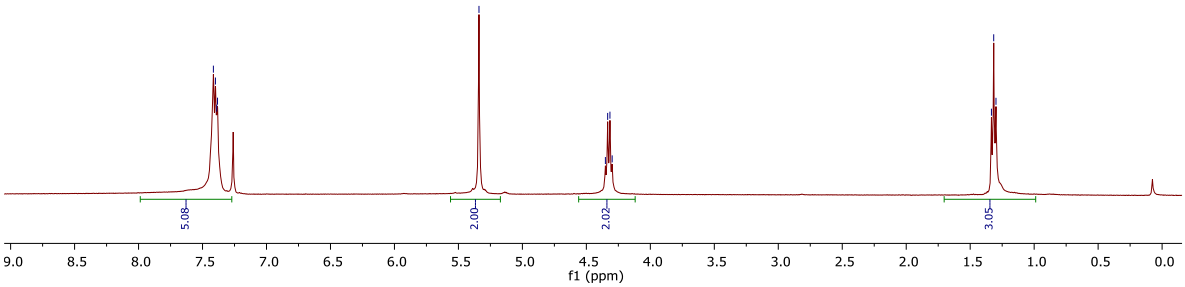


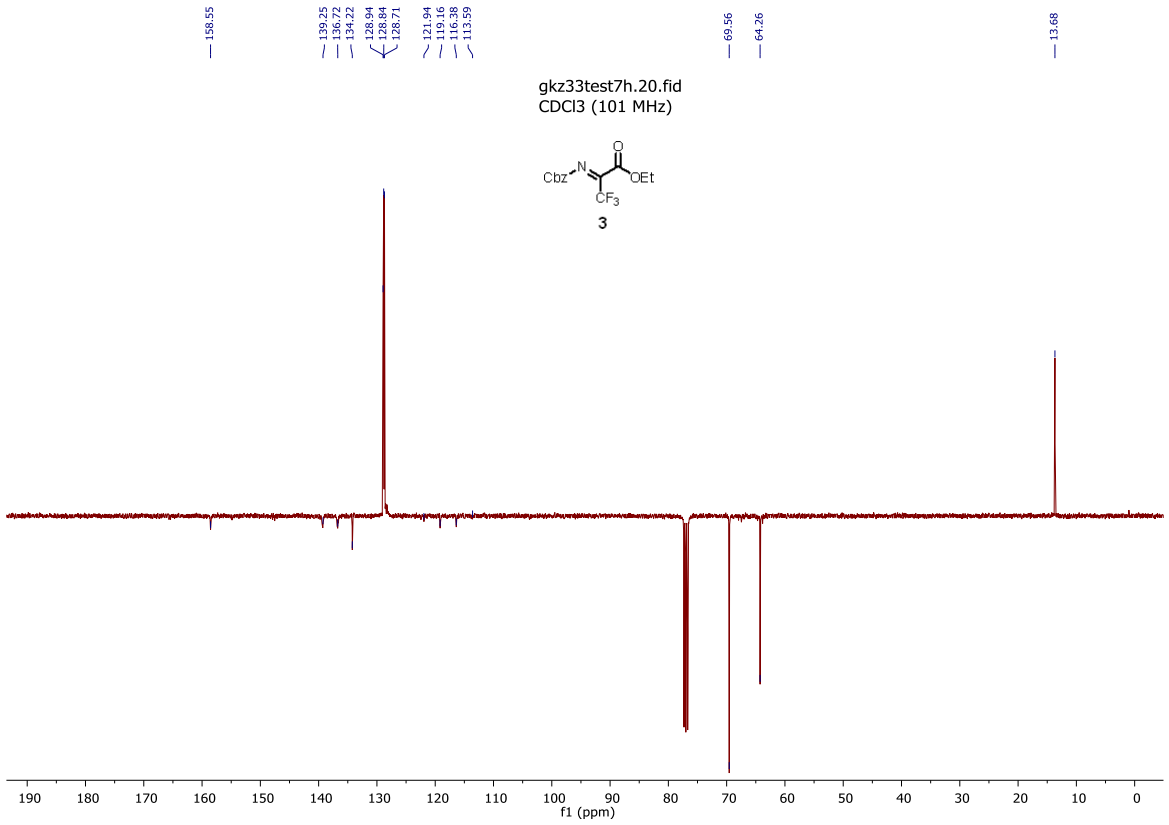
1

gkz33test7h.10.fid
CDCl3 (400 MHz)



3

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116.38
113.59
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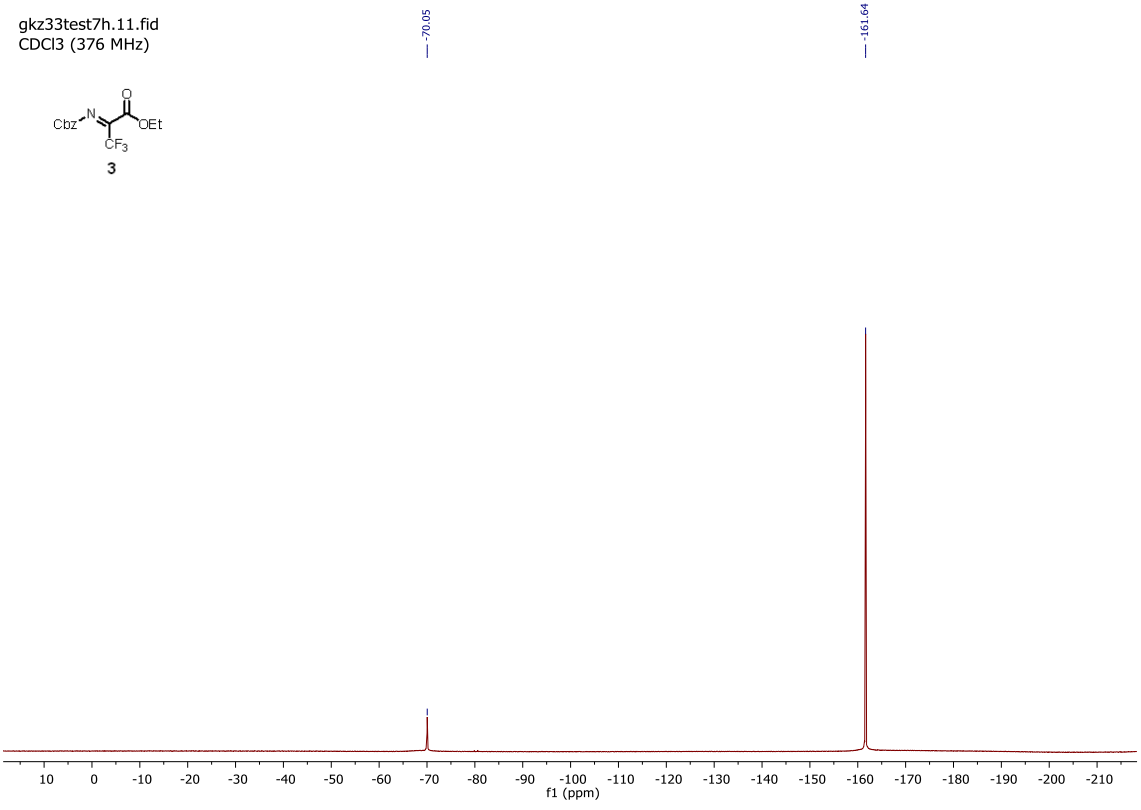
64.26
13.68
gkz33test7h.20.fid
CDCl3 (101 MHz)
Cbz
N
O
OEt
CF3
3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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O
OEt
CF3
3
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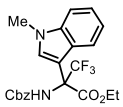
f1 (ppm)

CD_3CN (400 MHz)

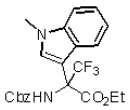


4c

CD_3CN (101 MHz)

4c

CDCl3 (376 MHz)



4c

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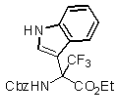
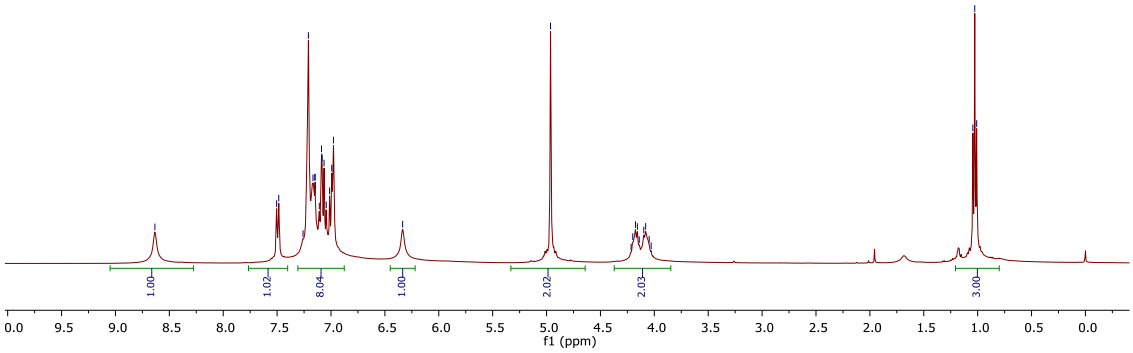
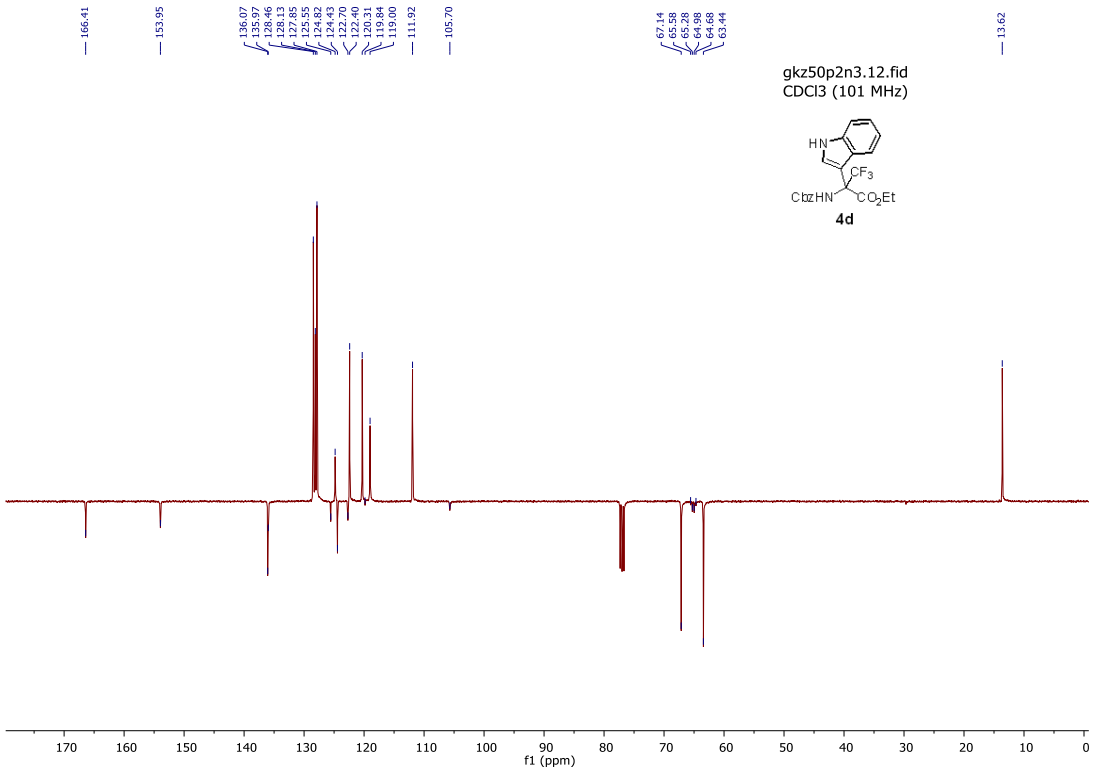
CDCl3 (400 MHz)



4d

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128.13
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125.55
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122.70
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119.84
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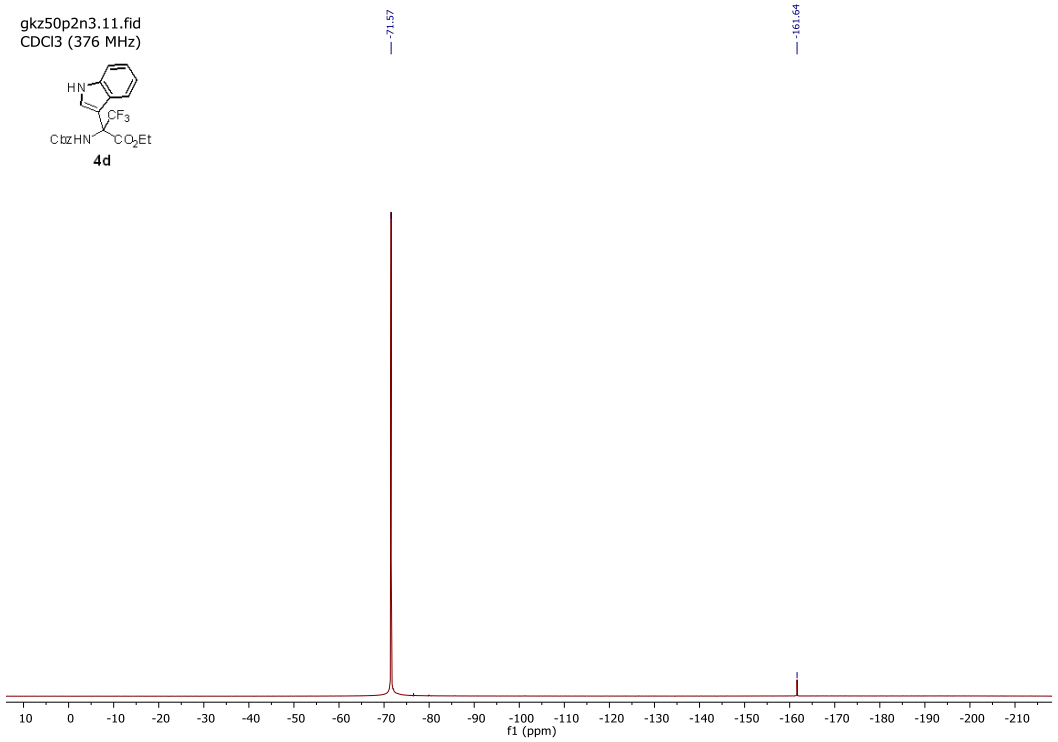
111.92
105.70
67.14
65.58
65.28
64.88
64.68
63.44
13.62
gkz50p2n3.12.fid
CDCl3 (101 MHz)
HN
CF3
CbzHN
CO2Et
4d
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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4d
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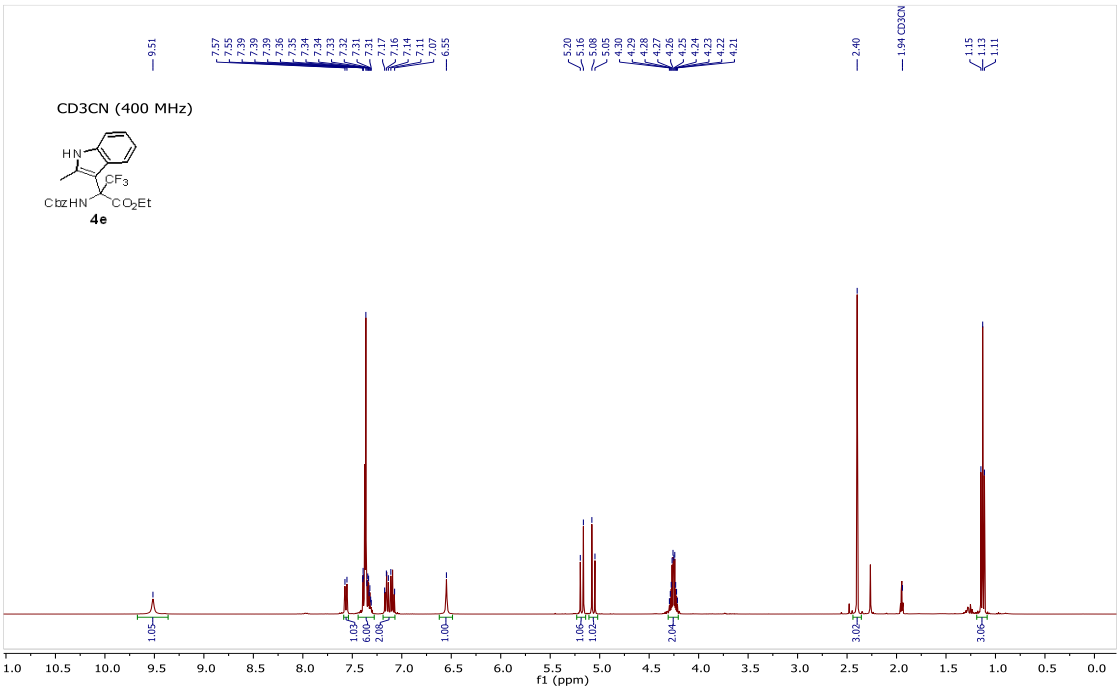
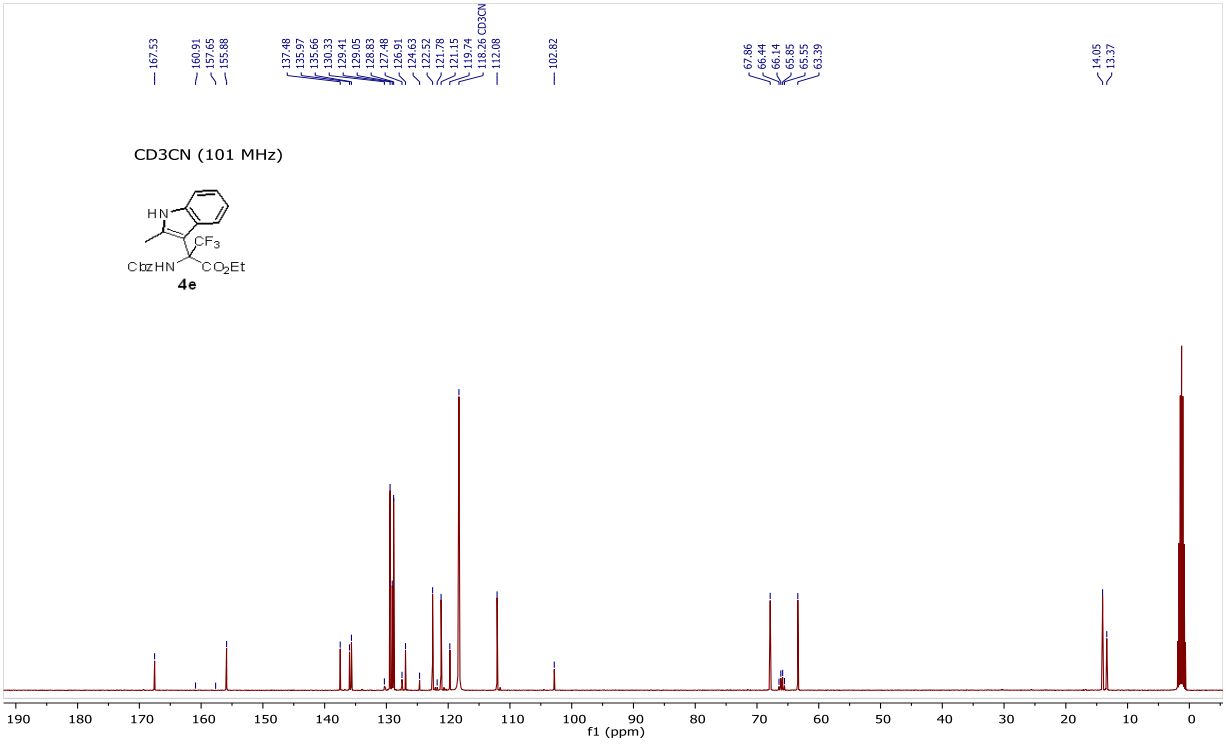
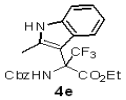
f1 (ppm)


CD3CN (400 MHz)
4e
f1 (ppm)


CD3CN (101 MHz)
4e
f1 (ppm)

CD3CN (376 MHz)



4e

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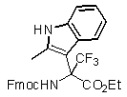
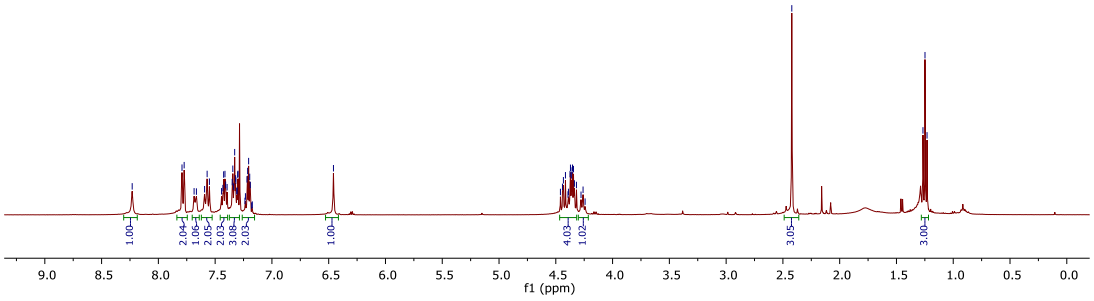
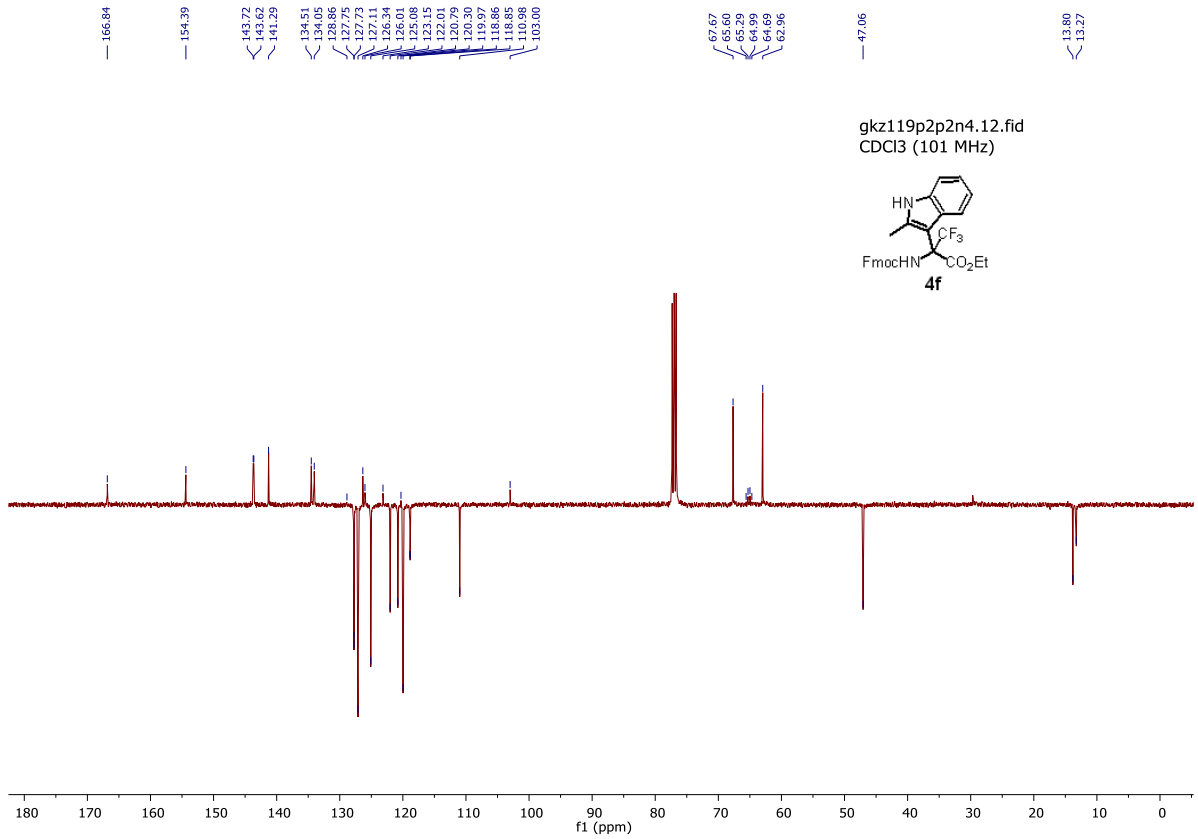
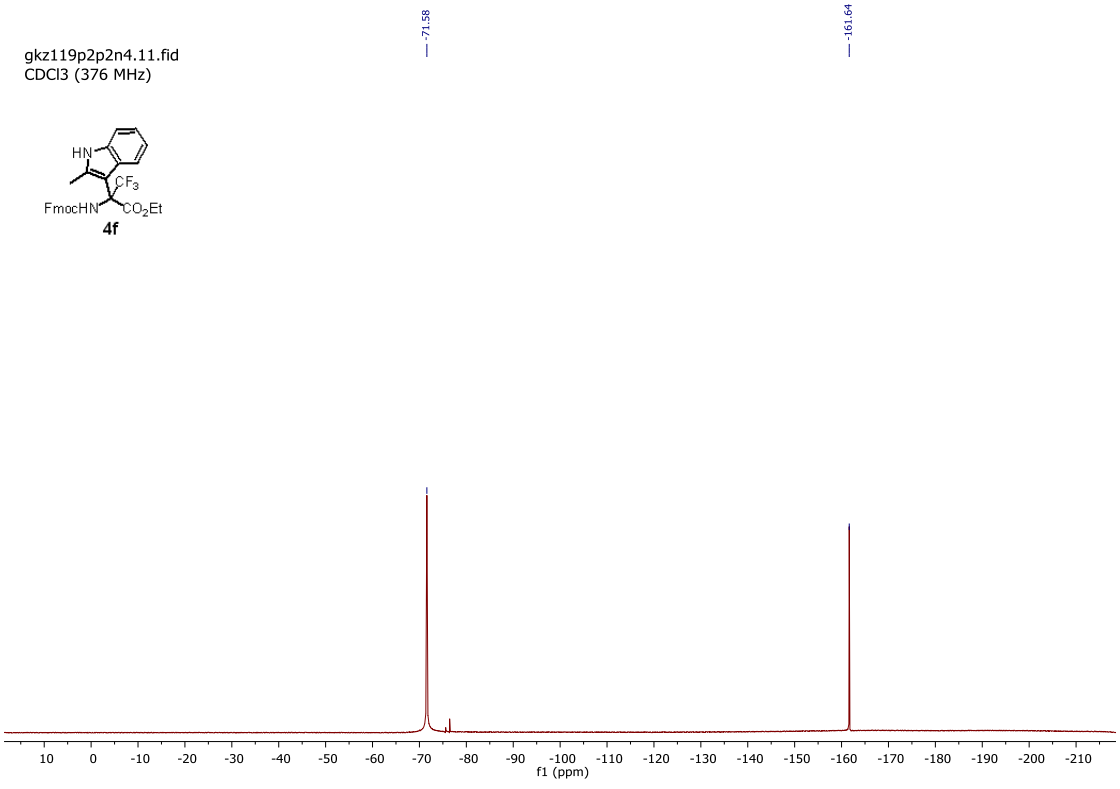
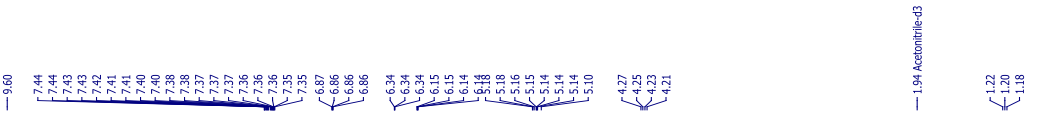


4f

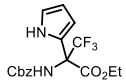



166.84
154.39
143.72
143.62
141.29
134.51
134.05
128.86
127.75
127.73
127.11
126.34
126.01
125.08
123.15
122.01
120.79
120.30
119.97
118.86
118.85
110.98
103.00
67.67
65.60
65.29
64.99
64.69
62.96
47.06
13.80
13.27
gkz119p2p2n4.12.fid
CDCl3 (101 MHz)
HN
CF3
FmocHN
CO2Et
4f
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

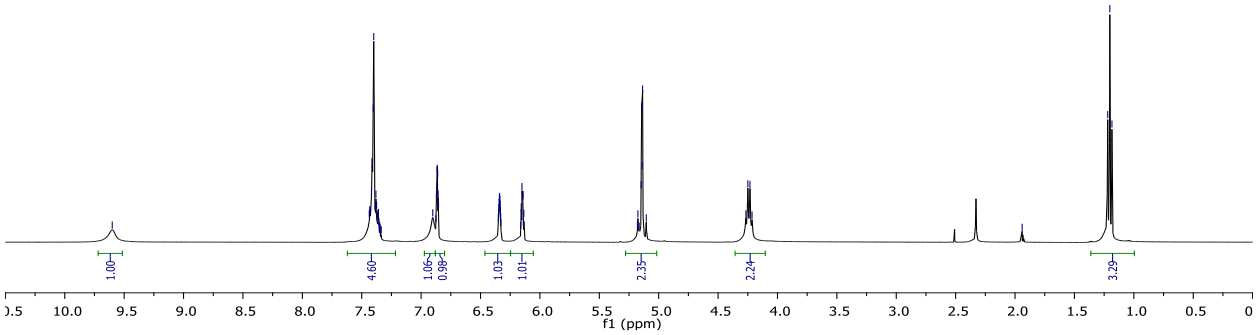

-71.58
-161.64
gkz119p2p2n4.11.fid
CDCl3 (376 MHz)
HN
CF3
FmocHN
CO2Et
4f
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)



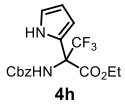
CD_3CN (400 MHz)



4h

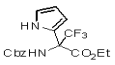


CD_3CN (101 MHz)



4h

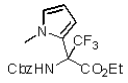
CD3CN (376 MHz)



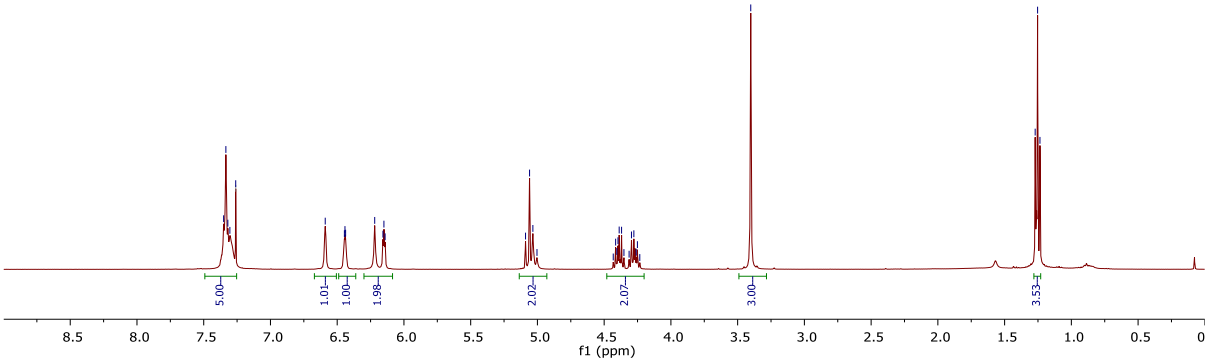
4h

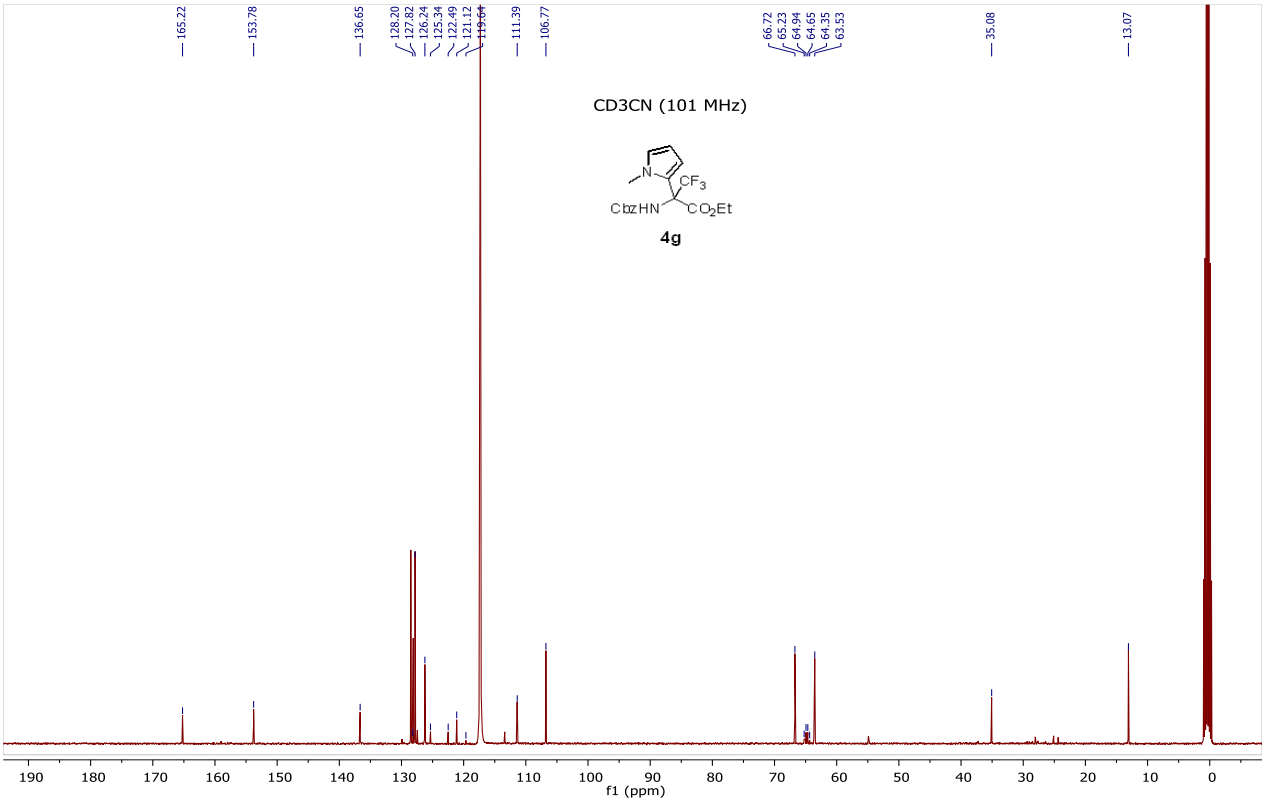
CDCl3 (400 MHz)

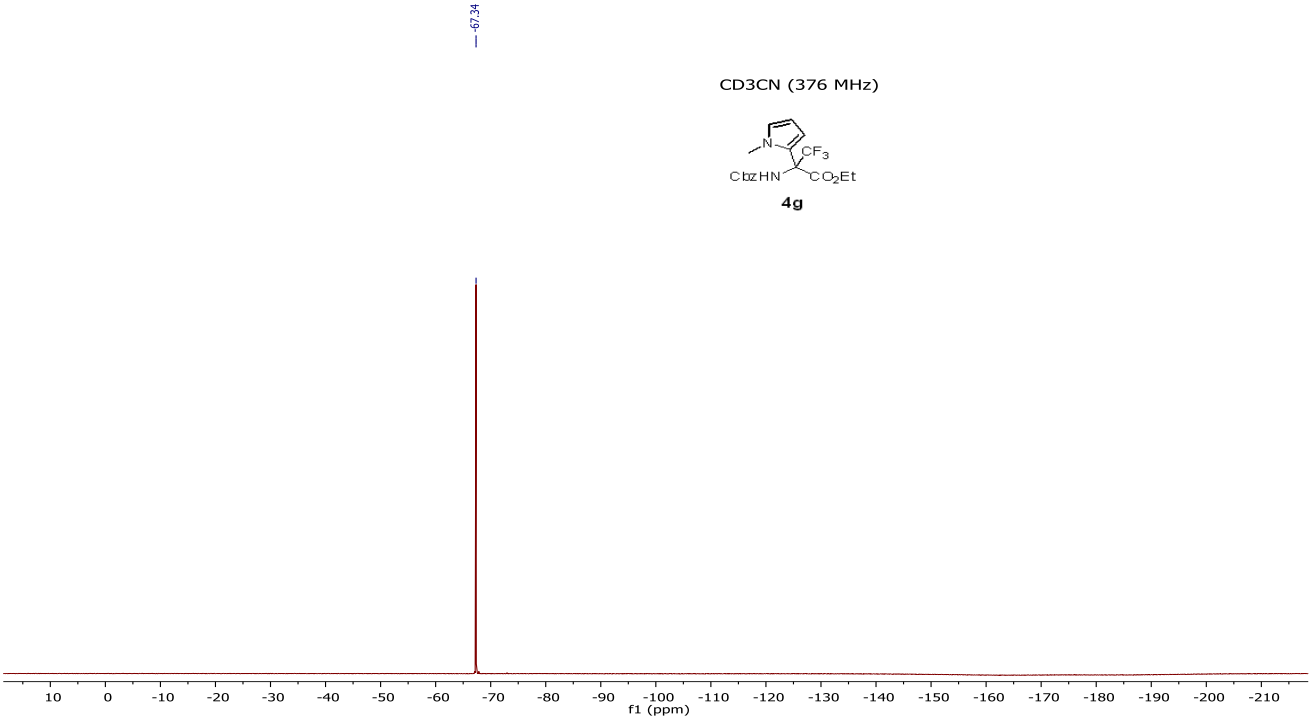
Minor regioisomer

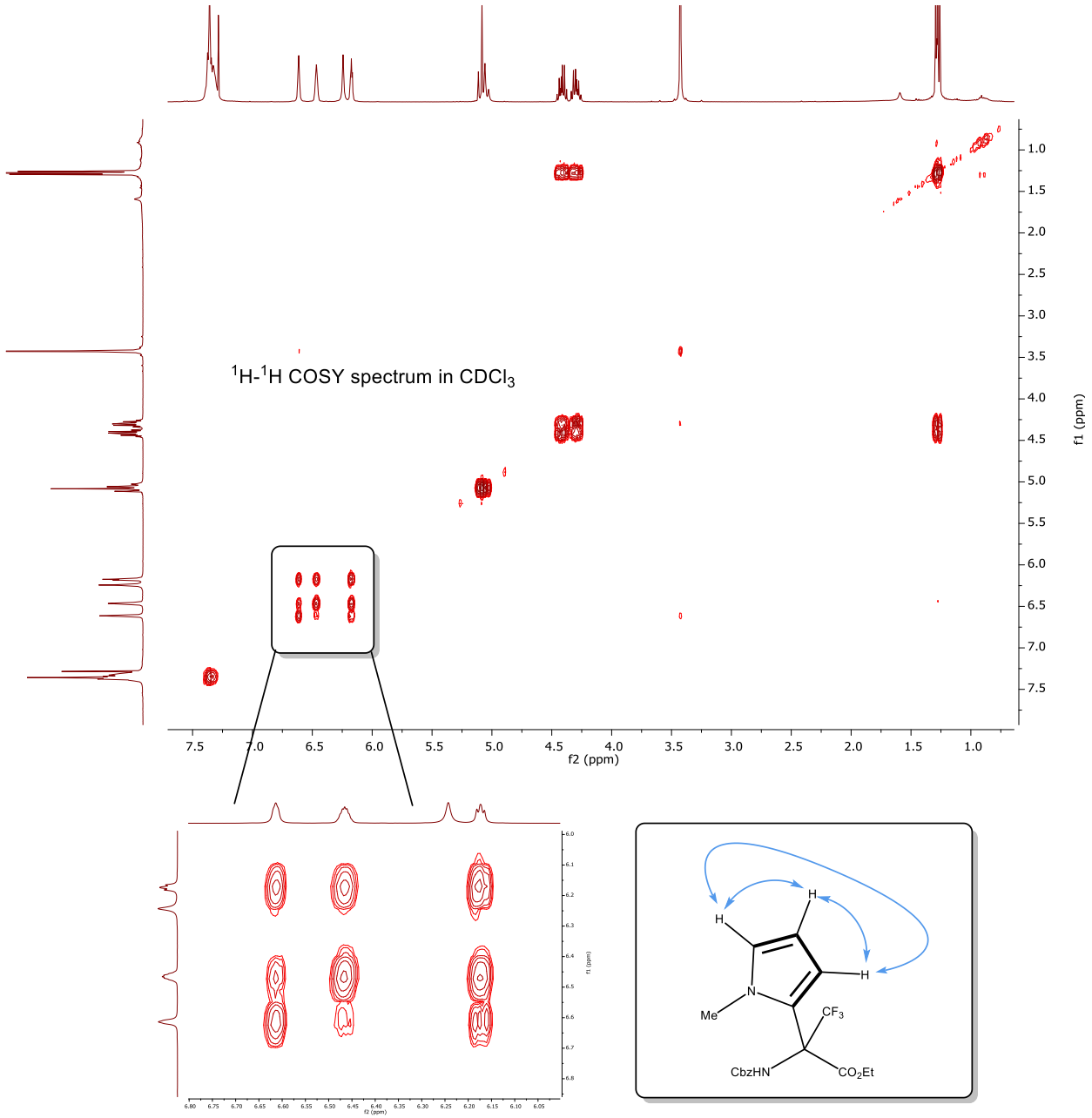


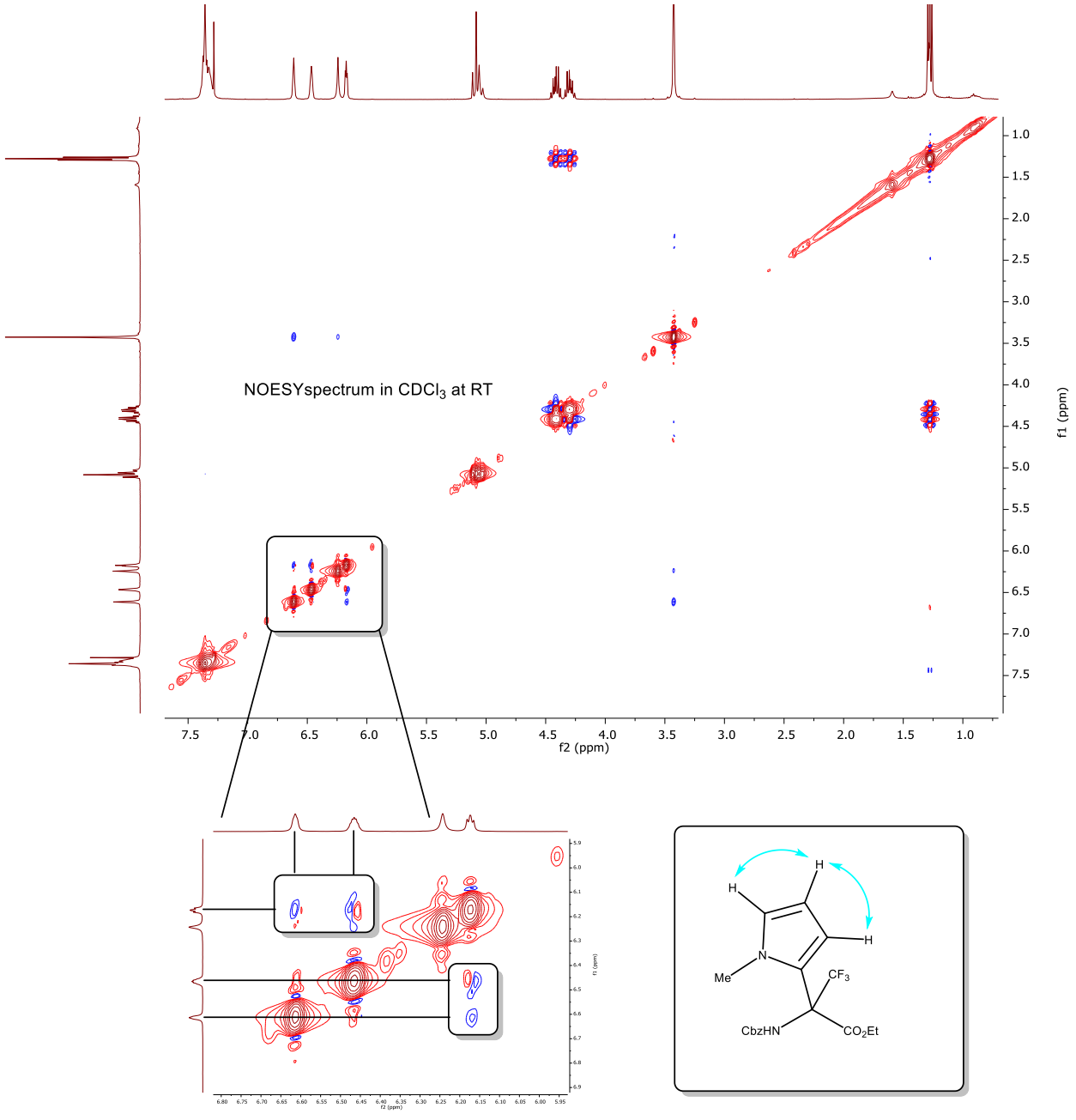
4g

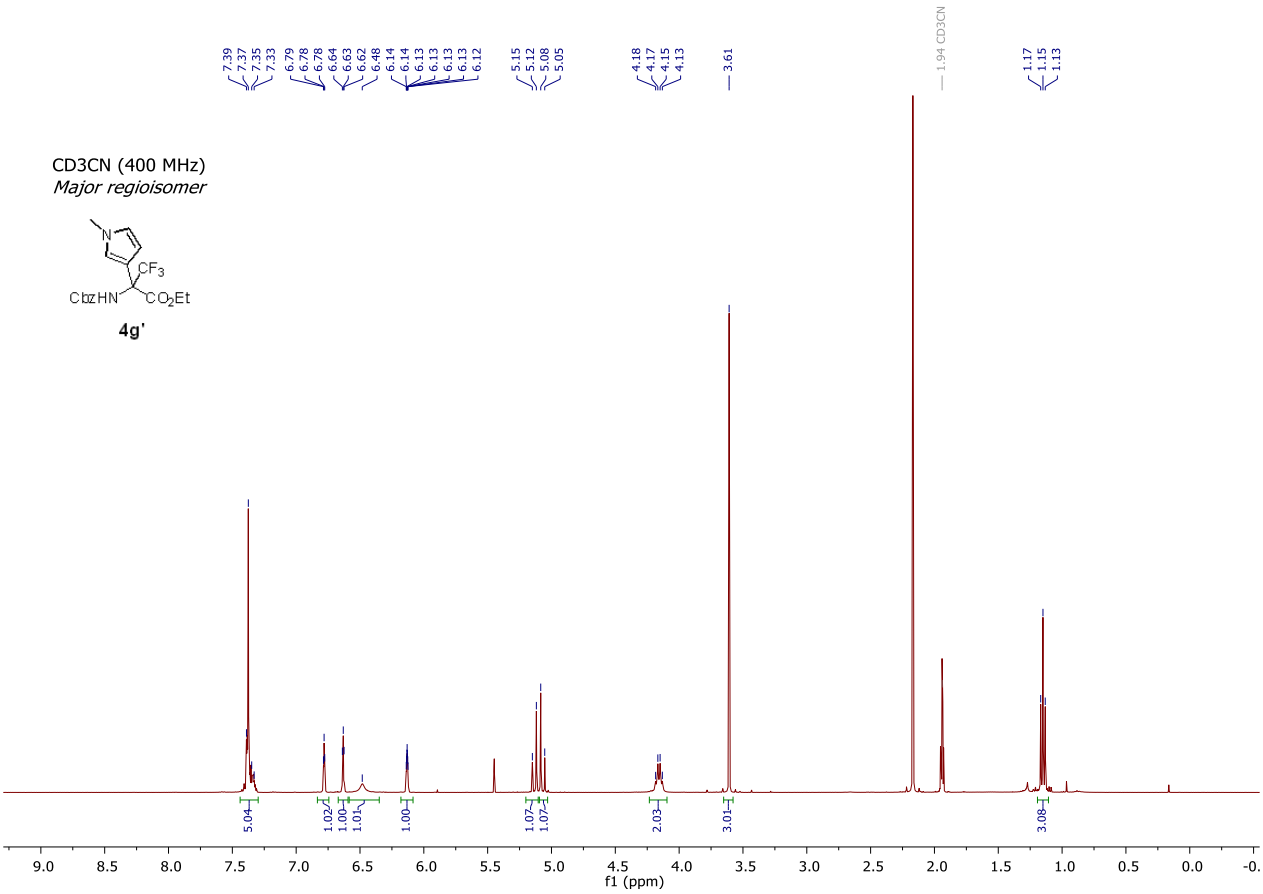


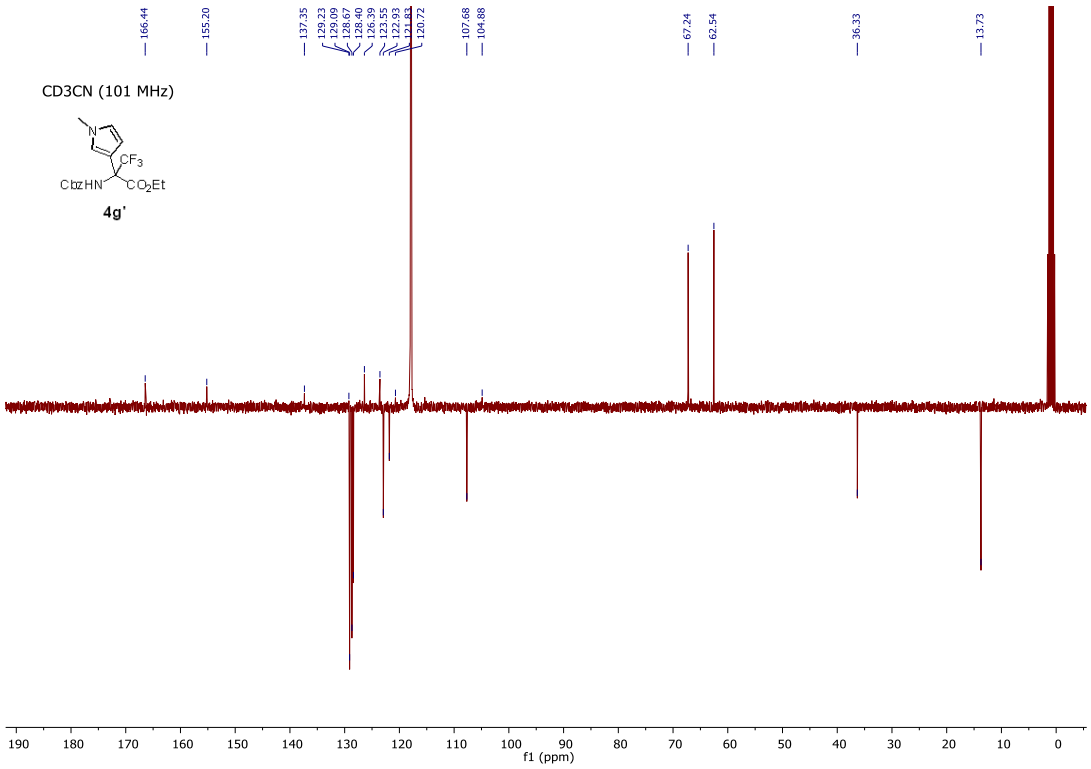

165.22
153.78
136.65
128.20
127.82
126.24
125.34
122.49
121.12
119.64
111.39
106.77
66.72
65.23
64.94
64.65
64.35
63.53
35.08
13.07
CD3CN (101 MHz)
CbzHN
CF3
CO2Et
4g
f1 (ppm)


-67.34
CD3CN (376 MHz)
CbzHN
CF3
CO2Et
4g
f1 (ppm)

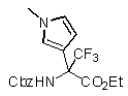

^{1}H-^{1}H COSY spectrum in CDCl$_3$
f1 (ppm)
f2 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
H
H
H
N
Me
CF$_3$
CbzHN
CO$_2$Et


NOESYspectrum in CDCl3 at RT
f2 (ppm)
f1 (ppm)
H
H
H
N
Me
CF3
CbzHN
CO2Et

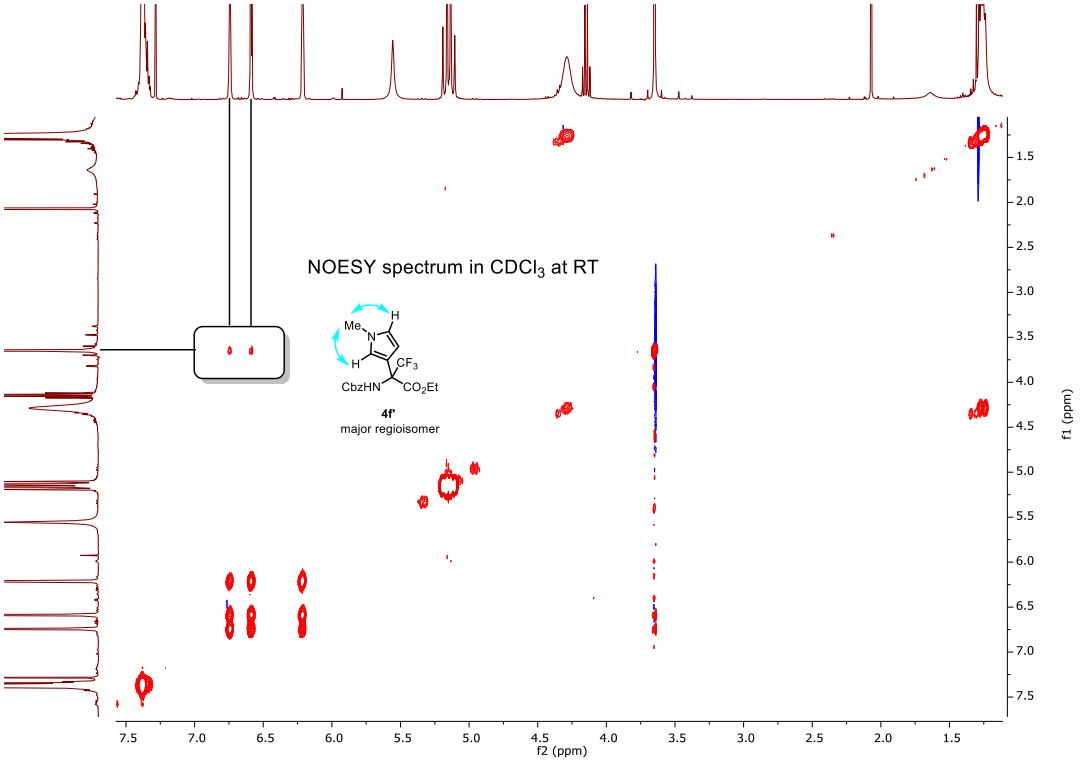

CD3CN (400 MHz)
Major regioisomer
4g'
f1 (ppm)

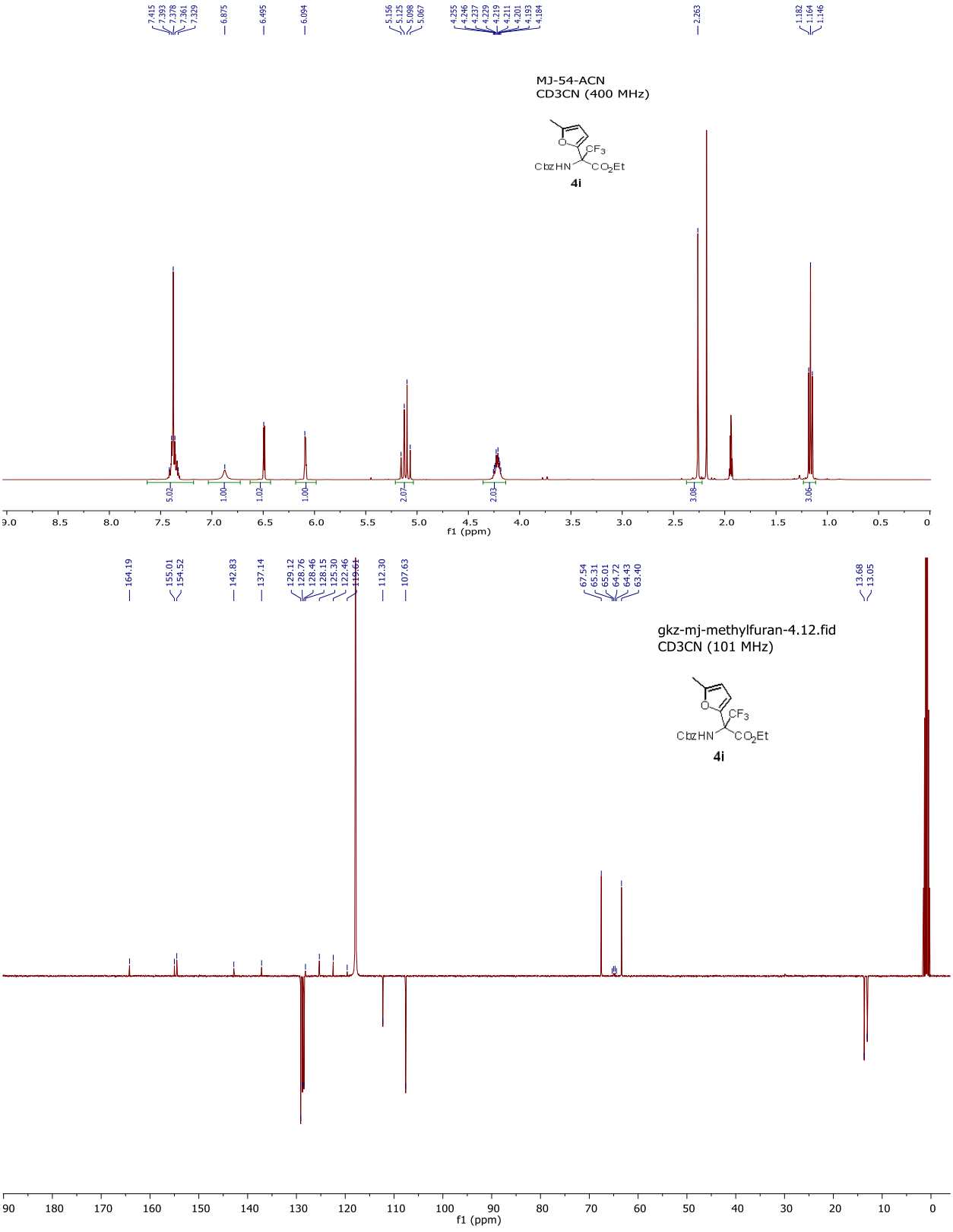

CD3CN (101 MHz)
4g'
f1 (ppm)

CDCl3 (376 MHz)

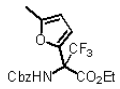


4g'

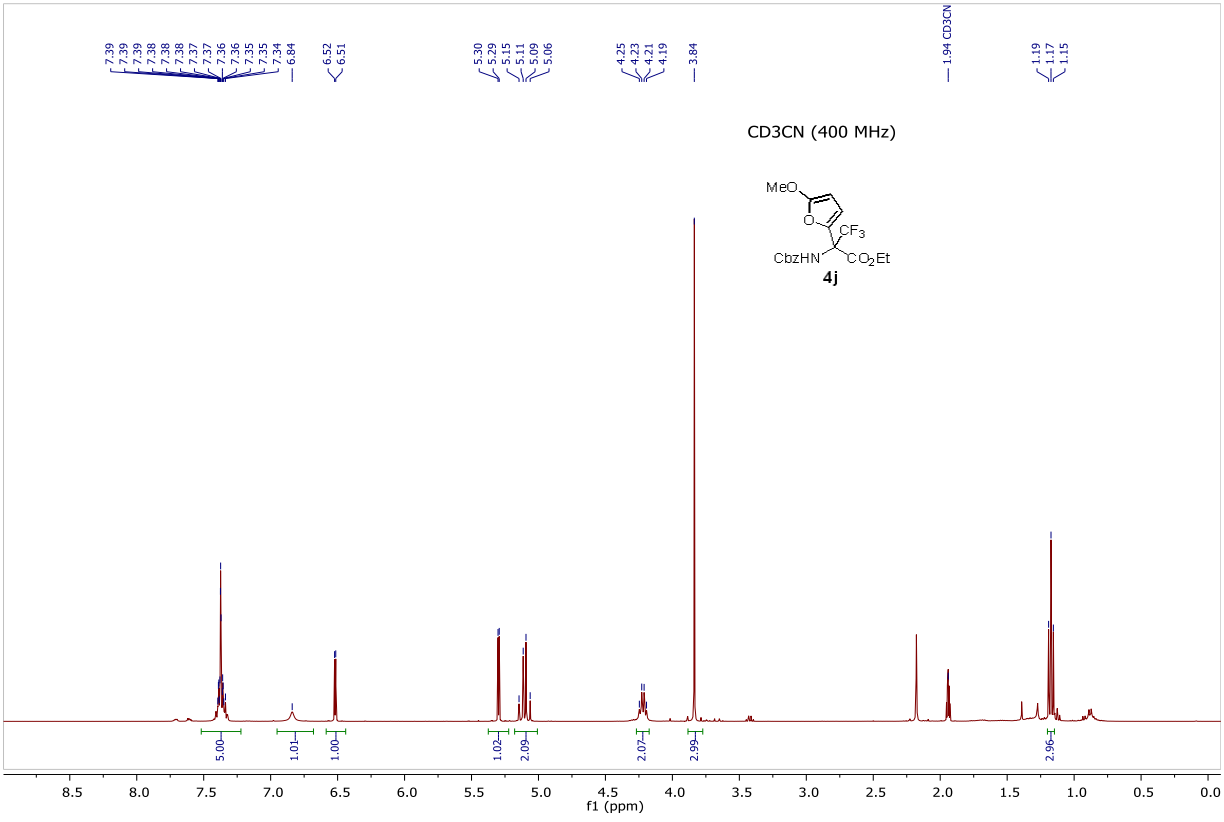



7.415
7.393
7.378
7.361
7.329
6.875
6.495
6.094
5.156
5.125
5.098
5.067
4.255
4.246
4.237
4.229
4.219
4.211
4.201
4.193
4.184
2.263
1.182
1.164
1.146
MJ-54-ACN
CD3CN (400 MHz)
CbzHN
CF3
CO2Et
4i
5.02
1.00
1.02
1.00
2.07
2.03
3.08
3.06
f1 (ppm)
164.19
155.01
154.52
142.83
137.14
129.12
128.76
128.46
128.15
125.30
122.46
119.64
112.30
107.63
67.54
65.31
65.01
64.72
64.43
63.40
13.68
13.05
gkz-mj-methylfuran-4.12.fid
CD3CN (101 MHz)
CbzHN
CF3
CO2Et
4i
f1 (ppm)

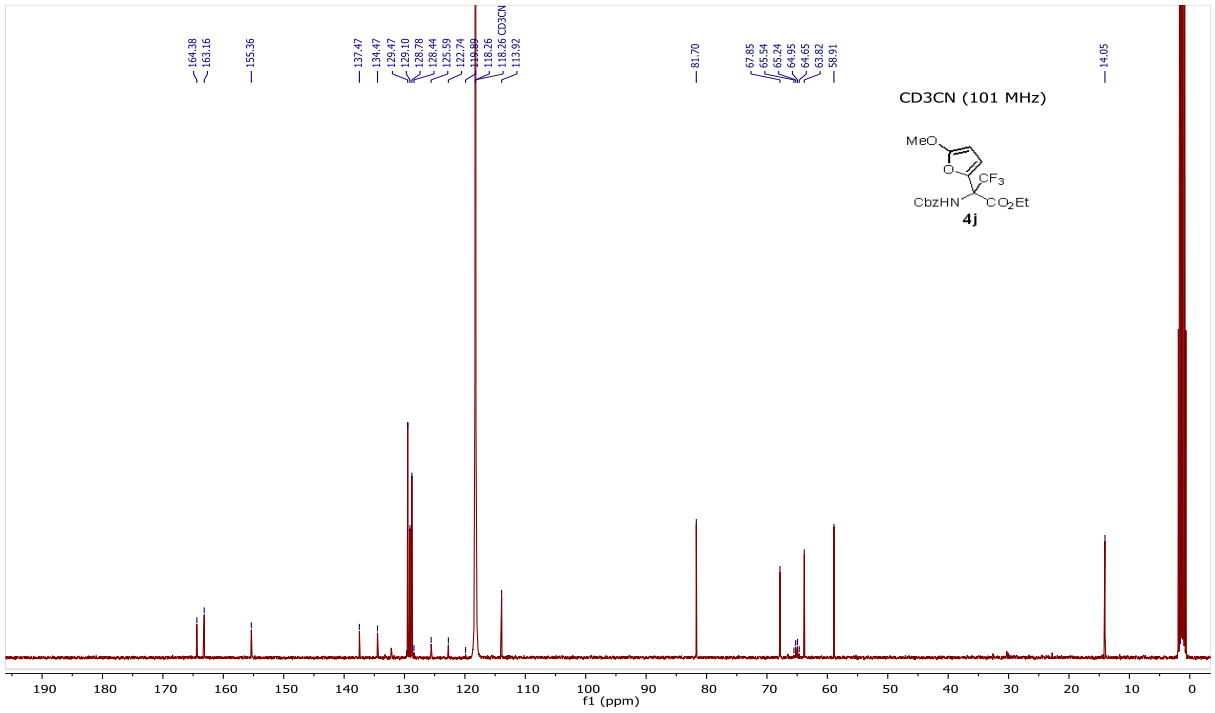
gkz-mz-19F-2.11.fid
CDCl3 (376 MHz)

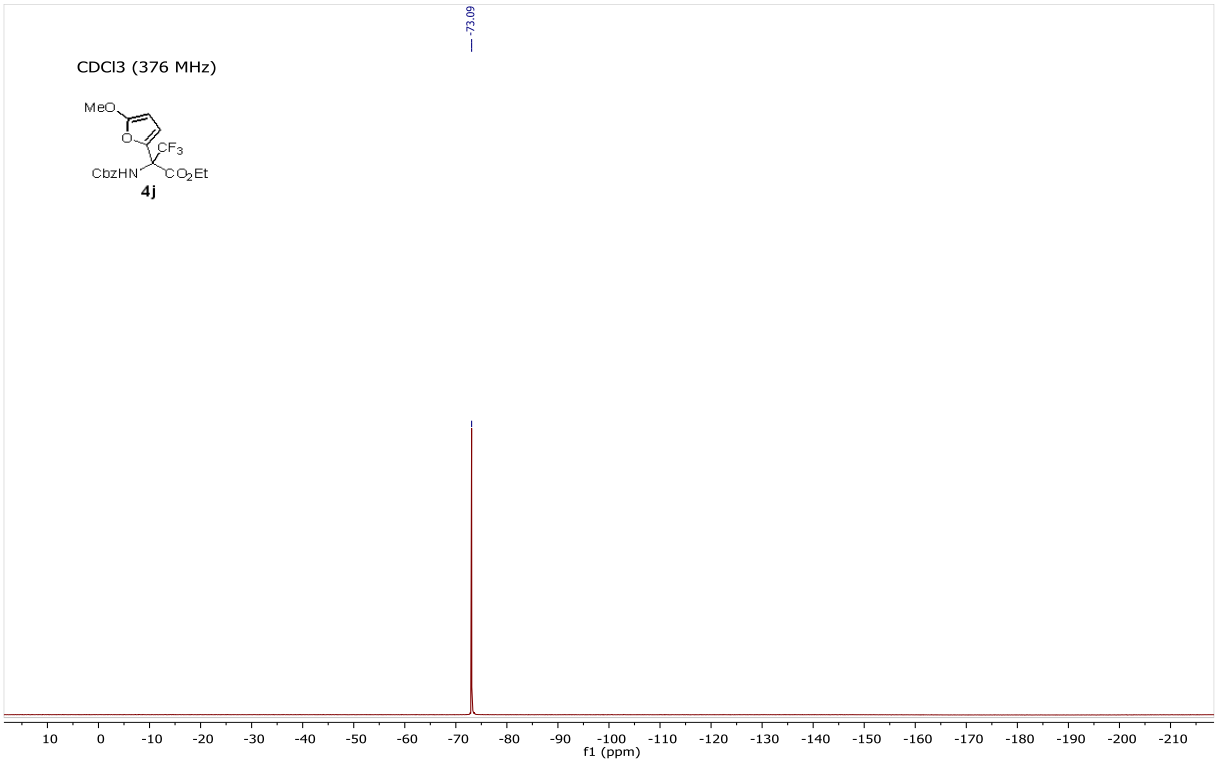


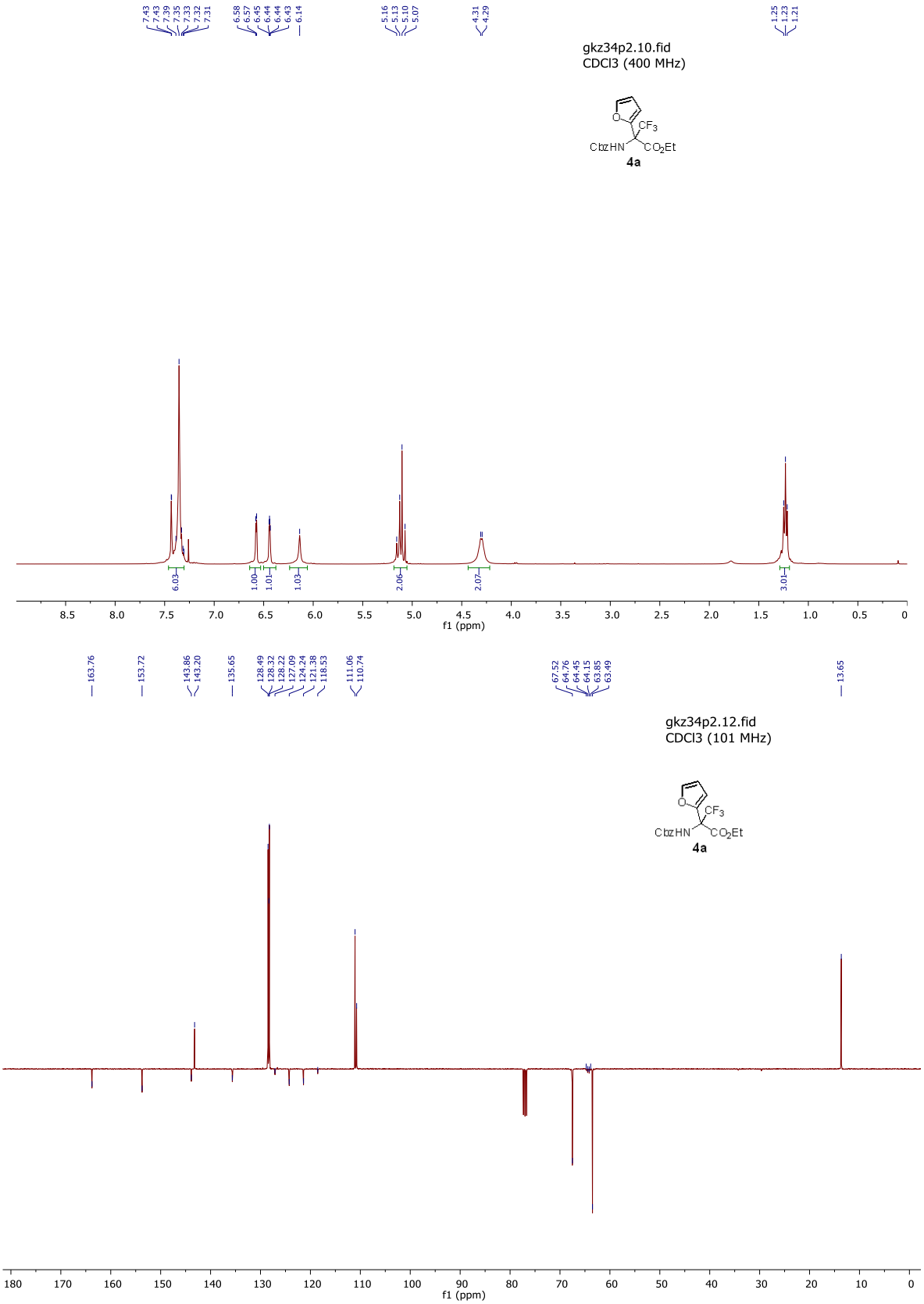
4i



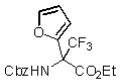
4j


164.38
163.16
155.36
137.47
134.47
129.47
129.10
128.78
128.44
125.59
122.74
118.26
118.26 CD3CN
113.92
81.70
67.85
65.54
65.24
64.95
64.65
63.82
58.91
14.05
CD3CN (101 MHz)
MeO
O
CF3
CbzHN
CO2Et
4j
f1 (ppm)


-73.09
CDCl3 (376 MHz)
MeO
O
CF3
CbzHN
CO2Et
4j
f1 (ppm)

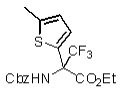

7.43
7.43
7.39
7.35
7.33
7.32
7.31
6.58
6.57
6.45
6.44
6.44
6.43
6.14
5.16
5.13
5.10
5.07
4.31
4.29
1.25
1.23
1.21
gkz34p2.10.fid
CDCl3 (400 MHz)
CF3
CbzHN
CO2Et
4a
6.03
1.00
1.01
1.03
2.06
2.07
3.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)
163.76
153.72
143.86
143.20
135.65
128.49
128.32
128.22
127.09
124.24
121.38
118.53
111.06
110.74
67.52
64.76
64.45
64.15
63.85
63.49
13.65
gkz34p2.12.fid
CDCl3 (101 MHz)
CF3
CbzHN
CO2Et
4a
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

gkz34p2.11.fid
CDCl3 (376 MHz)

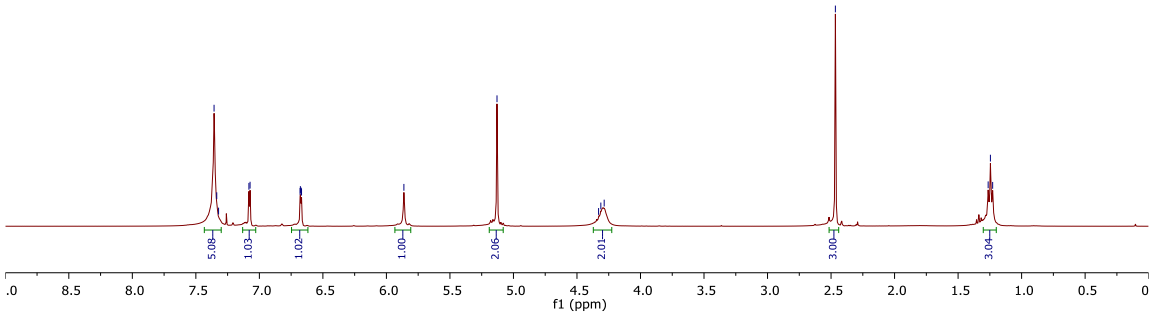


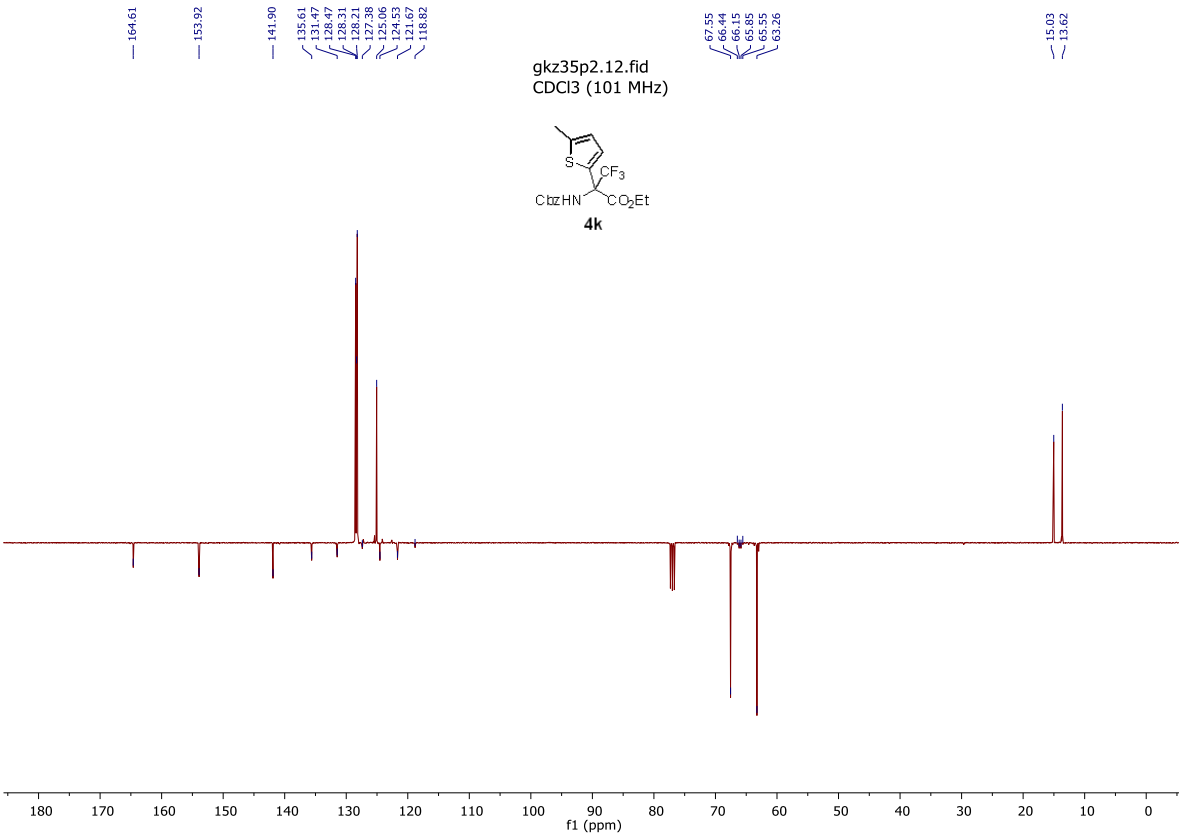
4a

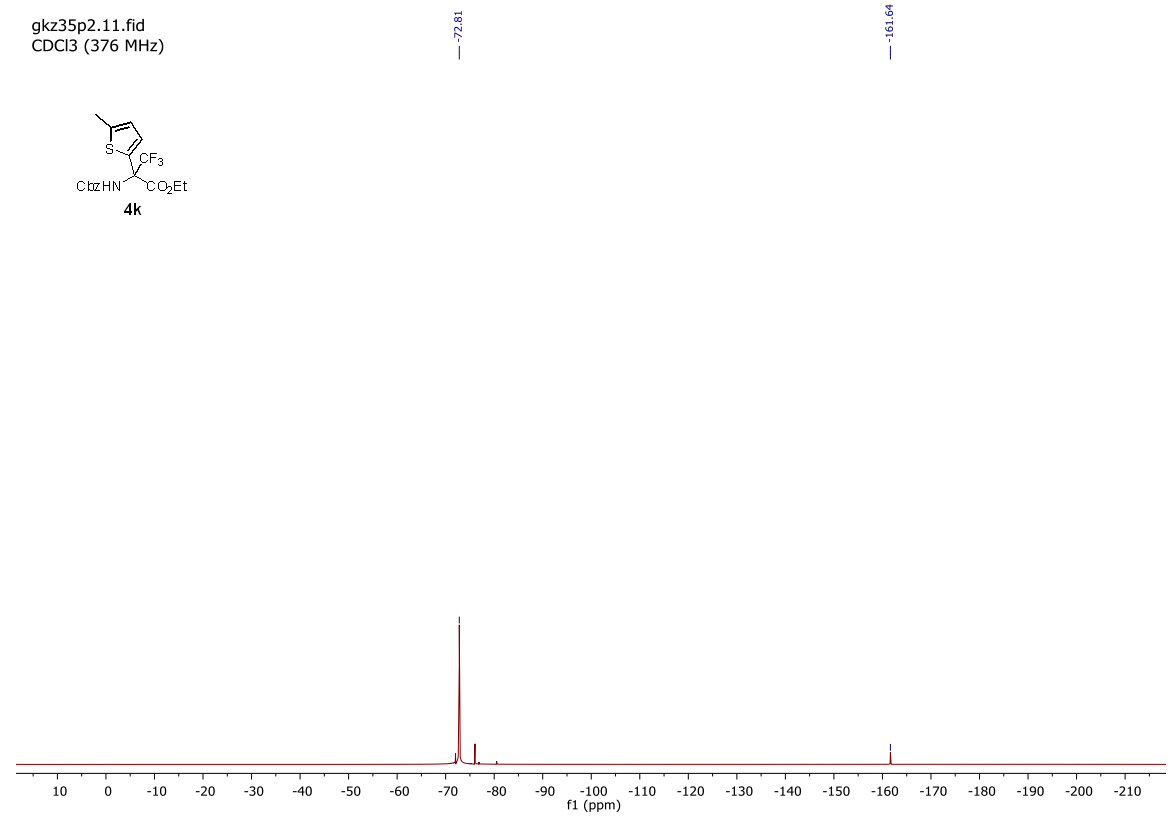
gkz35p2.10.fid
CDCl3 (400 MHz)

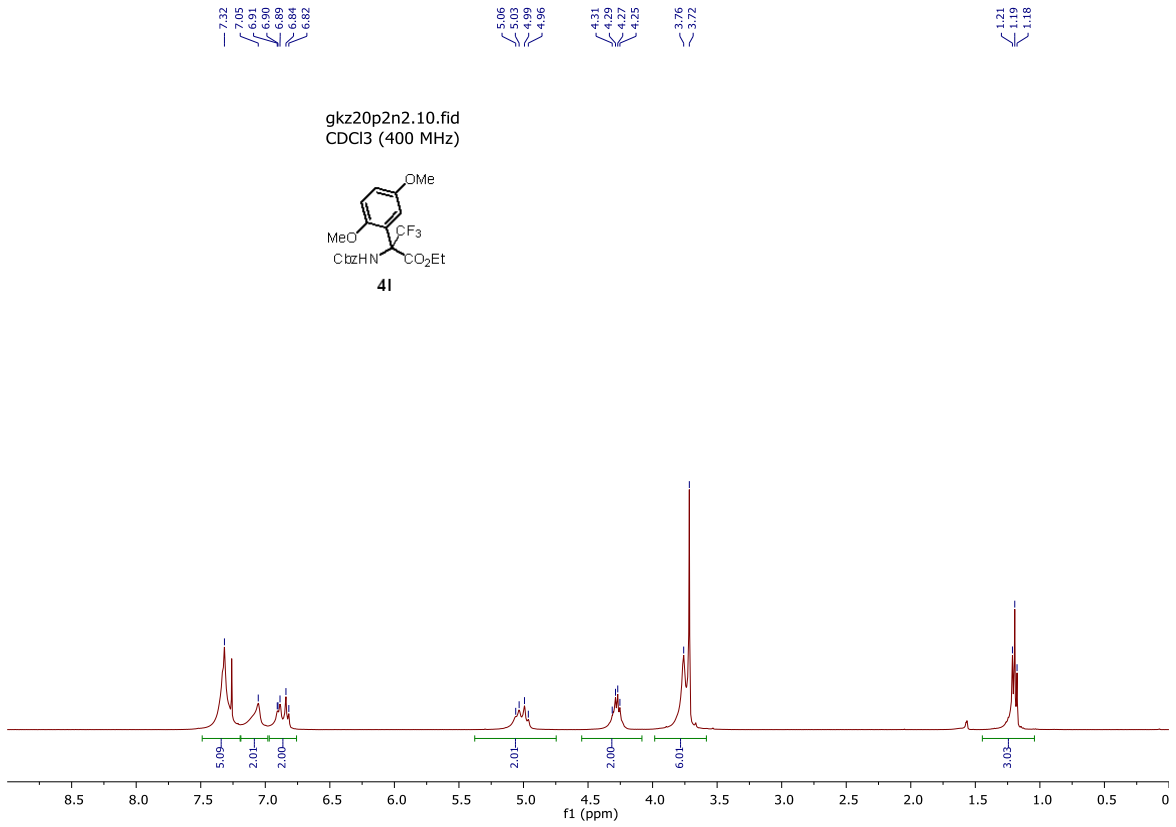


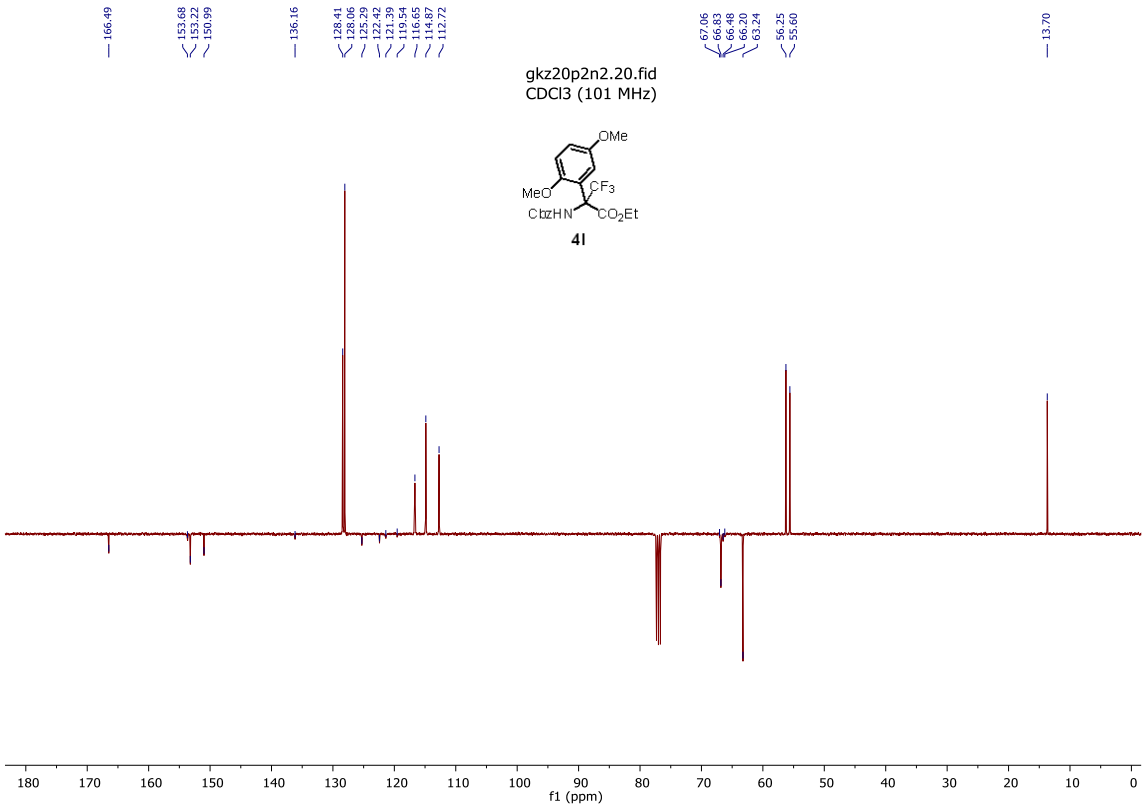
4k

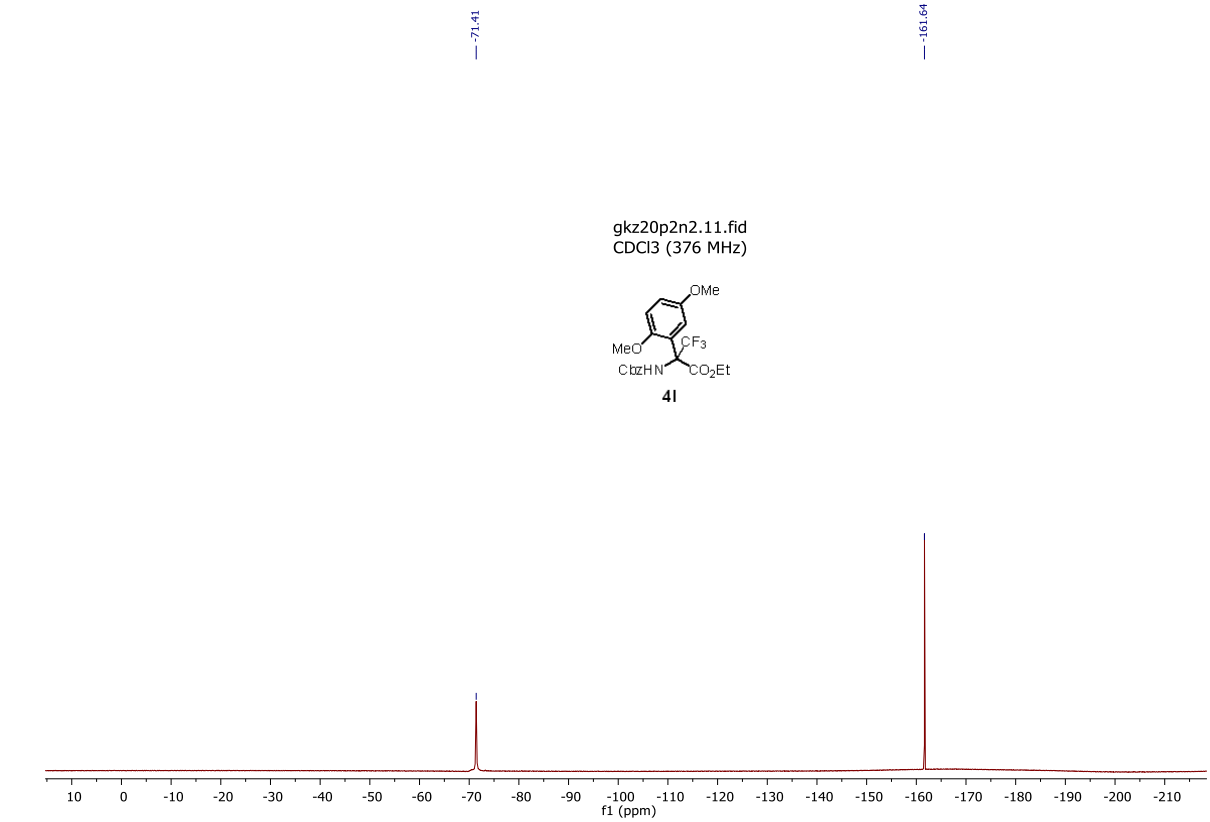


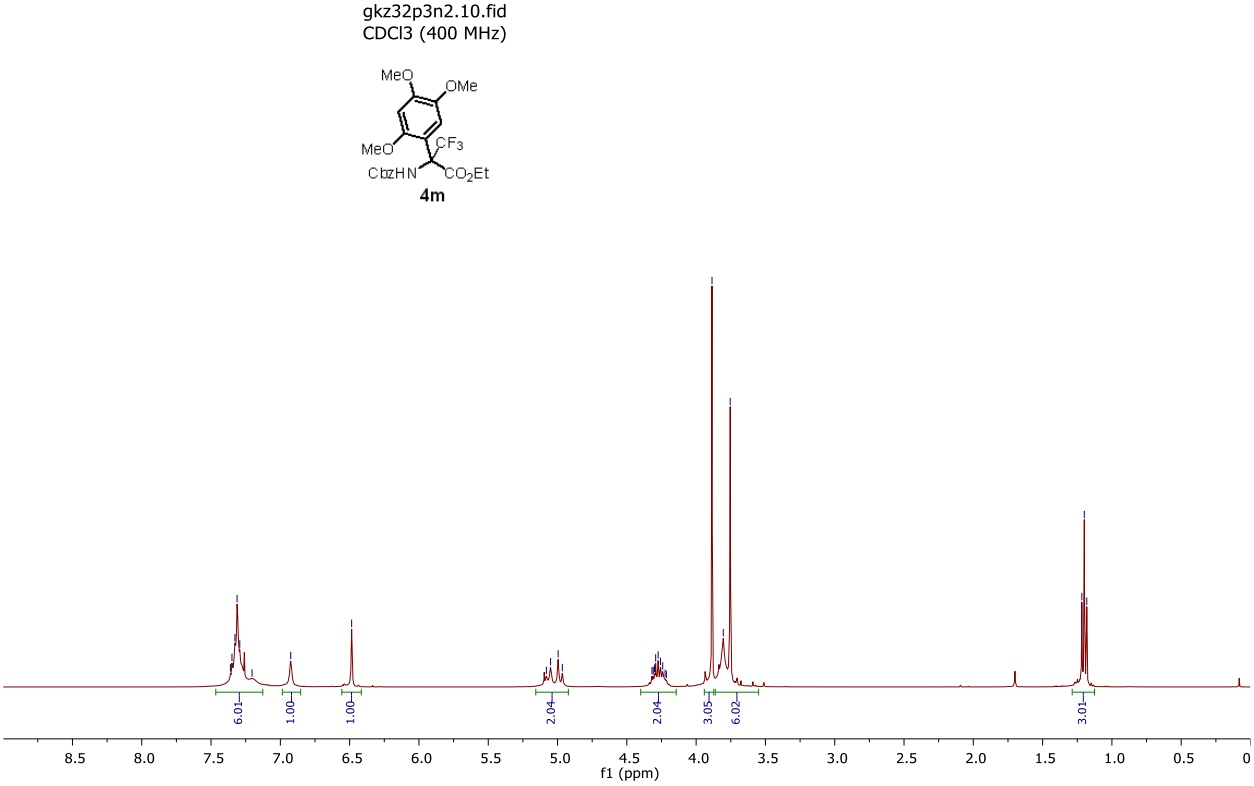

164.61
153.92
141.90
135.61
131.47
128.47
128.31
128.21
127.38
125.06
124.53
121.67
118.82
67.55
66.44
66.15
65.85
65.55
63.26
15.03
13.62
gkz35p2.12.fid
CDCl3 (101 MHz)
S
CF3
CbzHN
CO2Et
4k
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

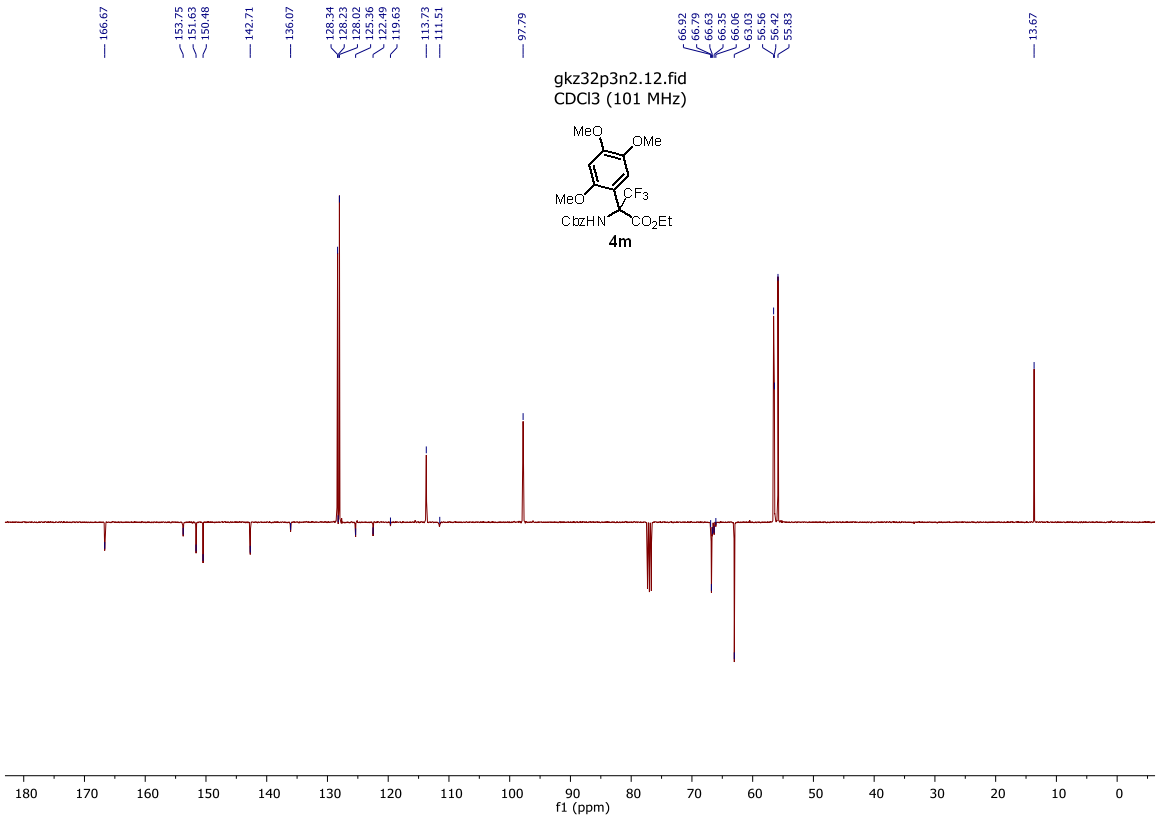

gkz35p2.11.fid
CDCl3 (376 MHz)
-72.81
-161.64
S
CF3
CbzHN
CO2Et
4k
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

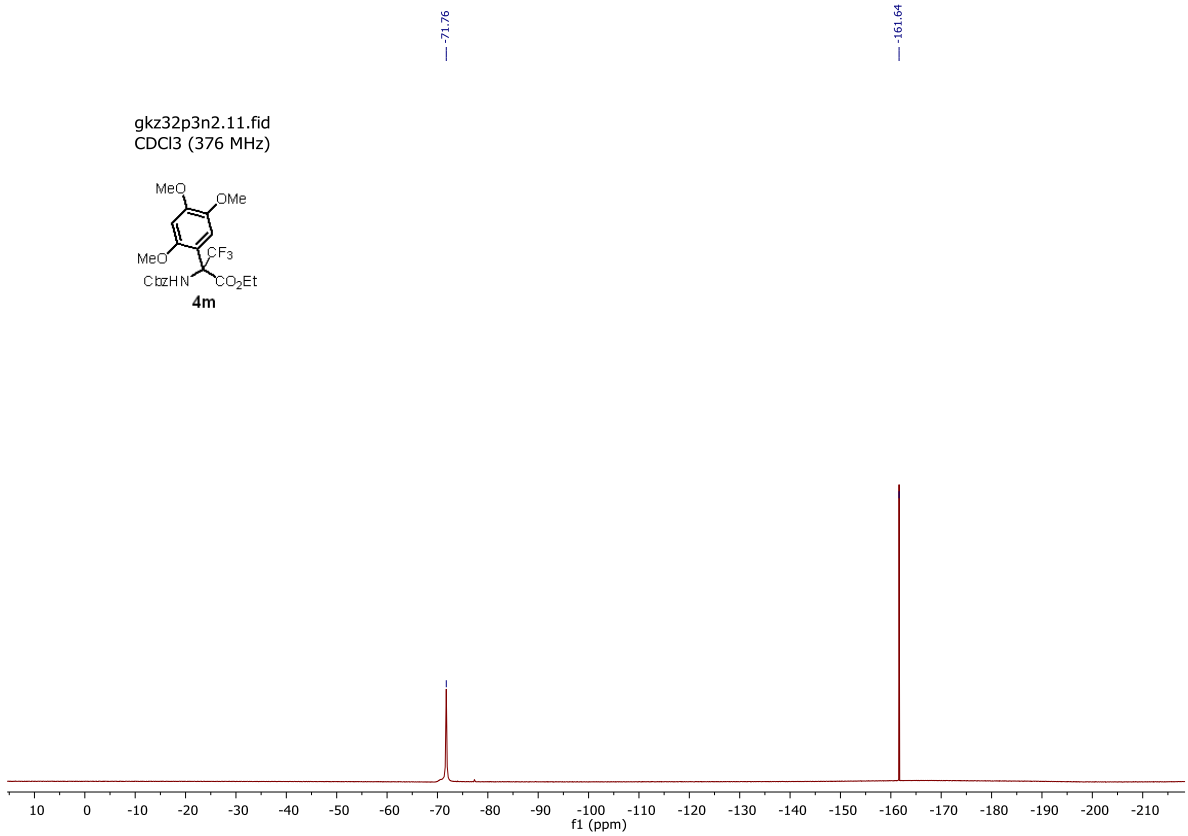

7.32
7.05
6.91
6.90
6.89
6.84
6.82
5.06
5.03
4.99
4.96
4.31
4.29
4.27
4.25
3.76
3.72
1.21
1.19
1.18
gkz20p2n2.10.fid
CDCl3 (400 MHz)
OMe
MeO
CF3
CbzHN
CO2Et
4l
5.09
2.01
2.00
2.01
2.00
6.01
3.03
f1 (ppm)

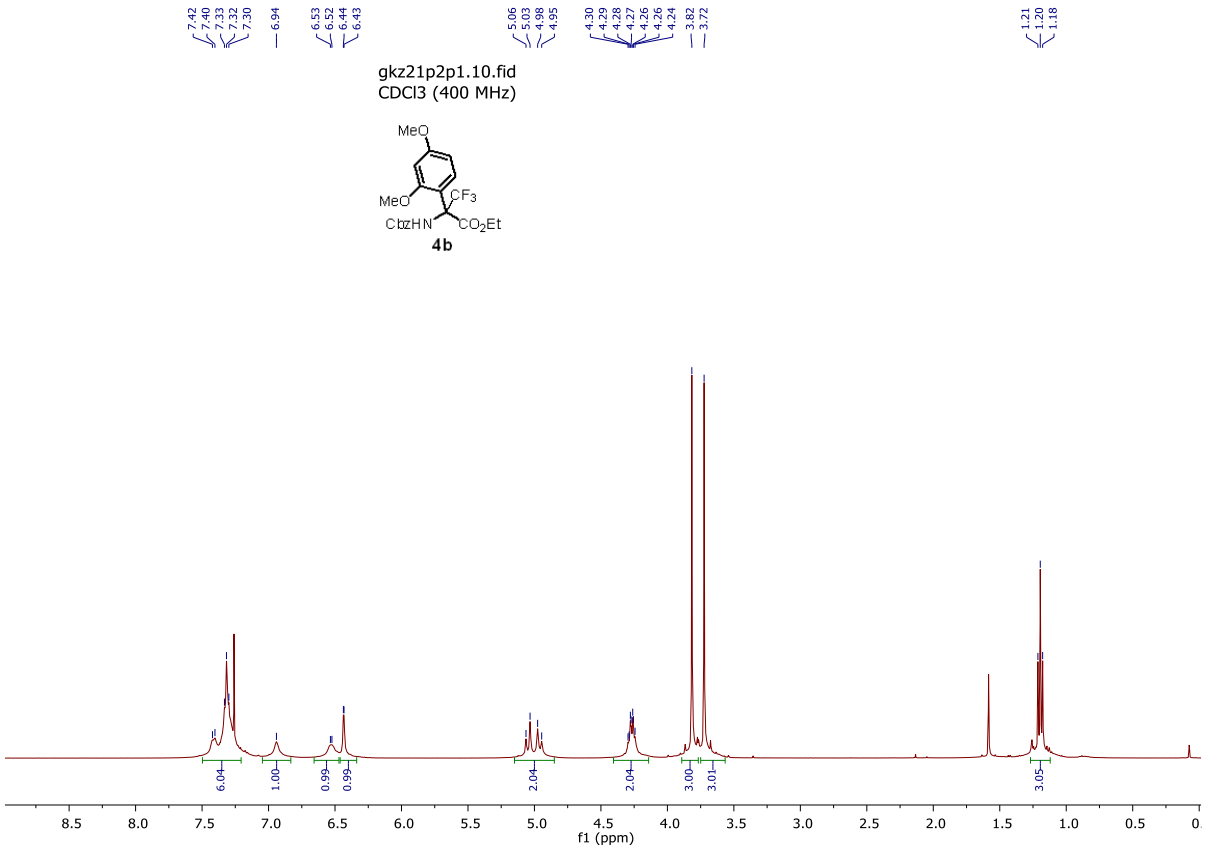

166.49
153.68
153.22
150.99
136.16
128.41
128.06
125.29
122.42
121.39
119.54
116.65
114.57
112.72
67.06
66.83
66.48
66.20
63.24
56.25
55.60
13.70
gkz20p2n2.20.fid
CDCl3 (101 MHz)
OMe
MeO
CF3
CbzHN
CO2Et
4l
f1 (ppm)

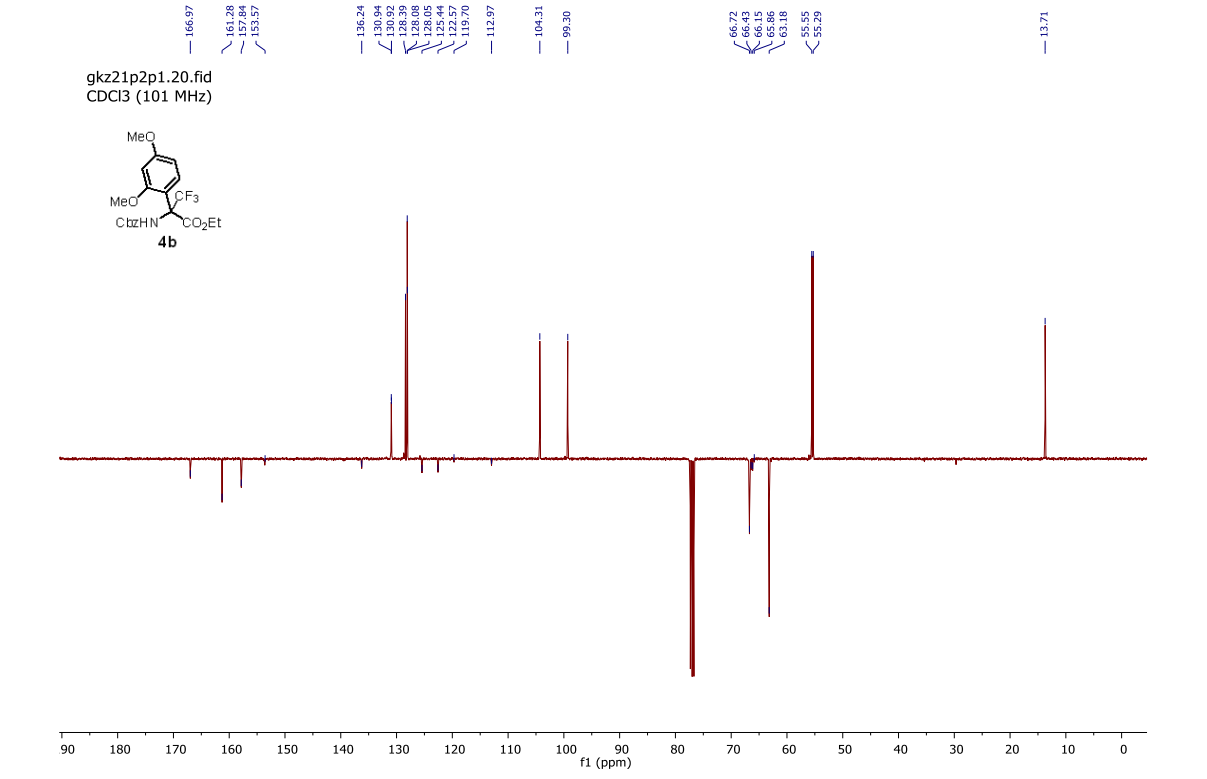

-71.41
-161.64
gkz20p2n2.11.fid
CDCl3 (376 MHz)
OMe
MeO
CF3
CbzHN
CO2Et
4l
f1 (ppm)
7.36
7.35
7.33
7.31
7.29
7.20
6.93
6.49
5.08
5.05
5.00
4.97
4.32
4.31
4.30
4.29
4.27
4.26
4.24
4.22
4.21
3.89
3.80
3.75
1.22
1.20
1.18


gkz32p3n2.10.fid
CDCl3 (400 MHz)
MeO
OMe
MeO
CF3
CbzHN
CO2Et
4m
6.01
1.00
1.00
2.04
2.04
3.05
6.02
3.01
f1 (ppm)

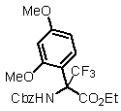

166.67
153.75
151.63
150.48
142.71
136.07
128.34
128.23
128.02
125.36
122.49
119.63
113.73
111.51
97.79
66.92
66.79
66.63
66.35
66.06
63.03
56.56
56.42
55.83
13.67
gkz32p3n2.12.fid
CDCl3 (101 MHz)
MeO
OMe
MeO
CF3
CbzHN
CO2Et
4m
f1 (ppm)


-71.76
-161.64
gkz32p3n2.11.fid
CDCl3 (376 MHz)
MeO
OMe
MeO
CF3
CbzHN
CO2Et
4m
f1 (ppm)


7.42
7.40
7.33
7.32
7.30
6.94
6.53
6.52
6.44
6.43
5.06
5.03
4.98
4.95
4.30
4.29
4.28
4.27
4.26
4.26
4.24
3.82
3.72
1.21
1.20
1.18
gkz21p2p1.10.fid
CDCl3 (400 MHz)
MeO
MeO
CF3
CbzHN
CO2Et
4b
6.04
1.00
0.99
0.99
2.04
2.04
3.00
3.01
3.05
f1 (ppm)

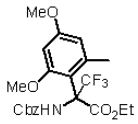

166.97
161.28
157.84
153.57
136.24
130.94
130.92
128.39
128.08
128.05
125.44
122.57
119.70
112.97
104.31
99.30
66.72
66.43
66.15
65.86
63.18
55.55
55.29
13.71
gkz21p2p1.20.fid
CDCl3 (101 MHz)
MeO
MeO
CF3
CbzHN
CO2Et
4b
f1 (ppm)

gkz21p2p1.11.fid
CDCl3 (376 MHz)

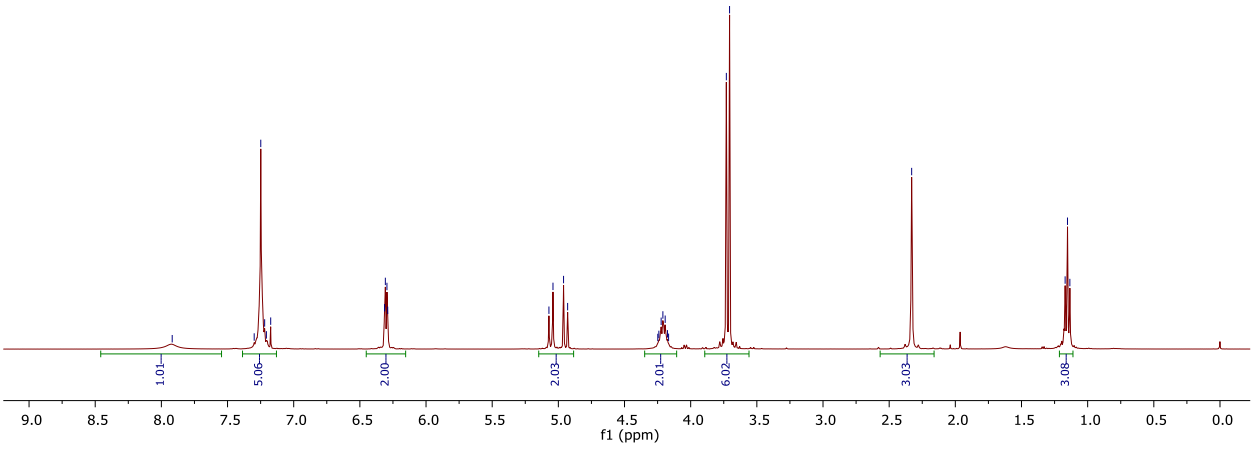


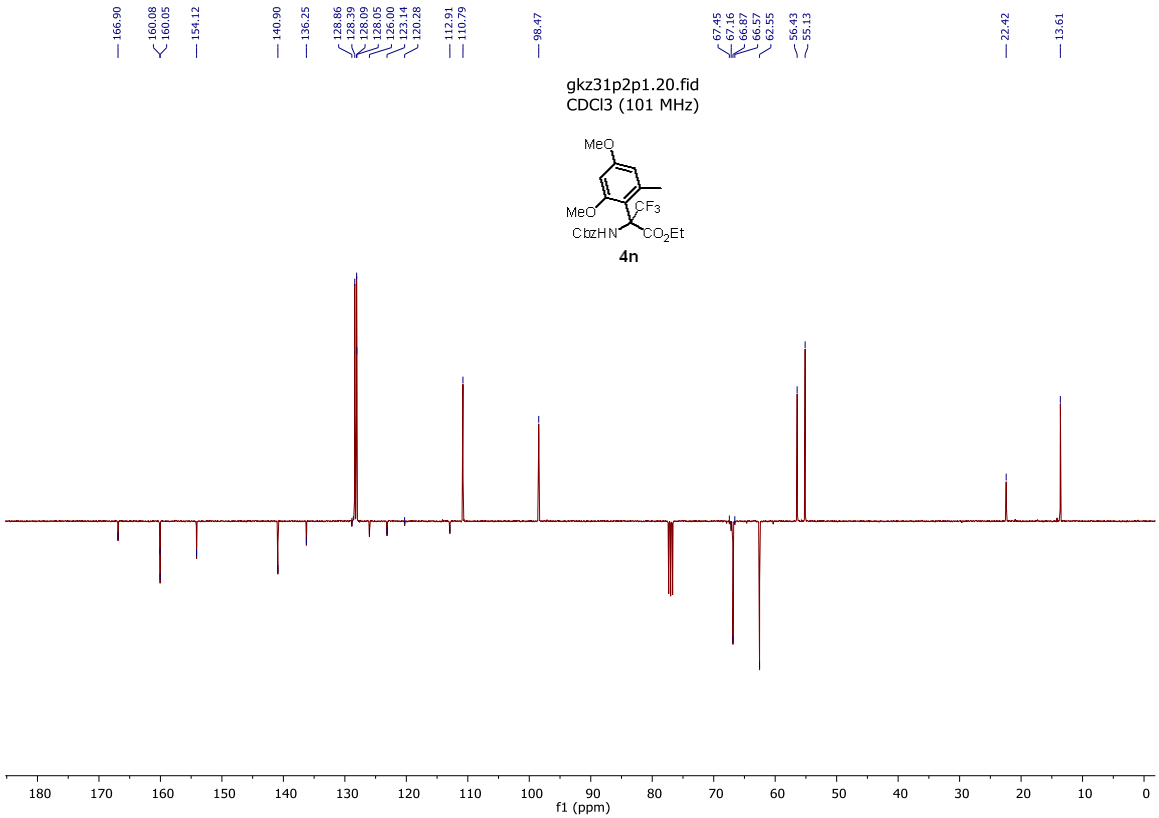
4b

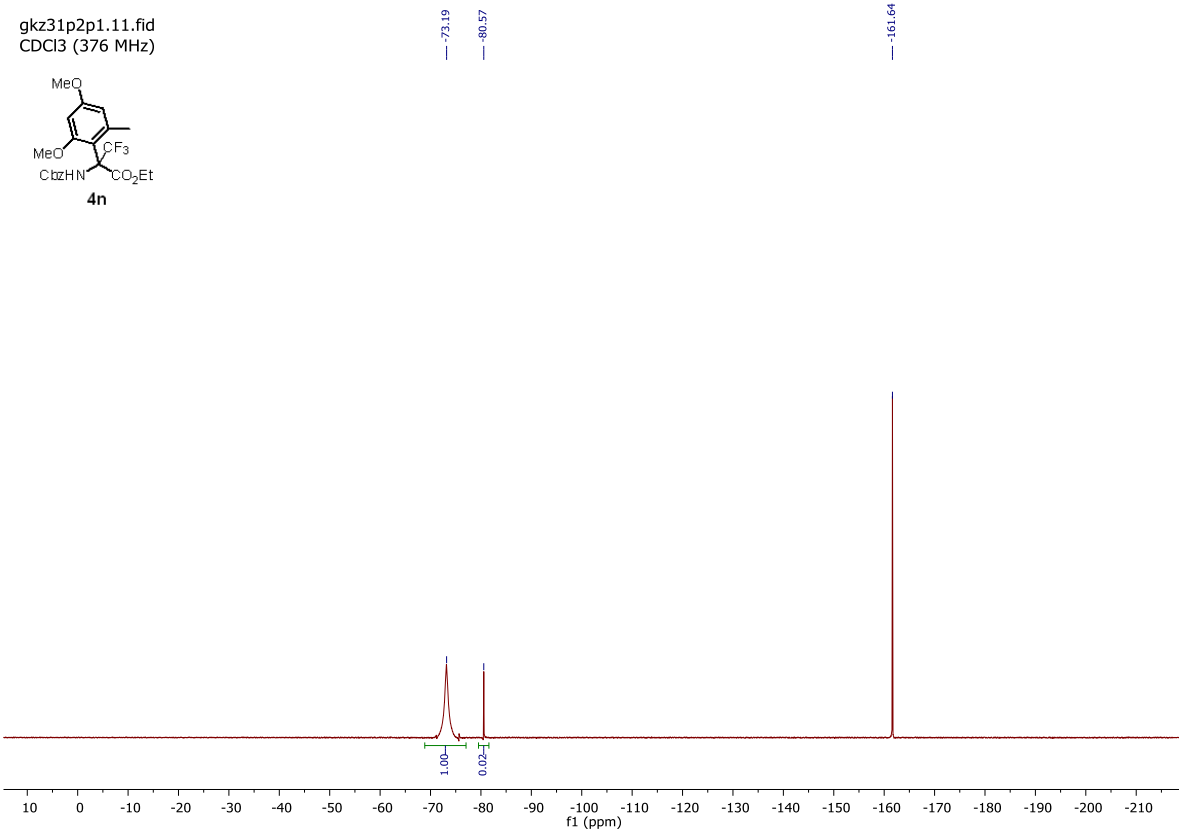
gkz31p2p1.10.fid
CDCl3 (400 MHz)



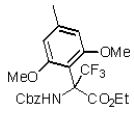
4n



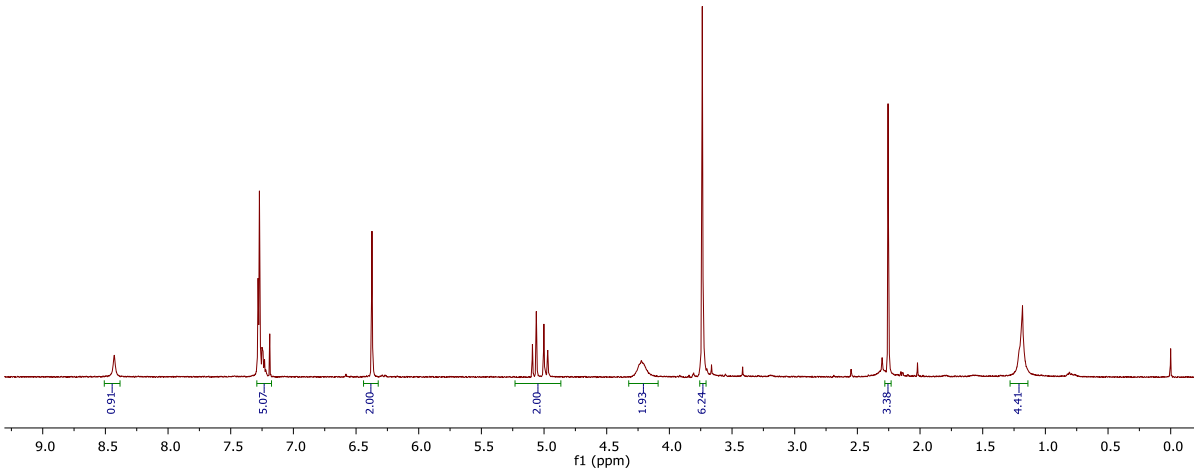

166.90
160.08
160.05
154.12
140.90
136.25
128.86
128.39
128.09
128.05
126.00
123.14
120.28
112.91
110.79
98.47
67.45
67.16
66.87
66.57
62.55
56.43
55.13
22.42
13.61
gkz31p2p1.20.fid
CDCl3 (101 MHz)
MeO
MeO
CF3
CbzHN
CO2Et
4n
f1 (ppm)


gkz31p2p1.11.fid
CDCl3 (376 MHz)
-73.19
-80.57
-161.64
MeO
MeO
CF3
CbzHN
CO2Et
4n
1.00
0.02
f1 (ppm)

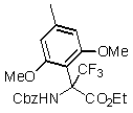
gkz31p3n6
CDCl3 (400 MHz)



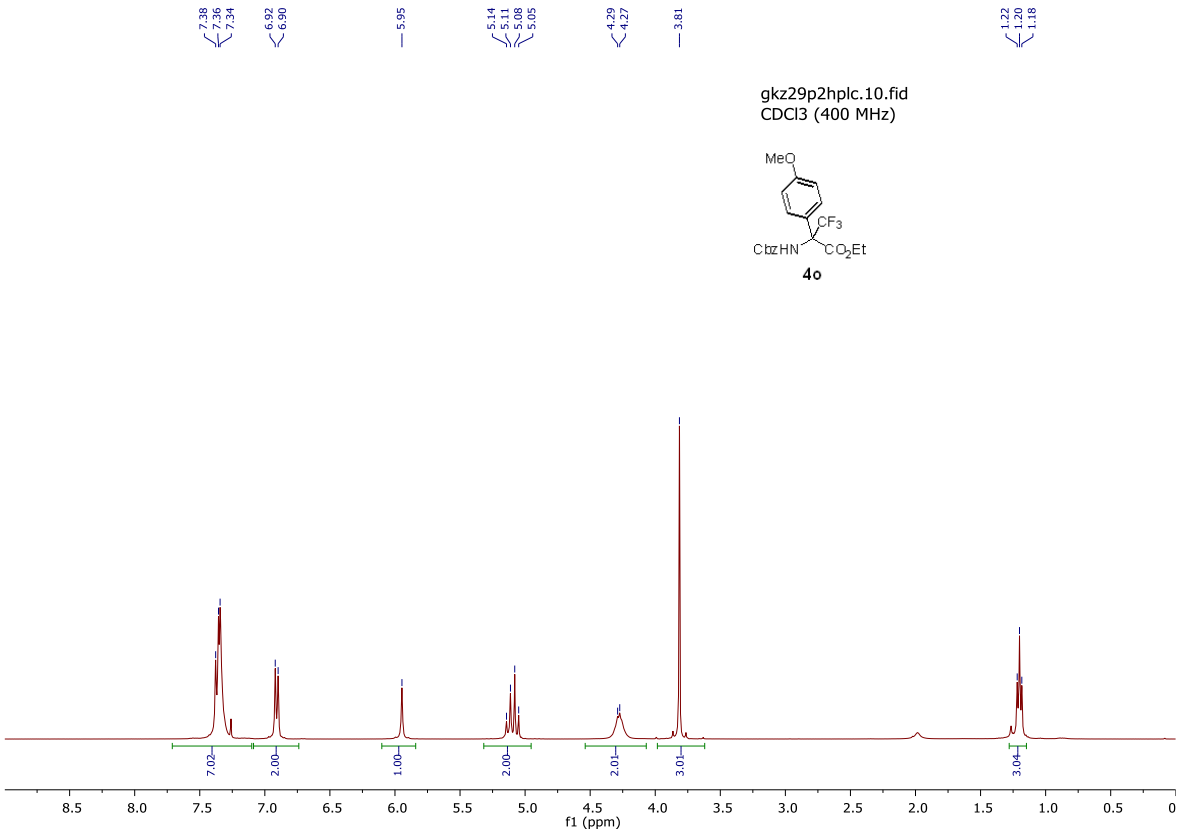
4n'

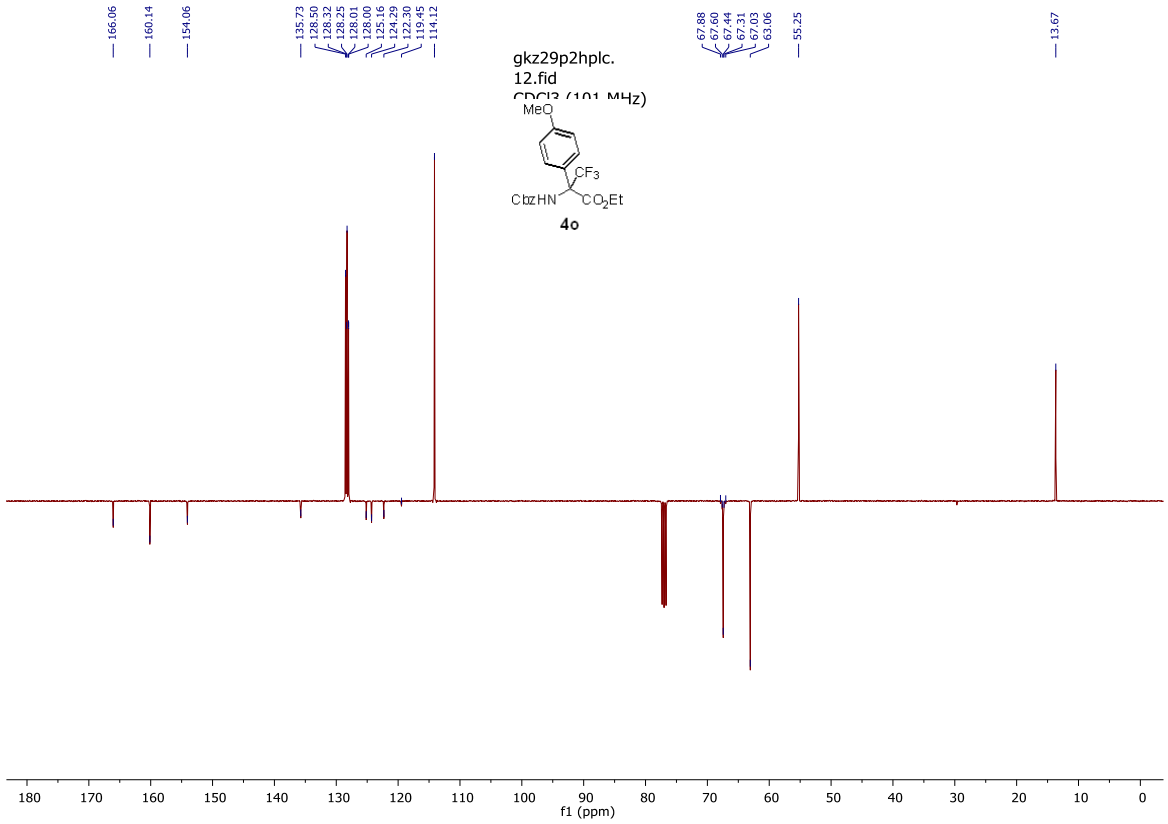


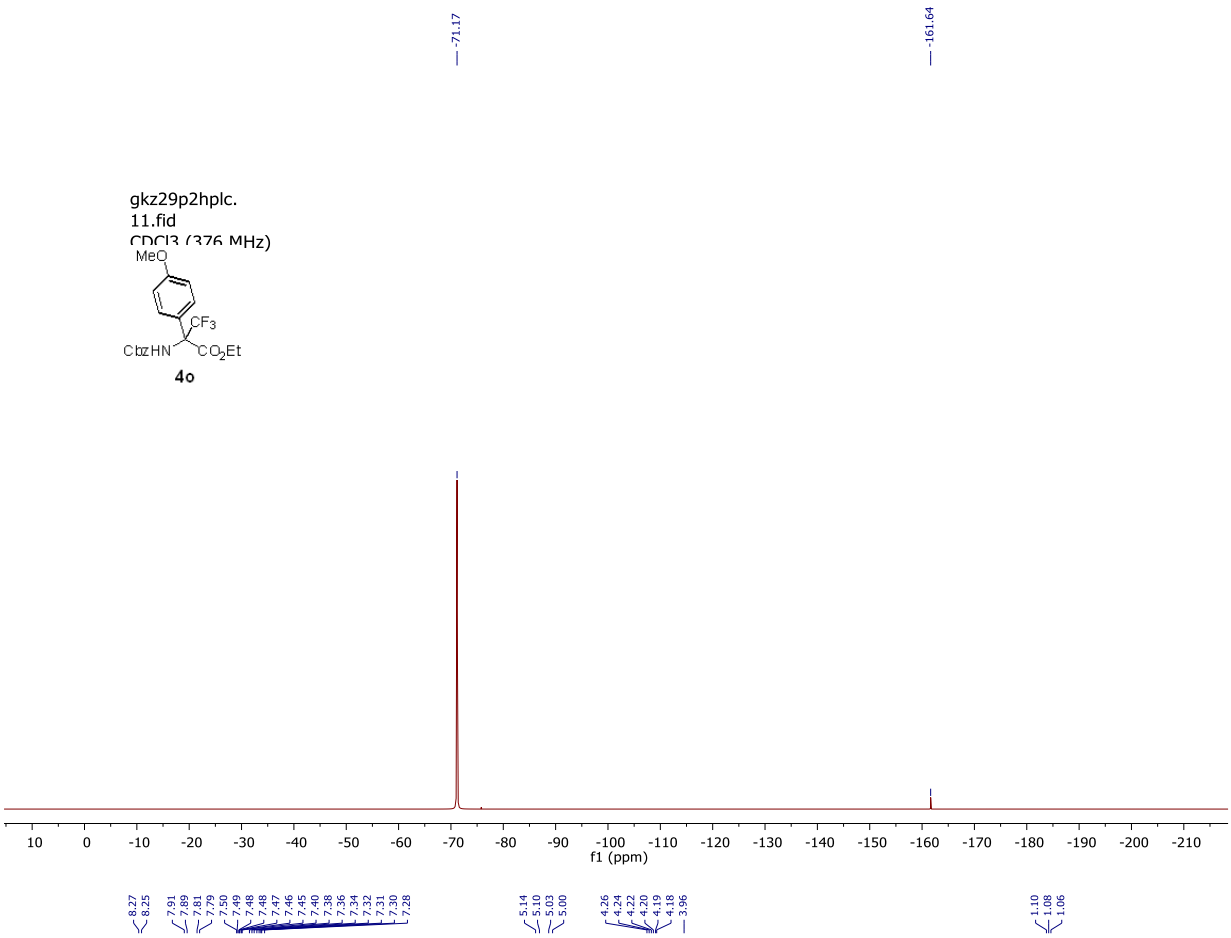
gkz31p3n3.11.fid
CDCl3 (376 MHz)

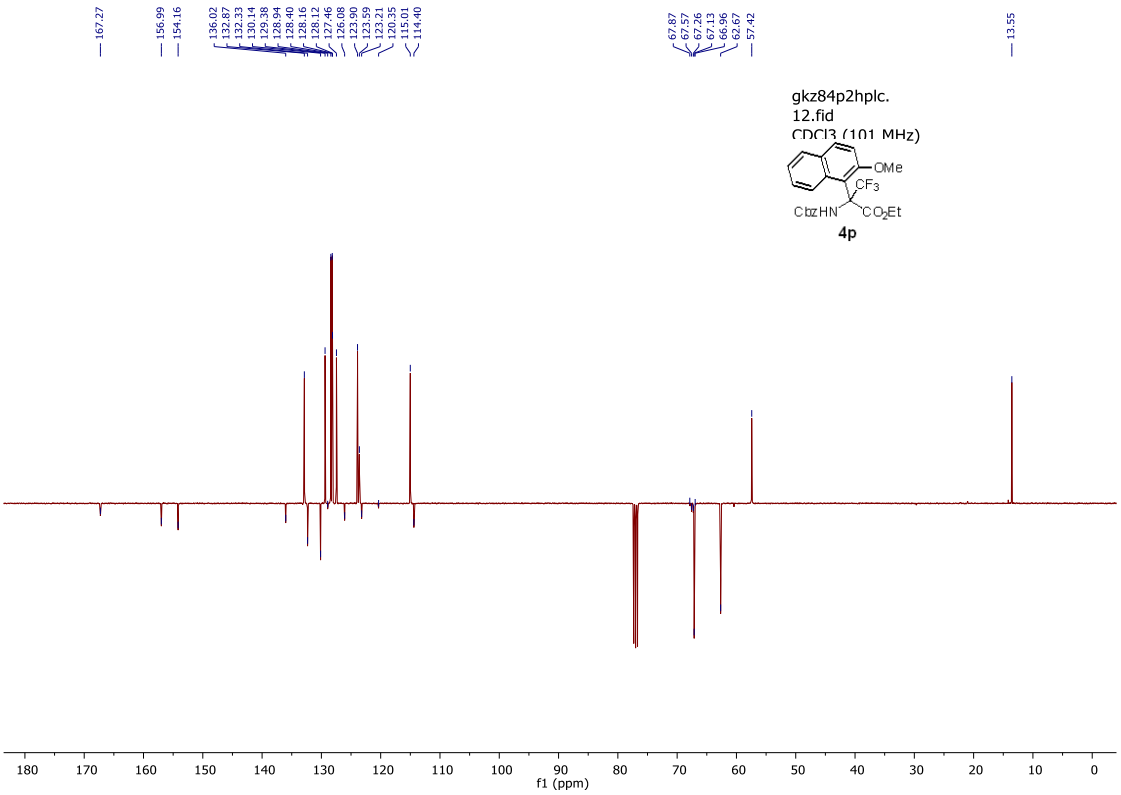


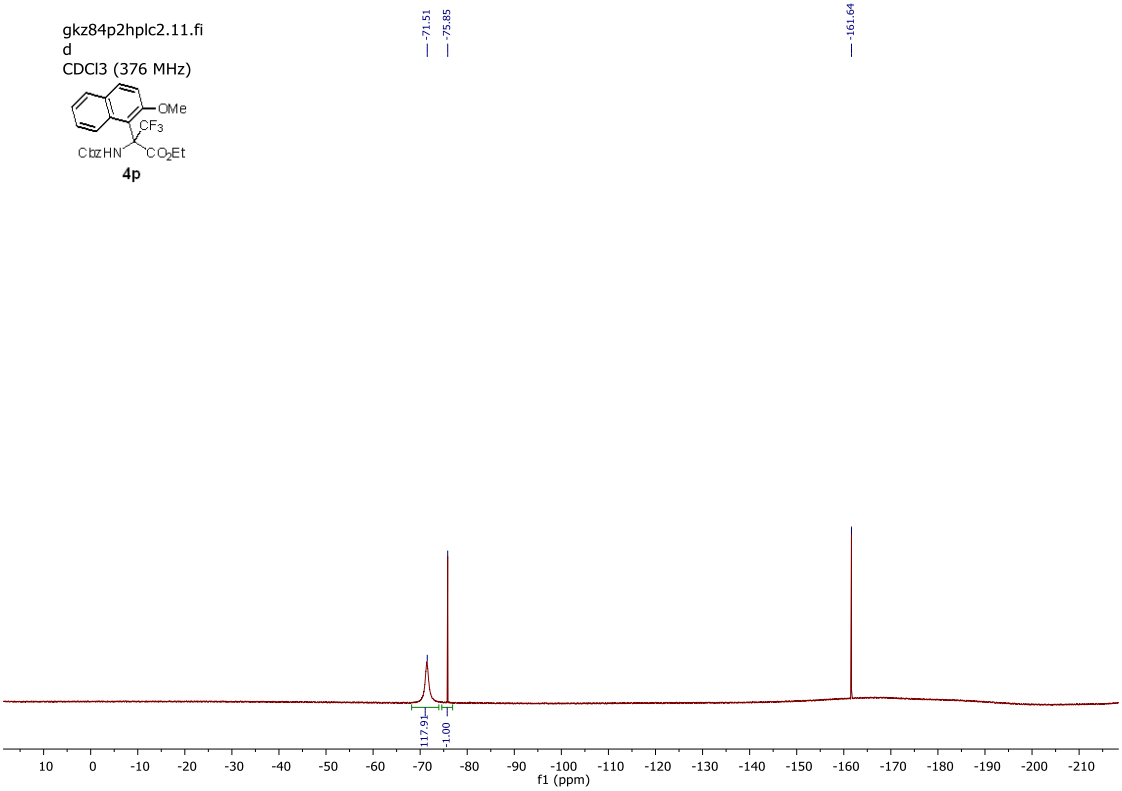
4n'


7.38
7.36
7.34
6.92
6.90
5.95
5.14
5.11
5.08
5.05
4.29
4.27
3.81
1.22
1.20
1.18
gkz29p2hplc.10.fid
CDCl3 (400 MHz)
MeO
CF3
CbzHN
CO2Et
4o
7.02
2.00
1.00
2.00
2.01
3.01
3.04
f1 (ppm)


166.06
160.14
154.06
135.73
128.50
128.32
128.25
128.01
128.00
125.16
124.29
122.30
119.45
114.12
67.88
67.60
67.44
67.31
67.03
63.06
55.25
13.67
gkz29p2hplc.
12.fid
MeO
CF3
CbzHN
CO2Et
4o
f1 (ppm)


-71.17
-161.64
gkz29p2hplc.
11.fid
CDCl3 (376 MHz)
MeO
CF3
CbzHN
CO2Et
4o
f1 (ppm)
gkz84p2hplc2.10.fi
d
CDCl3 (400 MHz)
OMe
CF3
CbzHN
CO2Et
4p
f1 (ppm)


167.27
156.99
154.16
136.02
132.87
132.33
130.14
129.38
128.94
128.40
128.16
128.12
127.46
126.08
123.90
123.59
123.21
120.35
115.01
114.40
67.87
67.57
67.26
67.13
66.96
62.67
57.42
13.55
gkz84p2hplc.
12.fid
CDCl3 (101 MHz)
OMe
CF3
CbzHN
CO2Et
4p
f1 (ppm)


gkz84p2hplc2.11.fi
d
CDCl3 (376 MHz)
OMe
CF3
CbzHN
CO2Et
4p
-71.51
-75.85
-161.64
117.91
1.00
f1 (ppm)