

## Synthesis of Chiral Bifunctional (Thio)Urea *N*-Heterocyclic Carbenes

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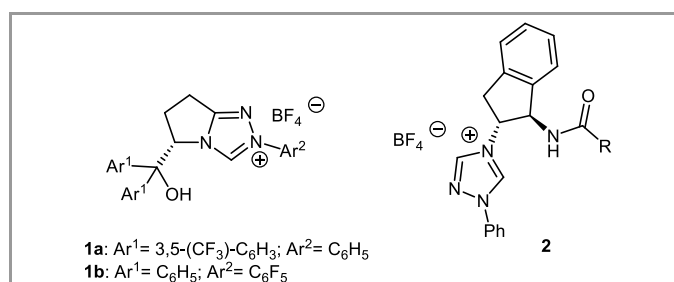
**Abstract:** The rapid and modular synthesis of the first bifunctional *N*-heterocyclic carbenes bearing a (thio)urea moiety as H-bond donor group was reported. Different analogues could be accessed in 7 steps from cheap (*S*)-pyroglutamic acid in good overall yields (14 to 30 %). The synthesized carbenes were active catalysts in the benzoin reaction.

**Key words:** Umpolung, asymmetric catalysis, carbenes, homogeneous catalysis, chiral pool.

The inversion of the inherent reactivity of molecules (*Umpolung*) is a powerful tool to increase the flexibility of complex molecule synthesis.<sup>1</sup> Nature uses *N*-heterocyclic carbene (NHC) for catalytic *Umpolung* through the coenzyme thiamine.<sup>2</sup> Synthetic *N*-heterocyclic carbenes have been highly efficient for catalytic asymmetric *Umpolung* reactions.<sup>3</sup> Despite the exploding interest in this field, intermolecular cross-condensation reactions remain challenging due to the competitive self-condensation of aldehydes (the benzoin reaction). For example, the asymmetric addition of acyl anion equivalents generated from *N*-heterocyclic carbenes and aldehydes on imines or Michael acceptors (the Stetter reaction) is still a difficult process, with only few successful reports.<sup>4</sup>

A selective activation of the electrophile could circumvent this limitation. The use of H-donor has been especially efficient for organocatalytic electrophilic activation.<sup>5</sup> Further development showed that the use of bifunctional catalysts can improve intermolecular processes through the activation of both reaction partners.<sup>6</sup>

In 2008, Ye reported a bifunctional *N*-heterocyclic carbene catalyst **1a** bearing an alcohol as H-bond donors for aza-Baylis-Hillman reactions (Figure 1).<sup>7</sup> Recently, Connon reported a bifunctional catalyst **2** based on an aminoindanol scaffold using an amide as H-bond donor.<sup>8</sup> Connon and Zeitler then showed that catalyst **1b** bearing a pentafluorophenyl group on the triazolium ring was highly efficient in the asymmetric benzoin reaction.<sup>9</sup> These first reports showed the potential of combining H-bonding with *N*-heterocyclic carbenes. Unfortunately, either yields and enantioselectivities were only moderate or the scope was limited to homo-condensation. The design of alternative structures is consequently required to develop more efficient and selective hetero-condensation reactions.



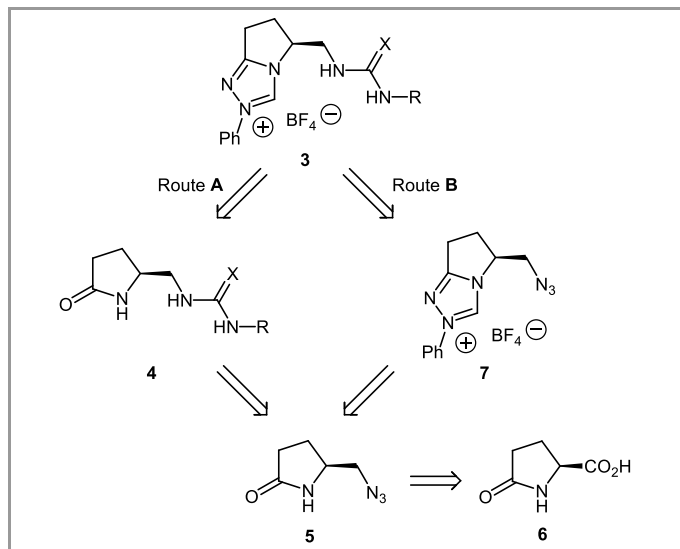
**Figure 1** Bifunctional catalysts designed by Ye and Connon

Surprisingly, (thio)ureas, which have been highly successful as H-bond donors in catalysis, have never been used in combination with *N*-heterocyclic carbenes for bifunctional activation. However, Scheidt reported a combination of urea catalysis together with the stoichiometric use of *N*-heterocyclic carbenes for the conjugate addition of preformed thiazolium carbinols to nitroalkenes.<sup>10</sup> We wish here to report a straightforward and modular synthesis of bifunctional *N*-heterocyclic carbene (thio)urea precatalysts as well as their primary evaluation in the benzoin reaction.

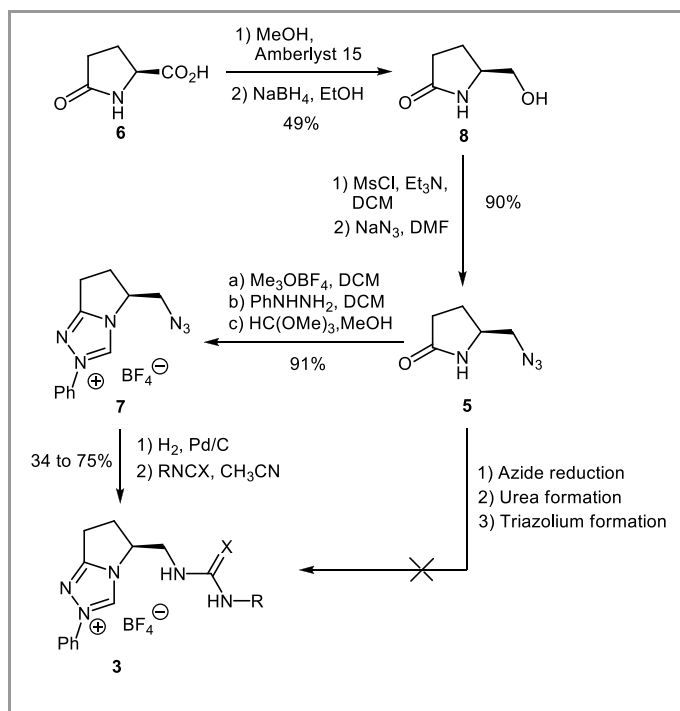
The main concern in the design of bifunctional *N*-heterocyclic carbene catalysts is the possible intramolecular self-quenching due to the presence of both the basic nucleophilic carbene and the acidic proton of the (thio)urea. To avoid this pitfall, triazolium precursors were chosen, as they lead to less basic *N*-heterocyclic carbene catalysts. Furthermore, the substituents on both the triazolium and the (thio)urea would allow tuning the acid-base properties. Since 13 years, numerous triazolium scaffolds have been successful.<sup>3</sup> Among them, the bicyclic structure based on pyroglutamic acid introduced by Leeper<sup>3b</sup> particularly attracted our interest, as it would allow a cheap and rapid access to the desired thio(urea) bifunctional catalysts **3** (Scheme 1).

A late stage introduction of diversity for both the triazolium and (thio)urea substituents is desirable in the synthesis, as these groups will play a crucial role for activity and stereoselectivity. Two strategies can be envisioned (Scheme 1). The precatalyst **3** can be obtained from the corresponding lactam **4**. Lactam **4** can be accessed from azide **5**, which is easily synthesized from pyroglutamic acid **6** (Route **A**).<sup>11</sup> Alternatively, precatalyst **3** can be obtained from the corresponding azide **7** by reduction and (thio)urea introduction. The triazolium will be formed from azidolactam **5** (Route **B**). The challenge of route **A** is to form the triazolium ring in pres-

ence of the (thio)urea group. The main challenges of route **B** are the reduction of the azide **7** in presence of the charged triazolium ring as well as the stability of the amine intermediate formed after reduction of the azide, which could attack intramolecularly the triazolium ring.



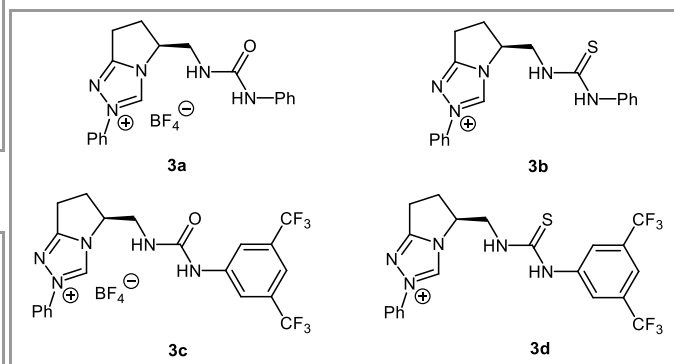
**Scheme 1** Retrosynthetic analysis for triazolium-(thio)ureas **3**



**Scheme 2** Synthesis of triazolium-thio(ureas) **3**

(*S*)-Pyroglutamic acid **6** was first converted in alcohol **8** via an esterification – reduction sequence on a 13 g scale without column chromatography (Scheme 2).<sup>11</sup> The alcohol was then mesylated and converted to azide **5** in high yield using a slightly modified reported procedure.<sup>11</sup> As preliminary investigations for the conversion of **5** into **3** using route **A** were not promising, we turned to synthesis strategy **B**. Triazolium **7** was formed in high yield using a procedure reported by Rovis.<sup>12</sup> A single

crystallization was sufficient for purification. Azide **7** was then reduced using Pd/C under hydrogen during one hour. Prolonged exposition to the reaction conditions led to the hydrogenation of the triazolium ring. Moreover, formation of the iminophosphorane intermediate with triphenylphosphine and direct transformation with phenylisocyanate into the urea was unsuccessful.<sup>13</sup> Noteworthy, the reduction of the azide failed if the triazolium was substituted with a pentafluorophenyl group. This was probably due to both triazolium ring hydrogenation as well as intramolecular attack of the amine on the triazolium, as both processes are expected to be accelerated in the presence of electron-withdrawing groups. Fortunately, these side-reactions were not observed with **7**. Triazolium-(thio)ureas **3** were finally obtained by reaction of the amines with the corresponding (thio)isocyanates. This last step allowed the easy generation of analogues (Figure 2).



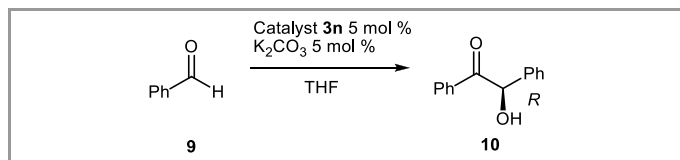
**Figure 2** Different triazolium-(thio)ureas synthesized

Once the precatalysts in hand, they were evaluated in the benzoin reaction. Activity in this reaction would show that the catalysts are not inhibited by intramolecular self-quenching. To our delight, benzoin product **10** was obtained when using triazolium **3a** with potassium carbonate in THF. On the other hand, running the reaction in toluene or dichloromethane did not afford any product. Triazolium-(thio)ureas **3a-c** gave good yields but only moderate enantioselectivities. Triazolium-thiourea **3d** gave benzoin product in low yield but very good enantioselectivity. Although the obtained yields and selectivities still need further improvement to reach the level of the best catalysts reported for asymmetric benzoin reactions, the observed activity constitutes an important proof of concept that a *N*-heterocyclic carbene and a (thio)urea can be combined in a single catalyst.

In this letter, we have reported the straightforward synthesis of (thio)urea bifunctional *N*-heterocyclic catalysts starting from cheap chiral pyroglutamic acid **6**. The main features of the synthesis were the triazolium ring formation in presence of the azide functionality and the selective reduction of the azide over the triazolium ring. The synthesis included a late stage introduction of diversity which allowed an easy access to diverse analogues. Four different triazolium (thio)ureas were synthesized in good overall yield (14% to 30%) over seven steps from (*S*)-pyroglutamic acid **6**. Alternatively the precatalysts

can be obtained from commercially available (*S*)-5-(hydroxymethyl)pyrrolidin-2-one **8** in five steps (overall yield: 28 to 61%).

**Table 1** Evaluation of triazolium-(thio)urea **3a-3d** in the benzoin reaction



Entry	Precatalyst	Yield (%) <sup>a</sup>	Ee (%)
1	<b>3a</b>	47	64
2	<b>3b</b>	81	60
3	<b>3c</b>	85	42
4	<b>3d</b>	17	90

<sup>a</sup>Reaction conditions: 1 mmol benzaldehyde, 5 mol % catalyst, 5 mol % K<sub>2</sub>CO<sub>3</sub> in THF (1 mL) at 23°C for 15 h.

The observed activity of the catalysts in the benzoin reaction demonstrated that the catalysts were stable toward intramolecular acid-base self-quenching. Thio(ureas) are known to activate electrophiles such as imines and nitroolefins stronger than simple carbonyl groups. Consequently, the synthesized catalysts would be expected to favor intermolecular reactions of aldehydes with such electrophiles over the homo-benzoin reaction. Investigations are currently undergoing toward this goal in our laboratory.

**(*S*)-5-(Azidomethyl)-2-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium tetrafluoroborate (**7**)**

(*S*)-5-(Azidomethyl)pyrrolidin-2-one (**5**) (1.00 g, 7.10 mmol, 1 equiv) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was added dropwise to a suspension of Me<sub>3</sub>OBF<sub>4</sub> (1.08 g, 7.10 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (35 ml). After 4.5 h, phenyl hydrazine (775 μl, 7.85 mmol, 1.1 equiv) was added to the colorless solution. After 3 h, the solution was reduced under vacuum. HC(OMe)<sub>3</sub> (14 ml) and MeOH (2 ml) were added under air. The reaction was stirred in a sealed tube at 80°C for 20 h. Once cooled, MeOH was added until precipitation and the resulting precipitate was collected by filtration. The mother liquors were concentrated under vacuum to half of the initial volume. The resulting precipitate was filtered. Both solids were combined and dried under vacuum to give a slightly brown solid (1.20 g). The mother liquors were concentrated under vacuum. The resulting oil was dissolved in CH<sub>3</sub>CN (10 ml) and slowly added to Et<sub>2</sub>O (150 ml). Filtration gave a slightly brown solid (986 mg). All solids were combined, dried in high vacuum to yield **7** (2.13 g, 6.48 mmol, 91%) as a slightly brown solid. R<sub>f</sub> 0.4 (DCM/MeOH, 9/1 UV). <sup>1</sup>H NMR (CD<sub>3</sub>CN) δ 9.81 (s, 1H, CH-triazolium), 7.84-7.78 (m, 2H, ArH), 7.67 (m, 3H, ArH), 4.91-4.82 (m, 1H, N-CH), 4.04 (dd, *J* = 13.2, 3.8 Hz, 1H, CH<sub>2</sub>-N<sub>3</sub>), 3.73 (dd, *J* = 13.2, 8.6 Hz, 1H, CH<sub>2</sub>-N<sub>3</sub>), 3.33-3.13 (m, 2H, CH<sub>2</sub>), 3.03-2.90 (m, 1H, CH<sub>2</sub>), 2.54 (m, 1H, CH<sub>2</sub>). <sup>13</sup>C NMR (CD<sub>3</sub>CN) δ 163.8, 138.1, 136.6, 131.9, 131.2, 122.2, 61.0, 53.3, 31.0, 22.2. IR (cm<sup>-1</sup>): 3123(w), 2115(s), 1586(m), 1519(w), 1468(w), 1446(w), 1392(w), 1292(m), 1227(m), 1034(s), 974(m), 916(w), 875(w), 771(s),

739(w), 711(m), 689(m), 671(w). HRMS(ESI) calcd for C<sub>12</sub>H<sub>13</sub>N<sub>6</sub><sup>+</sup> (M-BF<sub>4</sub>) 241.1202, found 241.1214.

**(*S*)-2-Phenyl-5-((3-phenylureido)methyl)-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium tetrafluoroborate (**3a**)**

Azide **7** (1.48 g, 4.50 mmol) was dissolved in MeOH (75 ml) under N<sub>2</sub>. Pd/C (148 mg) was then added. The flask was purged with H<sub>2</sub>. After 1 h under H<sub>2</sub> (3 atm), the reaction was filtered on a minimal quantity of celite and washed with MeOH (50 ml). Solvents were removed under vacuum to give the amine (1.34 g) as a yellow gum which was used without further purification. <sup>1</sup>H NMR (CD<sub>3</sub>CN) δ 9.88 (s, 1H, H-triazolium), 7.85-7.76 (m, 2H, ArH), 7.71-7.60 (m, 3H, ArH), 4.72 (m, 1H, NCH), 3.34-3.14 (m, 4H, CH<sub>2</sub> + NCH<sub>2</sub>), 3.01-2.87 (m, 2H, CH<sub>2</sub>), 2.62-2.36 (m, 3H, CH<sub>2</sub> + NH<sub>2</sub> + H<sub>2</sub>O).

Phenylisocyanate (240 μl, 2.20 mmol, 1 equiv) was added to a stirring solution of the amine (667 mg, 2.20 mmol, 1 equiv) in CH<sub>3</sub>CN (7.5 ml). The reaction was stirred at RT overnight. Solvents were removed under vacuum. The crude mixture was purified by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90/10) to give **3a** (706 mg, 1.68 mmol, 75% over two steps) as a slightly yellow solid. <sup>1</sup>H NMR (CD<sub>3</sub>CN) δ 9.81 (s, 1H, CH-triazolium), 7.79-7.74 (m, 2H, ArH), 7.66-7.61 (m, 3H, ArH), 7.45 (s, 1H, NH), 7.36 (dd, *J* = 9.0, 1.5 Hz, 2H, ArH), 7.23 (m, 2H, ArH), 6.97 (m, 1H, ArH), 5.77 (br t, *J* = 6.0 Hz, 1H, NH), 4.93 (m, 1H, NCH), 3.88-3.80 (m, 1H, NCH<sub>2</sub>), 3.52-3.41 (m, 1H, NCH<sub>2</sub>), 3.32-3.12 (m, 2H, CH<sub>2</sub>), 3.00-2.89 (m, 1H, CH<sub>2</sub>), 2.66-2.53 (m, 1H, CH<sub>2</sub>). <sup>13</sup>C NMR (CD<sub>3</sub>CN) δ 163.0, 155.7, 139.7, 137.5, 135.7, 130.9, 130.3, 128.8, 122.3, 121.3, 118.6, 61.5, 42.1, 30.1, 21.3. IR (cm<sup>-1</sup>): 3403 (w), 3133 (w), 1685 (m, 1597 (s), 1547 (s), 1500 (m), 1442 (m), 1394 (m), 1315 (w), 1229 (m), 1061 (s), 763 (s), 694 (m). HRMS(ESI) calcd for C<sub>19</sub>H<sub>20</sub>N<sub>5</sub>O<sup>+</sup> (M-BF<sub>4</sub>) 334.1668, found 334.1661.

**Supporting Information** for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

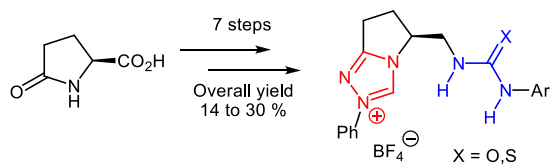
**Acknowledgment**

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**Chiral Bifunctional (Thio)Urea *N*-Heterocyclic Carbenes**

## Supporting information

### Synthesis of Chiral Bifunctional (Thio)Urea *N*-Heterocyclic Carbenes

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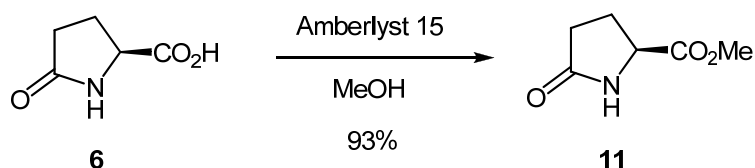
1. General Methods	S2
2. (Thio)Urea <i>N</i> -Heterocyclic Carbenes Synthesis	S3
3. Benzoin Reaction	S7
4. Spectra of New compounds	S8

## I. General Methods

All reactions were carried out in oven dried glassware under an atmosphere of nitrogen, unless stated otherwise. For quantitative flash chromatography technical grade solvents were used. For flash chromatography for analysis, HPLC grade solvents from Sigma-Aldrich were used. THF, Et<sub>2</sub>O, CH<sub>3</sub>CN, toluene, hexane and CH<sub>2</sub>Cl<sub>2</sub> were dried by passage over activated alumina under nitrogen atmosphere (H<sub>2</sub>O content < 10 ppm, *Karl-Fischer* titration). All chemicals and solvents were purchased from Acros, Aldrich, Fluka, VWR, Aplichem or Merck and used as such unless stated otherwise. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar pressure. TLC was performed on Merck silica gel 60 F<sub>254</sub> TLC glass plates or aluminium plates and visualized with UV light, permanganate stain, CAN stain, Ninhydrine or Anisaldehyde stain. Melting points were measured on a Büchi B-540 melting point apparatus using open glass capillaries, the data is uncorrected. <sup>1</sup>H-NMR spectra were recorded on a Bruker DPX-400 400 MHz spectrometer in chloroform-d, CD<sub>3</sub>CN, DMSO-d<sub>6</sub> or CD<sub>3</sub>OD, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal CD<sub>3</sub>CN signal at 1.94 ppm, the internal DMSO signal at 2.50 ppm or the internal methanol signal at 3.30 ppm as standard. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, app = apparent, coupling constant(s) in Hz, integration; interpretation). <sup>13</sup>C-NMR spectra were recorded with <sup>1</sup>H-decoupling on a Bruker DPX-400 100 MHz spectrometer in chloroform-d, CD<sub>3</sub>CN, DMSO-d<sub>6</sub> or CD<sub>3</sub>OD, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm, the internal CD<sub>3</sub>CN signal at 118.3 ppm, the internal DMSO signal at 39.5 ppm or the internal methanol signal at 49.0 ppm as standard. Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm<sup>-1</sup> (w = weak, m = medium, s = strong, br = broad). Gas chromatographic and low resolution mass spectrometric measurements were performed on a Perkin-Elmer Clarus 600 gas chromatographer and mass spectrometer using a Perkin-Elmer Elite fused silica column (length: 30 m, diameter: 0.32 mm) and Helium as carrier gas. High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API. HPLC measurement were done on a JASCO HPLC system with an AS2055 Autosampler, a PU 2089 Pump, a UV 2075 detector and a SEDEX 85 (SEDERE) detector using a CHIRALPAK IC column from DAICEL Chemical Industries Ltd. HPLC grade solvents from Sigma-Aldrich were used.

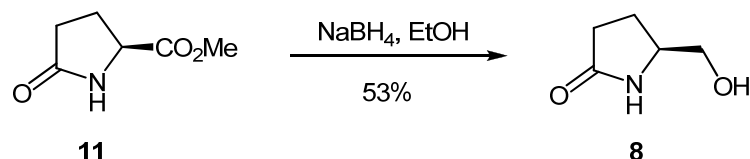
## II. (Thio)Urea *N*-Heterocyclic Carbenes Synthesis

### (*S*)-Methyl 5-oxopyrrolidine-2-carboxylate (**11**)



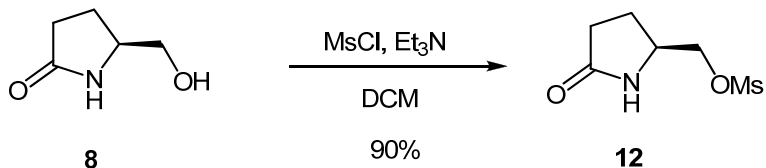
Following the reported method,<sup>1</sup> Amberlyst 15 (11.4 g) was added to a suspension of (*S*)-(-)-Pyrrolidone-5-carboxylic acid (**6**) (30.0g, 0.230 mol) in MeOH (150 mL) under air. The mixture was stirred overnight at reflux. After cooling, the mixture was filtered, the resin washed with MeOH and the solution was concentrated under vacuum to yield **11** (30.8 g, 0.215 mol, 93%) as a yellow oil.  $R_f$  0.28 (EtOAc, KMnO<sub>4</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.12-6.62 (br m, 1 H, NH), 4.25 (m, 1 H, CH), 3.74 (s, 3 H, CH<sub>3</sub>), 2.55-2.12 (m, 4 H, CH<sub>2</sub>). <sup>1</sup>H NMR spectra corresponded to the literature values.<sup>1</sup>

### (*S*)-5-(Hydroxymethyl)pyrrolidin-2-one (**8**)



NaBH<sub>4</sub> (8.13 g, 0.215 mol, 1 equiv) was added portionwise to a stirring solution of the ester **11** (30.8 g, 0.215 mol, 1 equiv) in EtOH (250 ml) at 0°C. The mixture was allowed to warm up to room temperature overnight. The reaction was then quenched dropwise at 0°C using concentrated HCl (15 ml). After filtration and concentration under vacuum, the oil crystallized at 0°C. The solid was then recrystallized in EtOAc (400 ml). After hot filtration, slow cooling down up to 0°C lead to crystallization. The mixture was filtered; the crystals were dried under vacuum to yield **8** (13.2 g, 0.115 mol, 53%) as colorless crystals.  $R_f$  0.70 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9/1, KMnO<sub>4</sub>). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.41 (s, 1 H, NH), 4.37 (s, 1 H, OH), 3.79 (m, 1 H, CH), 3.66 (d,  $J$  = 11.0 Hz, 1 H, CH<sub>2</sub>O), 3.44 (m, 1 H, CH<sub>2</sub>O), 2.42-2.26 (m, 2 H, CH<sub>2</sub>), 2.21-2.09 (m, 1 H, CH<sub>2</sub>), 1.85-1.71 (m, 1 H, CH<sub>2</sub>). <sup>1</sup>H NMR spectra corresponded to the literature values.<sup>1</sup>

### (*S*)-(5-Oxopyrrolidin-2-yl)methyl methanesulfonate (**12**)



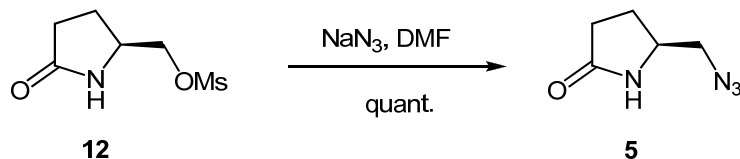
Following the reported procedure,<sup>1</sup> Et<sub>3</sub>N (9.4 ml, 67 mmol, 2 equiv) was added to a stirring solution of (*S*)-5-(hydroxymethyl)pyrrolidin-2-one (**11**) (4.0 g, 34 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (45 ml) at 0°C. MsCl (3.9 ml, 50 mmol, 1.5 equiv) was added dropwise over 10 min. After 1.5 h at 0°C, the reaction was quenched

<sup>1</sup> Bateman, L.; Breeden, S. W.; O'Leary, P., *Tetrahedron Asymmetry* **2008**, *19*, 391.



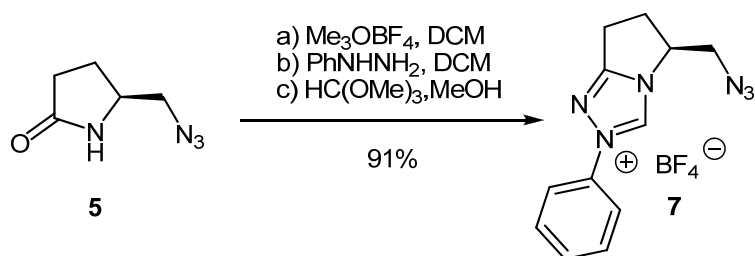
with 1 ml of distilled water. The mixture was concentrated under vacuum. The crude mixture was purified by flash column chromatography (AcOEt/MeOH 9/1) to yield mesylate **12** (5.9 g, 30 mmol, 90%) as a yellow oil.  $R_f$  0.30 (AcOEt/MeOH 9/1,  $\text{KMnO}_4$ ).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  6.34 (m, 1 H, NH), 4.26 (dd,  $J = 9.9$ , 3.5 Hz, 1 H,  $\text{CH}_2\text{O}$ ), 4.08 (m, 1 H,  $\text{CH}_2\text{O}$ ), 4.01 (m, 1 H, CH), 3.07 (s, 3 H,  $\text{CH}_3$ ), 2.48-2.23 (m, 3 H,  $\text{CH}_2$ ), 1.92-1.81 (m, 1 H,  $\text{CH}_2$ ).

**(S)-5-(Azidomethyl)pyrrolidin-2-one (5)**



Following a slight modification of a reported procedure,<sup>1</sup>  $\text{NaN}_3$  (5.1 g, 78 mmol, 2 equiv) was added to a solution of (S)-5-(5-oxopyrrolidin-2-yl)methyl methanesulfonate (**12**) (7.5 g, 39 mmol, 1 equiv) in DMF (45 ml). The reaction was stirred at 85°C for 15 h. The suspension was filtered and washed with EtOAc. The mother liquor was concentrated under reduced pressure with toluene. The crude mixture was purified by flash column chromatography (AcOEt/MeOH 95/5) to yield **5** (5.6 g, 39 mmol, quant.) as a yellow oil.  $R_f$  0.51 (AcOEt/MeOH 9/1, Anisaldehyde).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.57 (s, 1 H, NH), 3.79 (m, 1 H, CH), 3.41 (dd,  $J = 12.0$ , 4.5 Hz, 1 H,  $\text{CH}_2\text{N}_3$ ), 3.26 (dd,  $J = 12.0$ , 6.0 Hz, 1 H,  $\text{CH}_2$ ), 2.44-2.13 (m, 3 H,  $\text{CH}_2$ ), 1.84-1.72 (m, 1 H,  $\text{CH}_2$ ).  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  178.5, 55.9, 53.5, 29.7, 24.0. IR ( $\text{cm}^{-1}$ ): 3231(w), 2928(w), 2097(s), 1683(s), 1462(w), 1423(w), 1264(s), 651(m). HRMS (ESI-TOF) calcd for  $\text{C}_5\text{H}_8\text{N}_4\text{O}^+$  (M+H) 141.0776, found 141.0782. All values corresponded to the literature values.<sup>1</sup>

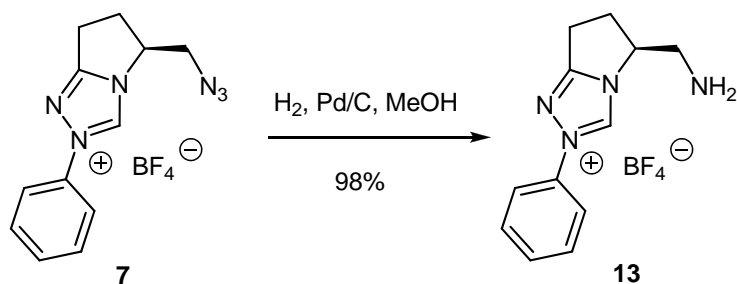
**(S)-5-(Azidomethyl)-2-phenyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (7)**



(S)-5-(Azidomethyl)pyrrolidin-2-one (**5**) (1.00 g, 7.10 mmol, 1 equiv) dissolved in  $\text{CH}_2\text{Cl}_2$  (5 ml) was added dropwise to a suspension of  $\text{Me}_3\text{OBF}_4$  (1.08 g, 7.10 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (35 ml). After 4.5 h, phenyl hydrazine (775  $\mu\text{l}$ , 7.85 mmol, 1.1 equiv) was added to the colorless solution. After 3 h, the solution was reduced under vacuum.  $\text{HC(OMe)}_3$  (14 ml) and MeOH (2 ml) were added under air. The reaction was stirred in a sealed tube at 80°C for 20 h. Once cooled, MeOH was added until precipitation and the resulting precipitate was collected by filtration. The mother liquors were concentrated under vacuum to half of the initial volume. The resulting precipitate was filtered. Both solids were combined and dried under vacuum to give a slightly brown solid (1.20 g.). The mother liquors were concentrated under vacuum. The resulting oil was dissolved in  $\text{CH}_3\text{CN}$  (10 ml) and slowly added to  $\text{Et}_2\text{O}$  (150 ml). Filtration gave a slightly brown solid (986 mg). All solids were combined, dried in high vacuum to yield **7** (2.13 g, 6.48 mmol, 91%) as a slightly brown solid.  $R_f$  0.4 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 9/1 UV).  $^1\text{H NMR}$  ( $\text{CD}_3\text{CN}$ )  $\delta$  9.81 (s, 1H, CH-triazolium), 7.84-7.78 (m, 2 H, ArH), 7.67 (m, 3 H, ArH), 4.91-4.82 (m, 1 H, N-CH), 4.04 (dd,  $J = 13.2$ , 3.8 Hz, 1 H,  $\text{CH}_2\text{-N}_3$ ), 3.73 (dd,  $J = 13.2$ , 8.6 Hz, 1 H,  $\text{CH}_2\text{-N}_3$ ), 3.33-3.13 (m, 2 H,  $\text{CH}_2$ ), 3.03-2.90 (m, 1 H,  $\text{CH}_2$ ), 2.54 (m, 1 H,  $\text{CH}_2$ ).  $^{13}\text{C NMR}$  ( $\text{CD}_3\text{CN}$ )  $\delta$  163.8, 138.1, 136.6, 131.9, 131.2, 122.2, 61.0, 53.3, 31.0, 22.2. IR ( $\text{cm}^{-1}$ ):

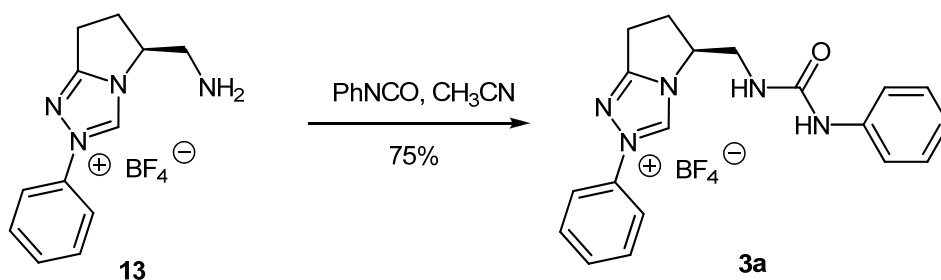
3123(w), 2115(s), 1586(m), 1519(w), 1468(w), 1446(w), 1392(w), 1292(m), 1227(m), 1034(s), 974(m), 916(w), 875(w), 771(s), 739(w), 711(m), 689(m), 671(w). HRMS(ESI) calcd for  $C_{12}H_{13}N_6^+$  (M-BF<sub>4</sub>) 241.1202, found 241.1214.

**(S)-5-(Aminomethyl)-2-phenyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (13)**



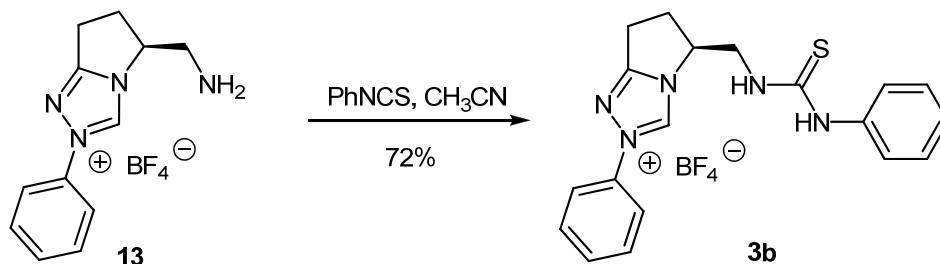
Azide **7** (1.48 g, 4.50 mmol) was dissolved in MeOH (75 ml) under N<sub>2</sub>. Pd/C (148 mg) was then added. The flask was purged with H<sub>2</sub>. After 1 h under H<sub>2</sub> (3 atm), the reaction was filtered on a minimal quantity of celite and washed with MeOH (50 ml). Solvents were removed under vacuum to give the amine **13** (1.34 g) as a yellow gum which was used without further purification. <sup>1</sup>H NMR (CD<sub>3</sub>CN) δ 9.88 (s, 1 H, H-triazolium), 7.85-7.76 (m, 2 H, ArH), 7.71-7.60 (m, 3 H, ArH), 4.72 (m, 1 H, NCH), 3.34-3.14 (m, 4 H, CH<sub>2</sub> + NCH<sub>2</sub>), 3.01-2.87 (m, 2 H, CH<sub>2</sub>), 2.62-2.36 (m, 3 H, CH<sub>2</sub> + NH<sub>2</sub> + H<sub>2</sub>O).

**(S)-2-Phenyl-5-((3-phenylureido)methyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (3a)**



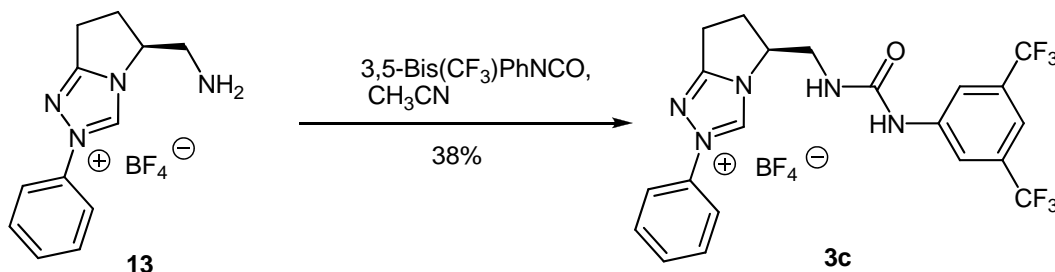
Phenylisocyanate (240 μl, 2.20 mmol, 1 equiv) was added to a stirring solution of the amine **13** (667 mg, 2.20 mmol, 1 equiv) in CH<sub>3</sub>CN (7.5 ml). The reaction was stirred at RT overnight. Solvents were removed under vacuum. The crude mixture was purified by flash column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90/10) to give **3a** (706 mg, 1.68 mmol, 75% over two steps) as a slightly yellow solid. <sup>1</sup>H NMR (CD<sub>3</sub>CN) δ 9.81 (s, 1 H, CH-triazolium), 7.79-7.74 (m, 2 H, ArH), 7.66-7.61 (m, 3 H, ArH), 7.45 (s, 1 H, NH), 7.36 (dd, *J* = 9.0, 1.5 Hz, 2 H, ArH), 7.23 (m, 2 H, ArH), 6.97 (m, 1 H, ArH), 5.77 (br t, *J* = 6.0 Hz, 1 H, NH), 4.93 (m, 1 H, NCH), 3.88-3.80 (m, 1 H, NCH<sub>2</sub>), 3.52-3.41 (m, 1 H, NCH<sub>2</sub>), 3.32-3.12 (m, 2 H, CH<sub>2</sub>), 3.00-2.89 (m, 1 H, CH<sub>2</sub>), 2.66-2.53 (m, 1 H, CH<sub>2</sub>). <sup>13</sup>C NMR (CD<sub>3</sub>CN) δ 163.0, 155.7, 139.7, 137.5, 135.7, 130.9, 130.3, 128.8, 122.3, 121.3, 118.6, 61.5, 42.1, 30.1, 21.3. IR (cm<sup>-1</sup>): 3403 (w), 3133 (w), 1685 (m), 1597 (s), 1547 (s), 1500 (m), 1442 (m), 1394 (m), 1315 (w), 1229 (m), 1061 (s), 763 (s), 694 (m). HRMS(ESI) calcd for  $C_{19}H_{20}N_5O^+$  (M-BF<sub>4</sub>) 334.1668, found 334.1661.

**(S)-2-Phenyl-5-((3-phenylthioureido)methyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (3b)**



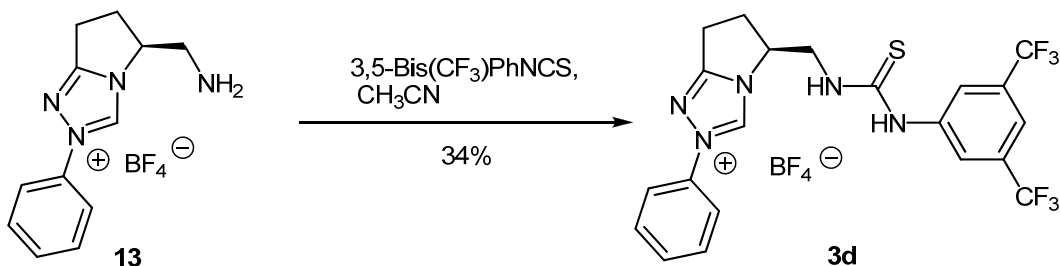
Phenylthioisocyanate (263  $\mu$ l, 2.20 mmol, 1 equiv) was added to a stirring solution of amine **13** (667 mg, 2.20 mmol, 1 equiv) in  $\text{CH}_3\text{CN}$  (7.5 ml). The reaction was stirred at RT overnight. Solvents were removed under vacuum. The crude mixture was purified by flash column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  90/10) to give **3b** (700 mg, 1.60 mmol, 72% over two steps) as a slightly yellow solid.  $^1\text{H}$  NMR ( $\text{CD}_3\text{CN}$ )  $\delta$  9.77 (s, 1 H, CH-triazolium), 8.49 (br s, 1 H, NH), 7.80-7.73 (m, 2 H, ArH), 7.68-7.61 (m, 3 H, ArH), 7.43-7.33 (m, 4 H, ArH), 7.28-7.22 (m, 1 H, ArH), 7.01 (br m, 1 H, NH), 5.09 (m, 1 H, CH-N), 4.15 (m, 1 H,  $\text{CH}_2\text{-NH}$ ), 4.02 (m, 1 H,  $\text{CH}_2\text{-NH}$ ), 3.34-3.14 (m, 2 H,  $\text{CH}_2$ ), 3.01-2.88 (m, 1 H,  $\text{CH}_2$ ), 2.62 (m, 1 H,  $\text{CH}_2$ ).  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{CN}$ )  $\delta$  183.8, 163.8, 138.5, 138.3, 136.6, 131.8, 131.2, 130.2, 127.3, 126.2, 122.2, 61.4, 47.0, 31.1, 22.0. IR ( $\text{cm}^{-1}$ ): 3361 (w), 3135(w), 3067(w), 1592(m), 1531(s), 1498(m), 1393(w), 1353(w), 1316(m), 1263(w), 1222(w), 1055(s), 764(m), 708(m), 689(m), 627(w). HRMS(ESI) calcd for  $\text{C}_{19}\text{H}_{20}\text{N}_5\text{O}^+$  (M- $\text{BF}_4$ ) 350.1440, found 350.1443.

**(S)-5-((3-(3,5-Bis(trifluoromethyl)phenyl)ureido)methyl)-2-phenyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (3c)**



3,5-Bis( $\text{CF}_3$ )-phenylisocyanate (143  $\mu$ l, 0.830 mmol, 1 equiv) was added to a stirring solution of the amine **13** (250 mg, 0.830 mmol, 1 equiv) in  $\text{CH}_3\text{CN}$  (2.5 ml). The reaction was stirred at RT overnight. Solvents were removed under vacuum. The resulting solid was triturated in  $\text{CH}_2\text{Cl}_2$ , filtered and solvent were removed under vacuum to give **3c** (182 mg, 0.330 mmol, 38% over two steps) as a white solid.  $R_f$  0.3 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 9/1 UV).  $^1\text{H}$  NMR ( $\text{CD}_3\text{CN}$ )  $\delta$  9.77 (s, 1 H, CH-triazolium), 7.97 (s, 2 H, ArH), 7.89 (s, 1 H, ArH), 7.78-7.71 (m, 2 H, ArH), 7.63-7.62 (m, 3 H, ArH), 7.56 (br s, NH), 5.92 (br t,  $J = 5.1$  Hz, 1 H, NH), 4.96 (m, 1 H, NCH), 3.87 (ddd,  $J = 15.0, 5.8, 3.8$  Hz, 1 H, N $\text{CH}_2$ ), 3.51 (dt,  $J = 15.0, 6.7$  Hz, 1 H, N $\text{CH}_2$ ), 3.24 (m, 2 H,  $\text{CH}_2$ ), 2.96 (m, 1 H,  $\text{CH}_2$ ), 2.62 (m, 1 H,  $\text{CH}_2$ ).  $^{13}\text{C}$  NMR ( $\text{CD}_3\text{CN}$ )  $\delta$  163.3, 155.6, 142.0, 137.7, 135.9, 131.4 (q,  $J = 33$  Hz), 131.2, 130.5, 123.5(q,  $J = 272$  Hz), 121.5, 118.0 (q,  $J = 4$  Hz), 115.2 (m), 61.5, 42.4, 30.3, 21.5. IR ( $\text{cm}^{-1}$ ): 3403(w), 2107(w), 1703(w), 1568(m), 1475(w), 1443(w), 1389(m), 1279(s), 1230(w), 1183(m), 1130(s), 1062(m), 884(w), 765(w), 741(w), 704(w), 684(w). HRMS(ESI) calcd for  $\text{C}_{21}\text{H}_{18}\text{F}_6\text{N}_5\text{O}^+$  (M- $\text{BF}_4$ ) 470.1415, found 470.1431.

**(S)-5-((3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)methyl)-2-phenyl-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (3d)**



3,5-Bis(CF<sub>3</sub>)-phenylthioisocyanate (127  $\mu$ l, 0.700 mmol, 1 equiv.) was added to solution of the amine **13** (210 mg, 0.700 mmol, 1 equiv) in CH<sub>3</sub>CN (2.5 ml). The reaction was stirred at RT overnight. Solvents were removed under vacuum. The resulting solid was triturated in CH<sub>2</sub>Cl<sub>2</sub>, filtered and solvent were removed under vacuum to give **3d** (106 mg, 0.180 mmol, 26% over two steps) as a white solid. The mother liquors were concentrated under vacuum. The resulting solid was triturated in CH<sub>2</sub>Cl<sub>2</sub>, filtered and solvents were removed under vacuum to give **3d** (31 mg, 0.050 mmol, 8% over two steps) as a white solid. R<sub>f</sub> 0.4 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 9/1 UV). <sup>1</sup>H NMR (CD<sub>3</sub>CN)  $\delta$  9.80 (s, 1 H, CH-triazolium), 8.79 (br s, 1 H, NH), 8.13 (s, 2 H, ArH), 7.77 (m, 3 H, ArH), 7.64 (m, 3 H, ArH), 7.33 (br t,  $J = 5.5$  Hz, 1 H, NH), 5.15 (m, 1 H, NCH), 4.19 (m, 1 H, NCH<sub>2</sub>), 4.08 (m, 1 H, NCH<sub>2</sub>), 3.27 (m, 2 H, CH<sub>2</sub>), 3.00 (m, 1 H, CH<sub>2</sub>), 2.65 (m, 1 H, CH<sub>2</sub>). <sup>13</sup>C NMR (CD<sub>3</sub>CN)  $\delta$  183.0, 162.9, 140.6, 137.2, 135.5, 131.2 (q,  $J = 33$  Hz), 130.8, 130.1, 124.1 (m), 123.4 (q,  $J = 271$  Hz), 121.1, 118.2 (m), 60.2, 45.8, 30.1, 21.0. IR (cm<sup>-1</sup>): 3361(w), 3125(w), 2114(w), 1592(w), 1542(w), 1474(w), 1384(m), 1278(s), 1179(m), 1133(s), 1055(m), 888(w), 764(w), 684(w). HRMS(ESI) calcd for C<sub>21</sub>H<sub>18</sub>F<sub>6</sub>N<sub>5</sub>S<sup>+</sup> (M-BF<sub>4</sub>) 486.1187, found 486.1198.

### III. Benzoin reaction

*General procedure:* Dry K<sub>2</sub>CO<sub>3</sub> (7 mg, 0.05 mmol, 0.05 equiv) was added to precatalyst **3n** (0.05 mmol, 0.05 equiv) and distilled benzaldehyde (101  $\mu$ l, 1.00 mmol, 1 equiv) in dry THF (1 mL). The reaction was sealed and stirred at 23°C for 15 h. The reaction was then diluted in Et<sub>2</sub>O (15 ml) and water (15 ml). After layer separation, the aqueous layer was extracted with Et<sub>2</sub>O (15 mL). The organic layers were combined, washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuum. The resulting yellow oil was purified by column chromatography (PET/EtOAc, 4/1) to afford the benzoin product **10**. R<sub>f</sub> 0.2 (PET/EtOAc, 4/1 UV). <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.94 (dm,  $J = 8.2$  Hz, 2 H, Ar H), 7.55 (tm,  $J = 7.2$  Hz, 1 H, Ar H), 7.42 (tm,  $J = 7.6$  Hz, 2 H, Ar H), 7.29-7.37 (m, 5 H, Ar H), 5.98 (m, 1 H, CHO), 4.58 (br s, 1 H, OH). The <sup>1</sup>H NMR was consistent with the reported values.<sup>2</sup>

HPLC analysis: Daicel Chiralpack IC column; 20°C; 0 to 20 min: 1 ml/min, 20 min to 30 min 1 to 0.7 ml/min; solvent system: <sup>i</sup>PrOH/hexanes, 0 to 5 min 5/95, 5 to 10 min 5/95 to 10/90, 10 to 20 min 10/90, 20 min to 30 min 10/90 to 40/60; major peak: 18.5 min, minor peak 21.4 min.

**3a:** (50 mg, 0.24 mmol, 47%), *ee*: 64%. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = -64.6 (c = 0.8 in MeOH). Consistent with reported value.<sup>2</sup>

**3b:** (86 mg, 0.41 mmol, 81%), *ee*: 60%.

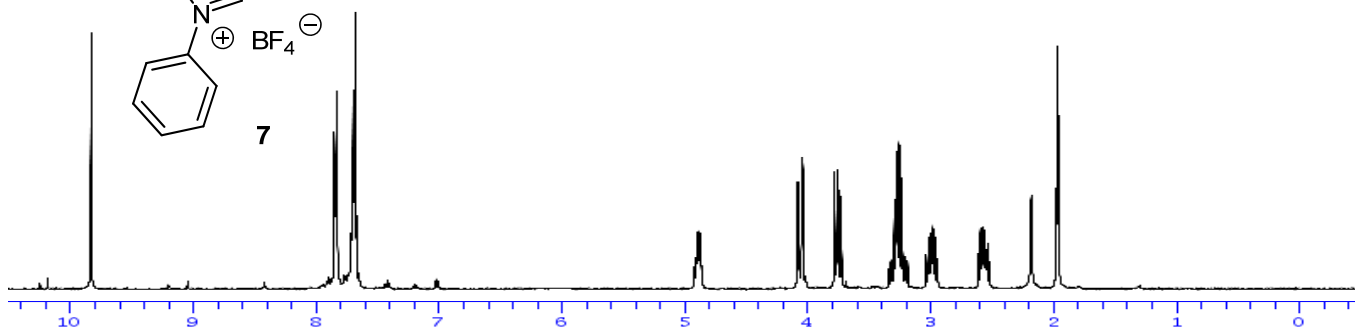
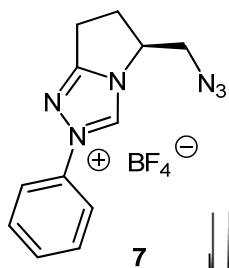
**3c:** (90 mg, 0.14 mmol, 85%), *ee*: 42%.

<sup>2</sup> O'Toole, S. E.; Connon, S. J., *Org. Biomol. Chem.* **2009**, 7, 3584.

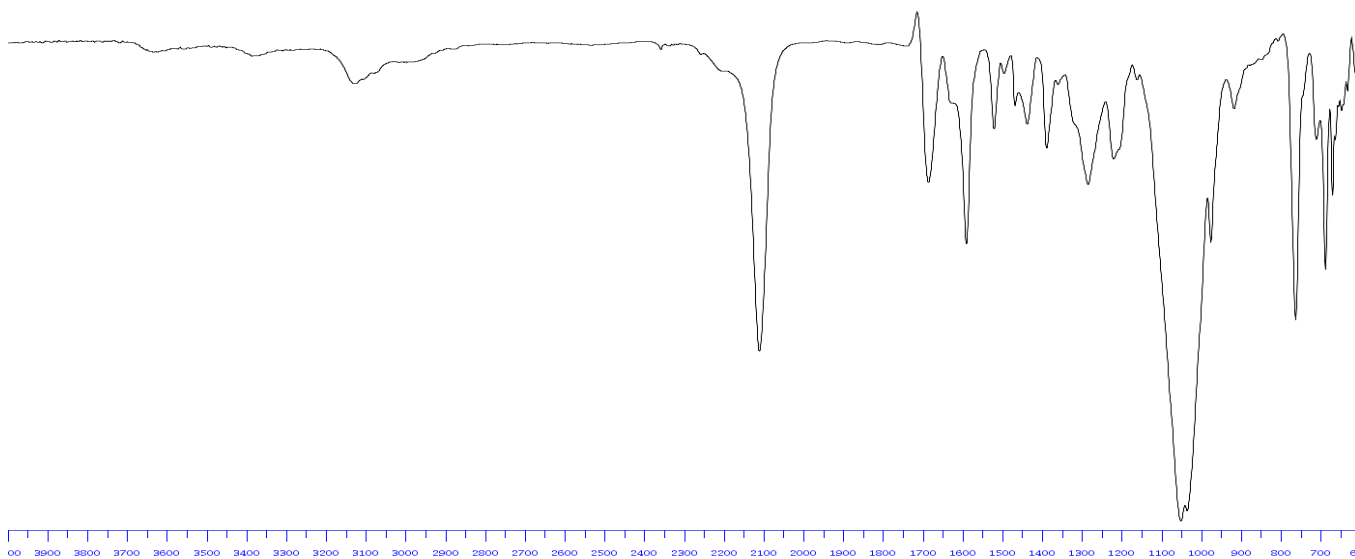
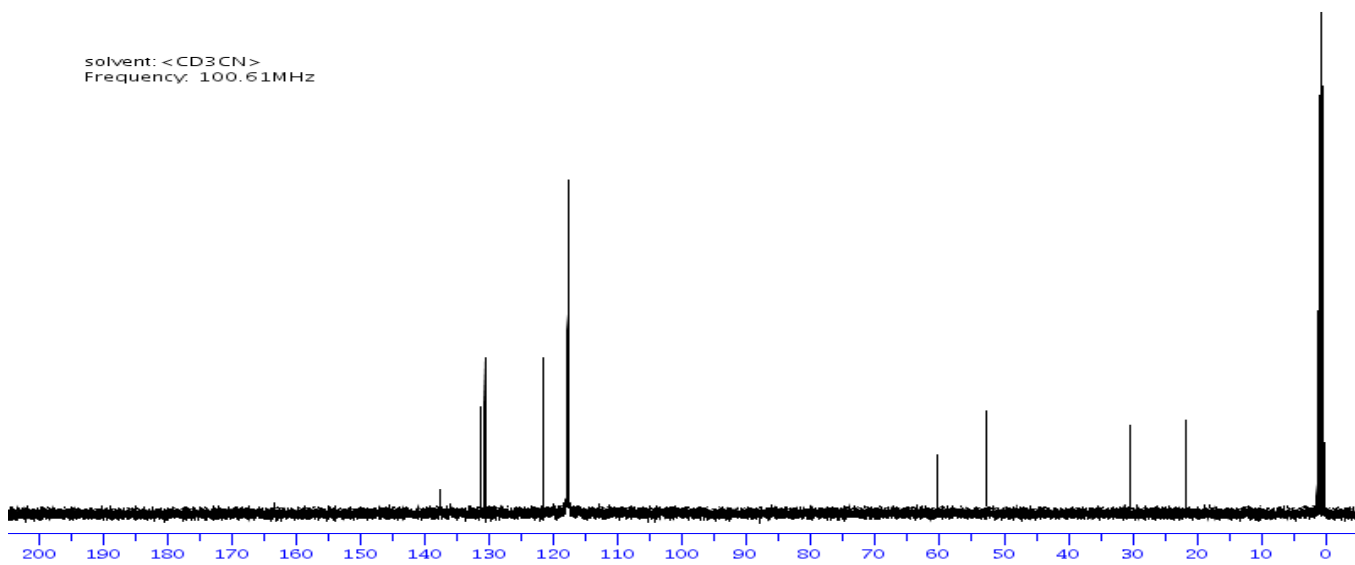
**3d**: (18 mg, 0.08 mmol, 17%), *ee*: 90%.

#### **IV. Spectra of New Compounds**

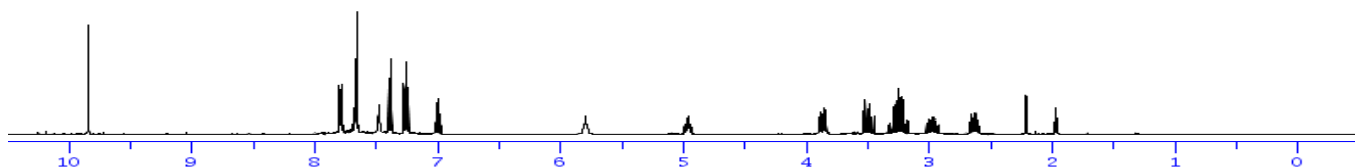
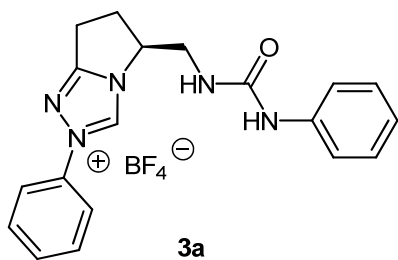
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Frequency: 400.13MHz



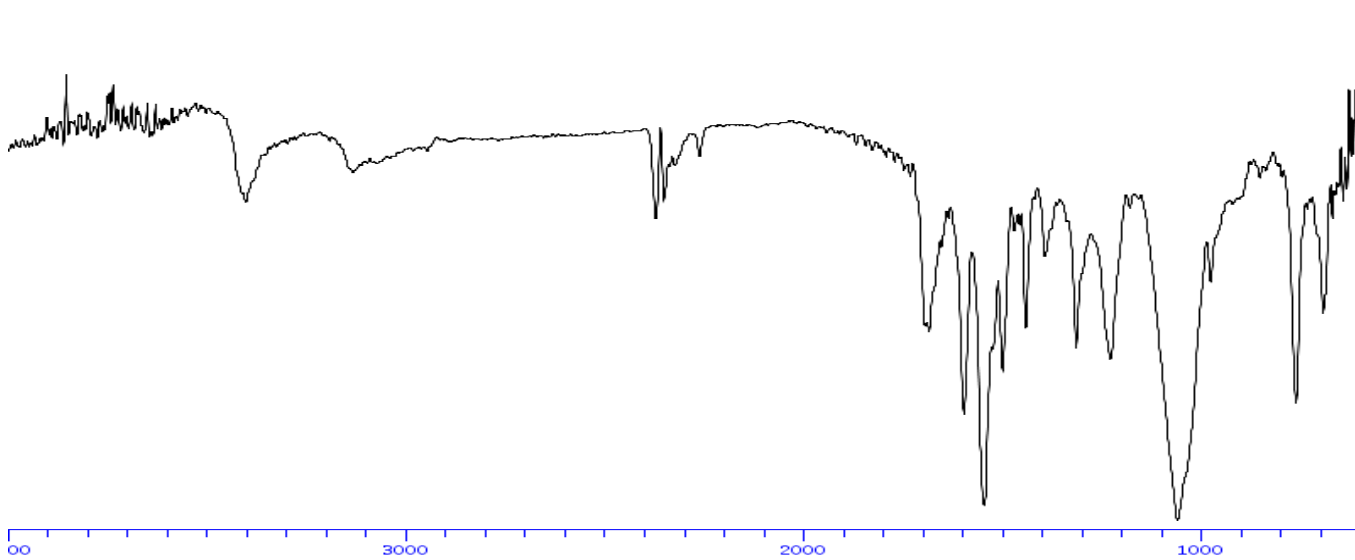
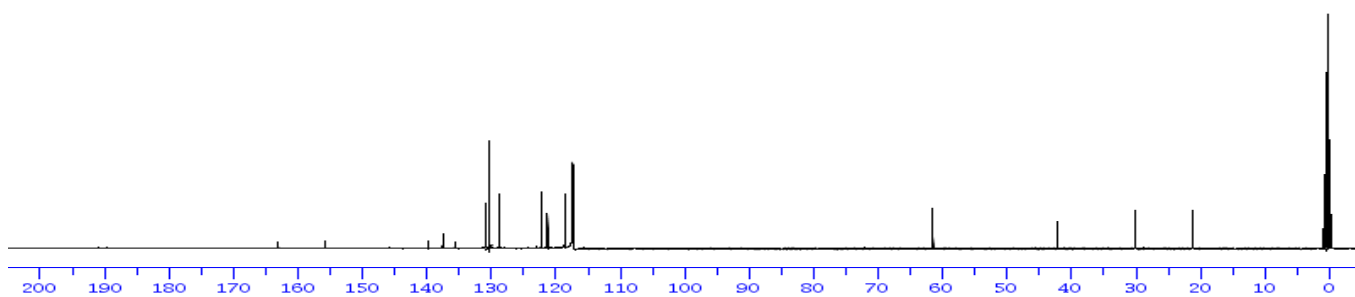
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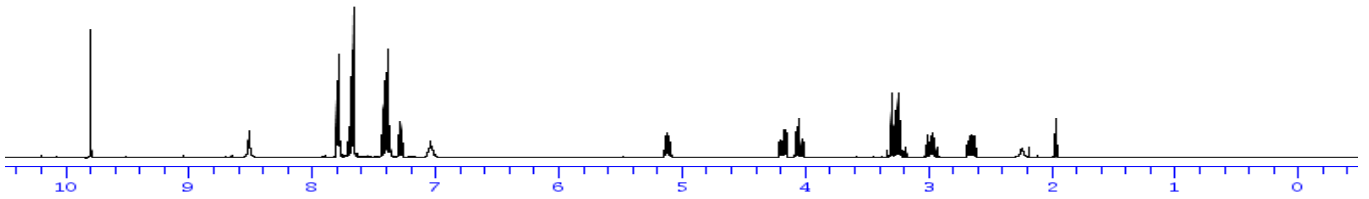
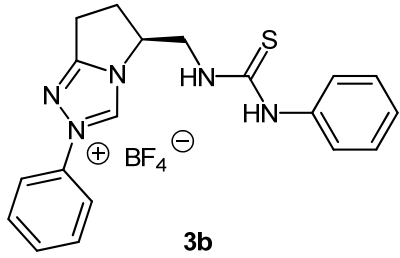
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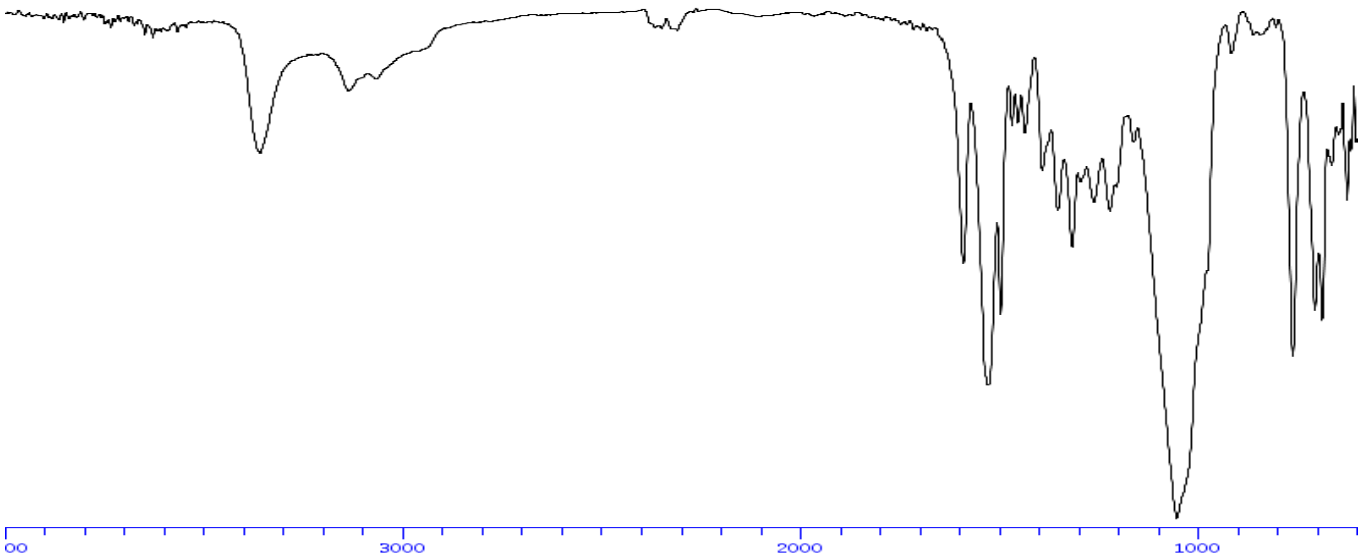
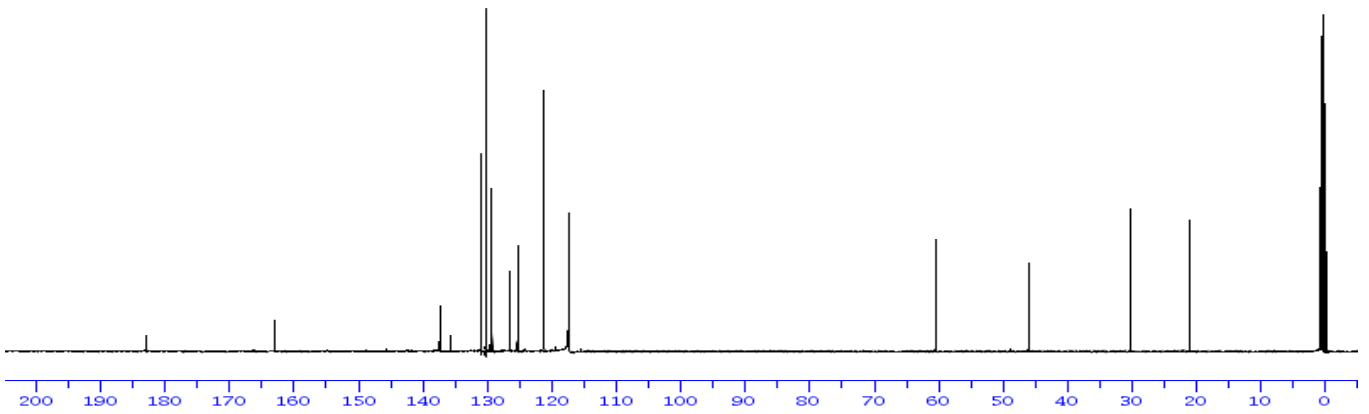
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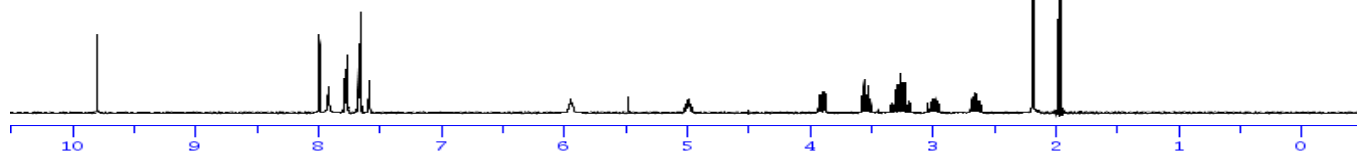
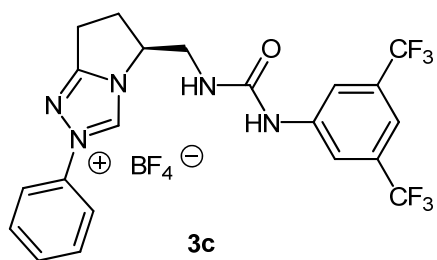


solvent: <CD3CN>  
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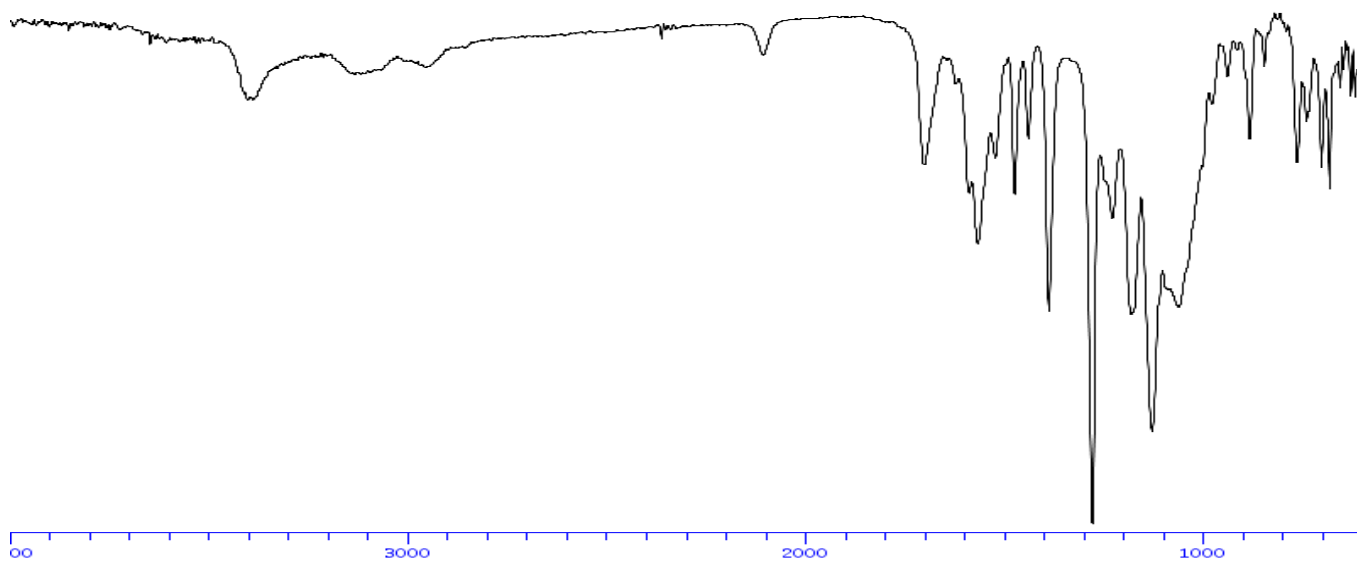
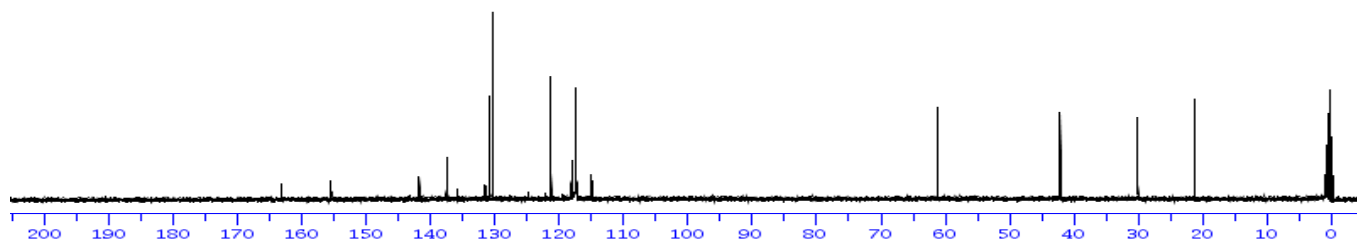




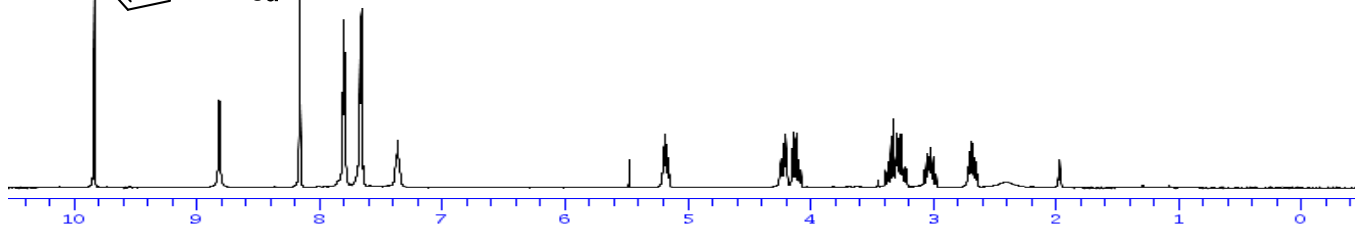
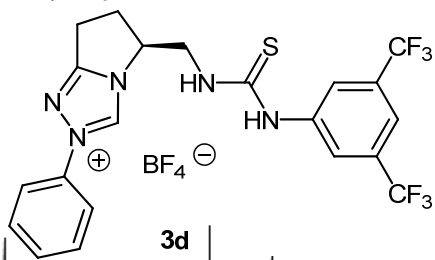
solvent: <CD3CN>  
Frequency: 400.13MHz



solvent: <CD3CN>  
Frequency: 100.612769MHz



solvent: <CD3CN>  
Frequency: 400.13MHz



solvent: <CDCl3>  
Frequency: 100.612769MHz

