Organic Syntheses

Synthesis of *N*-Acyl Pyridinium-*N*-Aminides and Their Conversion to 4-Aminooxazoles *via* a Gold-Catalyzed Formal (3+2)-Dipolar Cycloaddition

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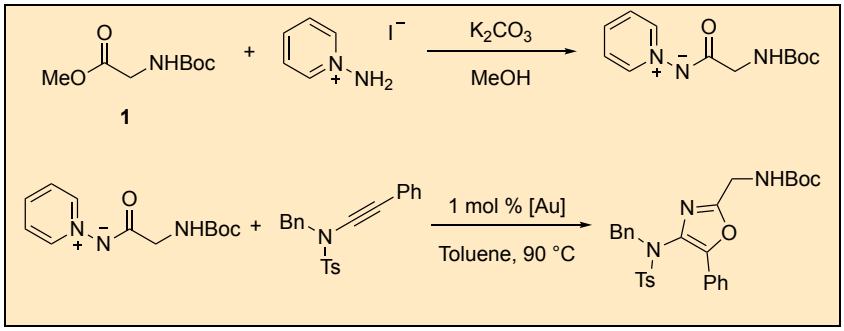
Checked by Manuela Brütsch, Estíbaliz Merino and Cristina Nevado



Procedure (Note 1)

A. *((tert-Butoxycarbonyl)glycyl)(pyridin-1-ium-1-yl)amide* (**2**). A 500 mL single-necked, round-bottomed flask equipped with a 3 cm stirrer bar and a needle-pierced septum is charged with methyl (*tert*-butoxycarbonyl)-glycinate **1** (Note 2) (6.80 g, 36.0 mmol, 1.20 equiv) and methanol (Note 3) (225 mL). 1-Amino pyridinium iodide (Note 4) (6.67 g, 30.0 mmol) is added and the reaction is stirred for 5 min at 22 °C. Potassium carbonate (Note 5) (9.95 g, 72.0 mmol, 2.40 equiv) is added and the reaction is stirred at 22 °C for 64 h (Note 6) (the yellow heterogeneous reaction turns colorless two seconds after the addition of potassium carbonate, and forms a dark purple solution, Figure 1). After removal of the stir bar, 200 mL of the methanol is removed under reduced pressure (200 mmHg to 70 mmHg, 40 °C) to give a

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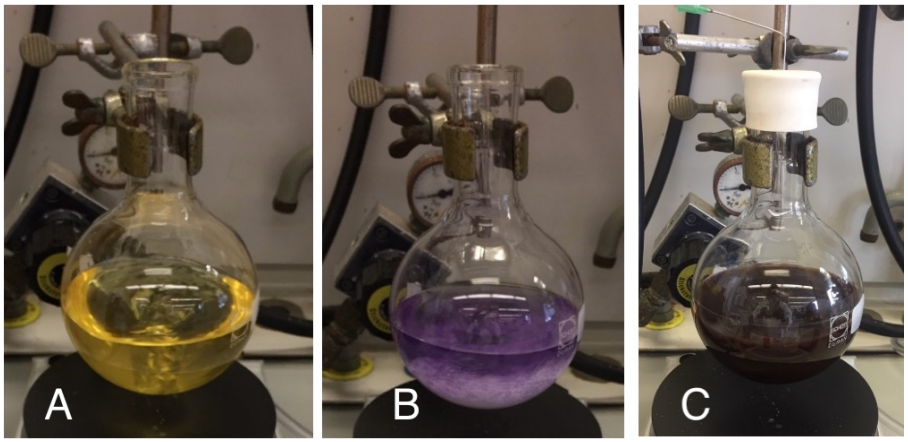


Figure 1. Change in reaction color: a) Reaction mixture before potassium carbonate addition; b) Reaction mixture 10 seconds after potassium carbonate addition; c) Reaction mixture after 64 h

brown-purple syrup, which is poured onto an alumina pad (Notes 7 and 8). The flask is rinsed with 10 mL of dichloromethane as well as 50 mL of eluent (dichloromethane-methanol, 9:1), and the product is eluted with 1.1 L of dichloromethane-methanol (9:1) (Note 9). The filtrate is concentrated (375 mmHg to 75 mmHg, 40 °C) and then transferred to a 500 mL single-necked round-bottomed flask and rinsed with dichloromethane (20 mL). The filtrate is concentrated further (375 mmHg to 15 mmHg, 40 °C) and then dried under vacuum (0.08 mmHg, 20 °C, 1 h) to give a brown powder (Note 10). A 3 cm Teflon coated stirrer bar is added, followed by acetone (175 mL) (Note 11). A water-cooled condenser is added to the flask and the mixture is heated to reflux until complete dissolution had occurred (15 min). The mixture is allowed to cool to room temperature over 3 h and then cooled to –22 °C in a freezer for 20 h. The resultant fine brown crystals

Figure 2. Compound 2 after recrystallization from acetone

are filtered off through a sintered S3 funnel, the flask is rinsed with diethyl ether (Note 12) (3 x 25 mL), and the contents were then added to the funnel. The powder is transferred to a 50 mL single-necked flask and dried under static vacuum (0.12 mmHg, 18 h) (6.39 g, 85%, 98% purity) (Figure 2) (Notes 13, 14, and 15).

B. *tert-Butyl ((4-((N-benzyl-4-methylphenyl)sulfonamido)-5-phenyloxazol-2-yl)methyl)carbamate (**4**).* A three-necked 250 mL round-bottomed flask equipped with a septum, a glass stopper, a vacuum tap and 2 cm Teflon coated stirrer bar is flame-dried under vacuum (0.12 mmHg) for 1 min and then backfilled with nitrogen. The evacuation/nitrogen purge is repeated a total of 3 times, and then the reaction vessel is allowed to cool to room temperature (22 °C) under a positive pressure of nitrogen. The flask is sequentially charged with *N*-benzyl-4-methyl-*N*-(phenylethynyl)benzene-sulfonamide (Note 16) (4.69 g, 13.0 mmol), dichloro(2-pyridinecarboxylato)gold (Note 17) (51.02 mg, 0.13 mmol) and ((*tert*-butoxycarbonyl)glycyl)(pyridin-1-ium-1-yl)amide (3.60 g, 14.3 mmol, 1.1 equiv). Toluene (130 mL) (Note 18) is added and the flask is placed in a preheated aluminium mantle and stirred at 90 °C (controlled by an external probe) for 5.5 h (Note 19). The heterogeneous mixture becomes a homogenous orange-brown solution over the first hour (Figure 3).

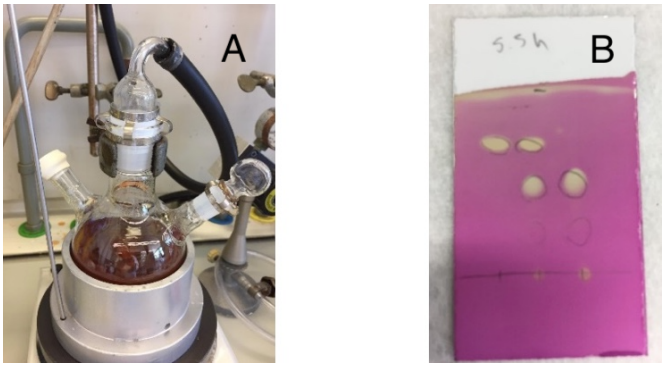


Figure 3. a) Reaction set-up for Step B; b) Reaction progress monitored by TLC. From left to right: Compound 3, control spot and reaction mixture

Upon completion, the flask is removed from the heating mantle and the reaction is allowed to cool to room temperature for 1 h. The crude reaction

mixture is filtered through a silica pad (Note 20) and then the reaction flask is rinsed with ethyl acetate (2 x 50 mL) (Note 21), which is then added to the silica pad. The pad is then flushed with ethyl acetate (320 mL) into a 1 L single-necked round-bottomed flask. The solvent is removed under reduced pressure (150–75 mmHg, 40 °C). The product is transferred, with the assistance of ethyl acetate washes (2 x 10 mL), to a 250 mL single-necked, round-bottomed flask and evaporated further (160 mmHg to 30 mmHg). The resultant white-yellowish solid is then broken up with a glass rod (Figure 4a). A 3 cm Teflon coated stir bar is added followed by ethanol (Note 22) (150 mL), and the flask is equipped with a water-cooled condenser. The flask is heated to reflux in an aluminium heating mantle and stirred for 25 min until complete dissolution to give a yellow solution. The flask is allowed to cool to room temperature and then placed in a freezer at –22 °C for 19 h. The resultant crystals were filtered off and washed with hexane (3 x 25 mL) (Note 23) to give fine off-white crystals (Figure 4b).

The crystals are transferred to a 100 mL single-necked flask and then toluene (30 mL) (Note 24) is added to give a slightly grey suspension (Figure 4c). The solvents are removed under reduced pressure (75 mmHg to 35 mmHg, 40 °C) and then the product is dried under vacuum (0.14 mmHg, 1 h, room temperature) to give a fine off white powder (Figure 4d) (Note 25). The powder is transferred to a 250 mL single-necked, round-bottomed flask (using 10 mL dichloromethane to rinse the flask) containing a 3 cm Teflon coated stir bar. Dichloromethane (80 mL) is added, the mixture is stirred for 10 min and then the yellow solution (Figure 4e) is filtered through cotton wool (Note 26), which is then washed with dichloromethane (4 x 10 mL), eluting under gravity into a 250 mL round-bottomed flask (Note 27). The solvent is evaporated (450 mmHg – 35 mmHg, 40 °C) to give a white solid (Figure 4f), which is broken up with a glass rod and then dried under vacuum (60 °C, 0.12 mmHg, 96 h) (6.67 g, 96%, >99% purity) (Notes 28, 29, 30, and 31).

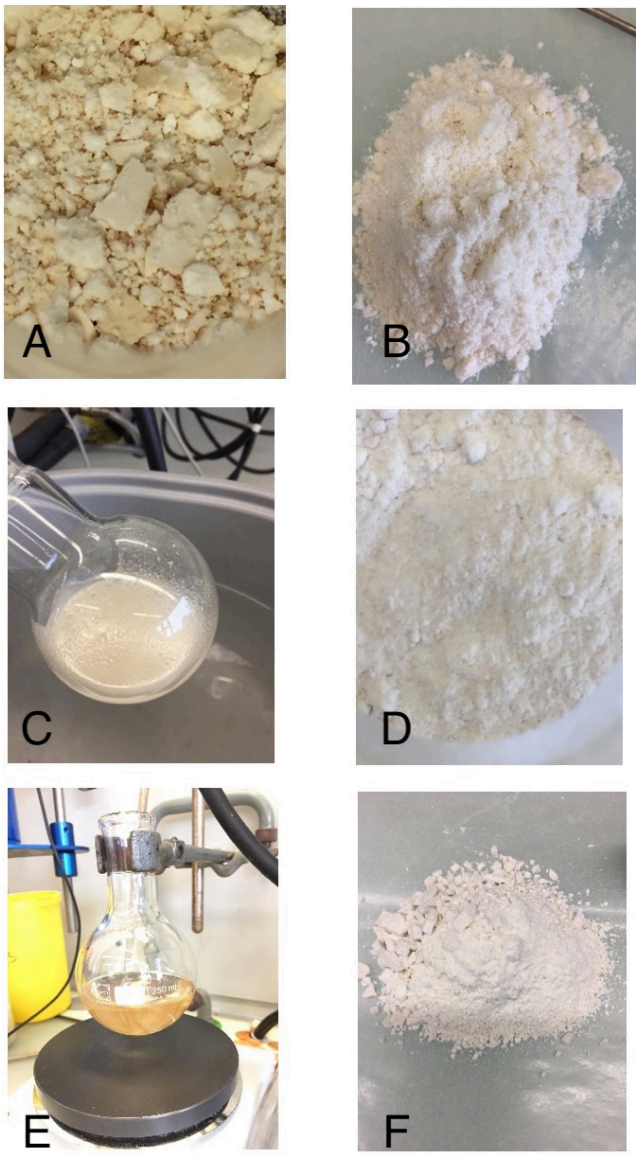


Figure 4. a) Solid after filtration through a silica pad; b) Solid after first crystallization; c) Grey suspension of the white crystals in toluene; d) The final product before filtration through cotton; e) Yellow solution of the product before filtration through cotton; f) Compound 4

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical). See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with methyl (*tert*-butoxycarbonyl)glycinate, methanol, 1-amino pyridinium iodide, potassium carbonate, alumina, dichloromethane, diethyl ether, 1,3,5-trimethoxybenzene, *N*-benzyl-4-methyl-*N*-(phenylethynyl)benzenesulfonamide, dichloro(2-pyridinecarboxylato)gold, toluene, silica gel, ethyl acetate, and ethanol.
2. Methyl (*tert*-butoxycarbonyl)glycinate (**1**) (97%) was purchased from Fluorochem and used as received.
3. Methanol (99.9%) was purchased from Acros Organics and used as received.
4. 1-Amino pyridinium iodide (97%) was purchased from Fluorochem. Prior to use, it was dissolved in methanol and the resulting suspension filtered to remove the non-dissolved materials. The mother liquors were evaporated and the obtained solid recrystallized with ethanol.
5. Potassium carbonate (99%) was purchased from Alfa Aesar and used as received.
6. TLC analysis is used to determine reaction completion: the R_f of the product is 0.17 (in 88:12 dichloromethane-methanol), on aluminium backed silica gel 60 F_{254} plates. The product was visualised with UV

light (254 nm) and the starting material (ester **1**, R_f 0.90) was visualized with $KMnO_4$ (heating 130 °C, 30 seconds).

7. Activated, neutral Brockmann type 1 aluminium oxide (60 mesh, 58 Å pore size) was purchased from Alfa Aesar and used as received.
8. Alumina was slurried with dichloromethane, and an alumina pad was used that was 9.0 cm in diameter and 7.0 cm deep.
9. Dichloromethane (99%) was purchased from Biosolve and used as received.
10. The authors point out that at this stage of the process silica gel flash column chromatography may be used to purify aminides instead of recrystallization. (Silica: 230-400 mesh size, 60 Å pore size, 40-63 μm particle size, which was purchased from Sigma-Aldrich and used as received). TLC on aluminium backed silica gel 60 F_{254} plates. R_f = 0.31 in dichloromethane-methanol [9:1]. Visualized with 254 nm UV light only. The crude powder was dissolved in CH_2Cl_2 (40 mL). Silica (20 g) was added and the solvent was then removed (500 mmHg to 30 mmHg, 40 °C). The product-adsorbed silica was then loaded onto a column (6.5 cm diameter, 15 cm depth, 180 g silica, slurry loaded with eluent) and eluted with dichloromethane-methanol [9:1] (2.65 L) with 30 mL fractions. Rotary evaporation of the collected fractions (500 mmHg to 30 mmHg, 40 °C) gave a pale yellow solid, which was dried under high vacuum (0.15 mmHg, 20 °C) for 6 h (6.69 g, 89%).
11. Acetone (99.8%) was purchased from Sigma-Aldrich and used as received.
12. Diethyl ether (99.8%) was purchased from Biosolve and used as received.
13. A reaction performed on half scale provided 3.71 g (90%) of the product.
14. These stable, hygroscopic brown crystals should be stored in a desiccator. The compound exists as a mixture of rotamers. mp 165–167 °C; IR (thin film) 3234, 2969, 1712, 1580, 1542, 1471, 1416, 1363, 1270, 1243, 1153, 1138, 1046, 934, 817, 770, 679, 612, 492 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.46 (s, 9H), 3.94 (d, J = 4.5 Hz, 2H), 5.34 (s, 1H), 7.66 (t, J = 7.0 Hz, 2H), 7.92 (t, J = 7.7 Hz, 1H), 8.69 (d, J = 6.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 28.4 ($3CH_3$), 44.1 (CH_2), 78.9 (C), 126.1 (2CH), 137.2 (CH), 143.0 (2CH), 155.9 (C), 172.4 (C); HRMS (ESI) m/z calcd for $C_{12}H_{18}N_3O_3$ 252.13427, found 252.13413 $[M+H]^+$.
15. Purity of the product was determined to be 98% by quantitative ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard.

16. *N*-Benzyl-4-methyl-*N*-(phenylethynyl)benzenesulfonamide was synthesized according to an *Org. Synth.* procedure.[6a] The data matched those reported.
17. Dichloro(2-pyridinecarboxylato)gold (no assay) was purchased from Sigma Aldrich and used as received.
18. Toluene was collected in an oven-dried (140 ºC for 24 h) 250 mL Schlenk flask, which had been purged with argon atmosphere by three evacuation-backfill cycles from a dry solvent system (Innovative Technology).
19. TLC analysis is used to determine reaction completion: the R_f of the product in 3:2 hexane-ethyl acetate is 0.34, on aluminium backed silica gel 60 F_{254} plates. The product and limiting reagent (ynamide **3**, R_f 0.59) were visualised with UV light (254 nm) and $KMnO_4$ (heating 130 °C, 30 seconds). The pyridine by-product (R_f 0.14) was visualised with UV light (254 nm) only.
20. Silica was added to a sintered (S3) funnel (7.0 cm internal diameter) to a depth of 3 cm. This was wetted with ethyl acetate (50 mL).
21. Ethyl acetate (100%) was purchased from Biosolve and used as received.
22. Ethanol (99.96%) was purchased from Biosolve and used as received.
23. Hexane (98%) was purchased from Fisher Chemical and used as received.
24. Toluene (99.7%) was purchased from Biosolve and used as received.
25. The authors reported a gray/lilac powder.
26. A 2.8 cm diameter column was packed with cotton wool, to a depth of 3.5 cm.
27. The used cotton wool is a gray color.
28. The oxazole **4** contains traces of dichloromethane. Removal of the final vestiges of solvent from within the crystal structure required heating under vacuum.
29. A reaction performed on half scale provided 3.31 g (95%) of the product.
30. The product is a bench stable powder. Analysis by ^{1}H NMR indicates the presence of a mixture of carbamate rotamers. mp 164–165°C; IR (thin film) 3276, 2974, 1715, 1447, 1391, 1367, 1349, 1331, 1153, 1129, 1089, 1057, 1043, 1026, 844, 822, 752, 732, 706, 690, 668, 653, 604, 578, 555, 540 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.48 (s, 9H), 2.46 (s, 3H), 4.37 (d, J = 5.1 Hz, 2H), 4.55 (s, 2H), 4.98 (s, 1H), 7.09–7.04 (m, 3H), 7.15–7.13 (m, 2H), 7.35–7.27 (m, 5H), 7.68 (d, J = 7.2 Hz, 2H), 7.77 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 21.6, 28.3, 38.2, 53.9, 80.2, 125.5, 126.4,

127.9, 128.1, 128.3, 128.6, 128.8, 129.1, 129.5, 131.1, 134.6, 135.3, 144.0, 148.1, 155.3, 157.6; HRMS (ESI) *m/z* calcd for $C_{29}H_{32}N_3O_5S$ 534.20572, found 534.20563 $[M+H]^+$; Anal. calcd. for $C_{29}H_{31}N_3O_5S$: C; 65.27, H; 5.86, N; 7.87, found: C; 65.08, H; 5.83, N; 7.60.

31. Purity of the product was determined to be >99% by quantitative ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard.

Working with Hazardous Chemicals

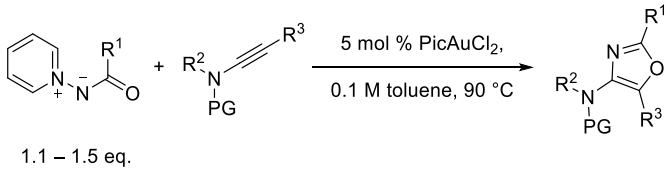
The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

Oxazoles have been used in key steps in several total syntheses,[2] have been isolated in many natural products[3] and have been produced at large scale in the pharmaceutical and agrochemical[4] industries: convergent routes into diversely functionalized oxazoles are attractive propositions. The gold-catalyzed formal (3+2)-dipolar cycloaddition between an *N*-heteroaryl-*N*-acyl aminide and an ynamide produces 4-aminooxazole derivatives in a highly convergent and atom economical fashion.[5] As Scheme 1 depicts, the aminide furnishes C-2 of the oxazole, whilst the ynamide equips C-4 and C-5.



Scheme 1. **The synthesis of 4-aminooxazole derivatives**

The formal dipolar cycloaddition displays the exquisite chemoselectivity of gold catalysis providing a wealth of oxazoles with diverse substitution patterns (Figure 5). Functionality at C-2 includes electron donating, electron withdrawing, aromatic, heteroaromatic, alkyl and cycloalkyl groups, with either oxygen, carbon or nitrogen directly bonded to the oxazole. The reaction tolerates stereogenic centers, secondary unprotected amines and acyclic acetals and can also form disubstituted oxazoles from formyl aminides (or terminal ynamides). Using the functionality appended to the ynamide, the oxazole synthesis incorporates electron withdrawing groups, sulfur substituted systems, aromatic groups and alkyl chains at the 5-position. The 4-amino group can be protected as a cyclic carbamate, a phosphoramidate or a sulfonamide.[5]

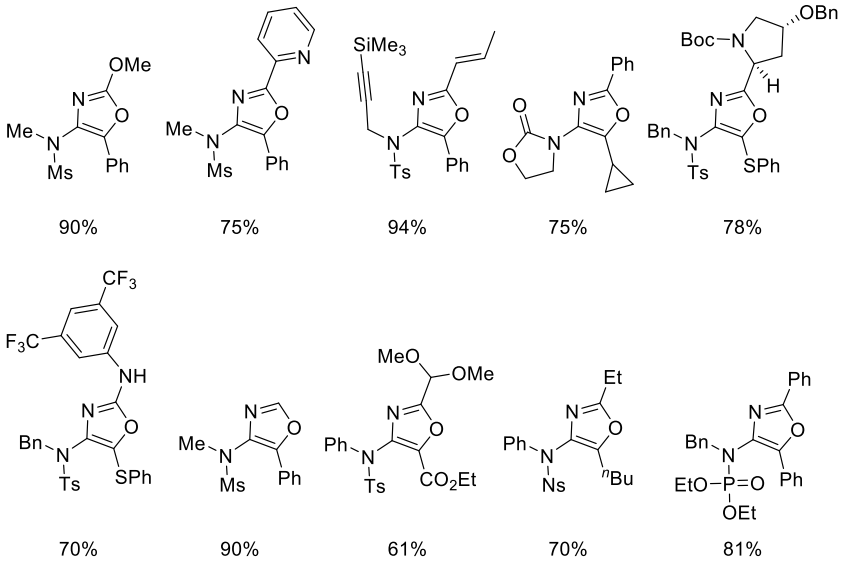


Figure 5. Selected examples of products from the formal cycloaddition

The broad applicability of this method requires access to both ynamides[6] and *N*-acyl pyridinium-*N*-aminides with substantial structural and functional group variety.

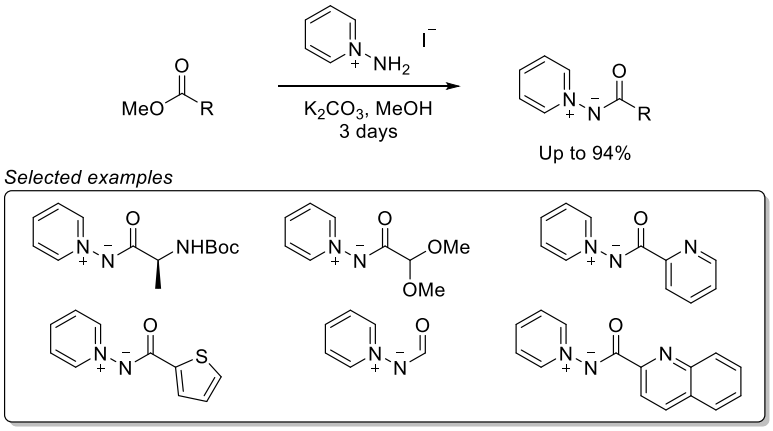
N-Acyl pyridinium-*N*-aminides have been exploited across a variety of cycloadditions and transition metal catalysed transformations to allow elaboration of the pyridine ring.[7] The anionic nitrogen atom acts as a directing group for C-H activation. Charette and co-workers showed how such pyridinium ylides undergo a range of intermolecular reactions in which the pyridyl unit is incorporated into the desired product.[8]

The potential of acyl pyridinium ylides to act as $^{1,3}N,O$ dipole equivalents is unveiled in the gold-catalysed oxazole synthesis. The aminides function as nucleophilic nitrenoids where the pyridinium moiety acts as a leaving group to reveal the acyl nitrenoid character of the aminide.

The synthesis of acyl aminides has been shown by Knaus,[9a] Akita,[9b] Charette[9c] and Alvarez-Builla,[9d] but formation of an acid chloride or anhydride is often prerequisite. Such features restrict the functionality tolerated.

An improved protocol was developed in order to access aminides by Davies *et al.* which incorporated a broader range of functionality at the now

critical acyl position.[5] The aminide is synthesized from its respective methyl ester using 1-aminopyridinium iodide and potassium carbonate (Scheme 2), although a one-pot approach from carboxylic acids was also established. The diverse array of methyl esters at the chemist's disposal, commercial availability of the amidating reagent, and the simple reaction set-up make this an attractive route to functionalized systems.



Scheme 2. The synthesis of pyridinium aminides

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Appendix
Chemical Abstracts Nomenclature (Registry Number)

1-Aminopyridinium iodide: Pyridinium, 1-amino, iodide (1:1); (6295-87-0)
Potassium carbonate: Carbonic acid, potassium salt (1:2); (584-08-7)

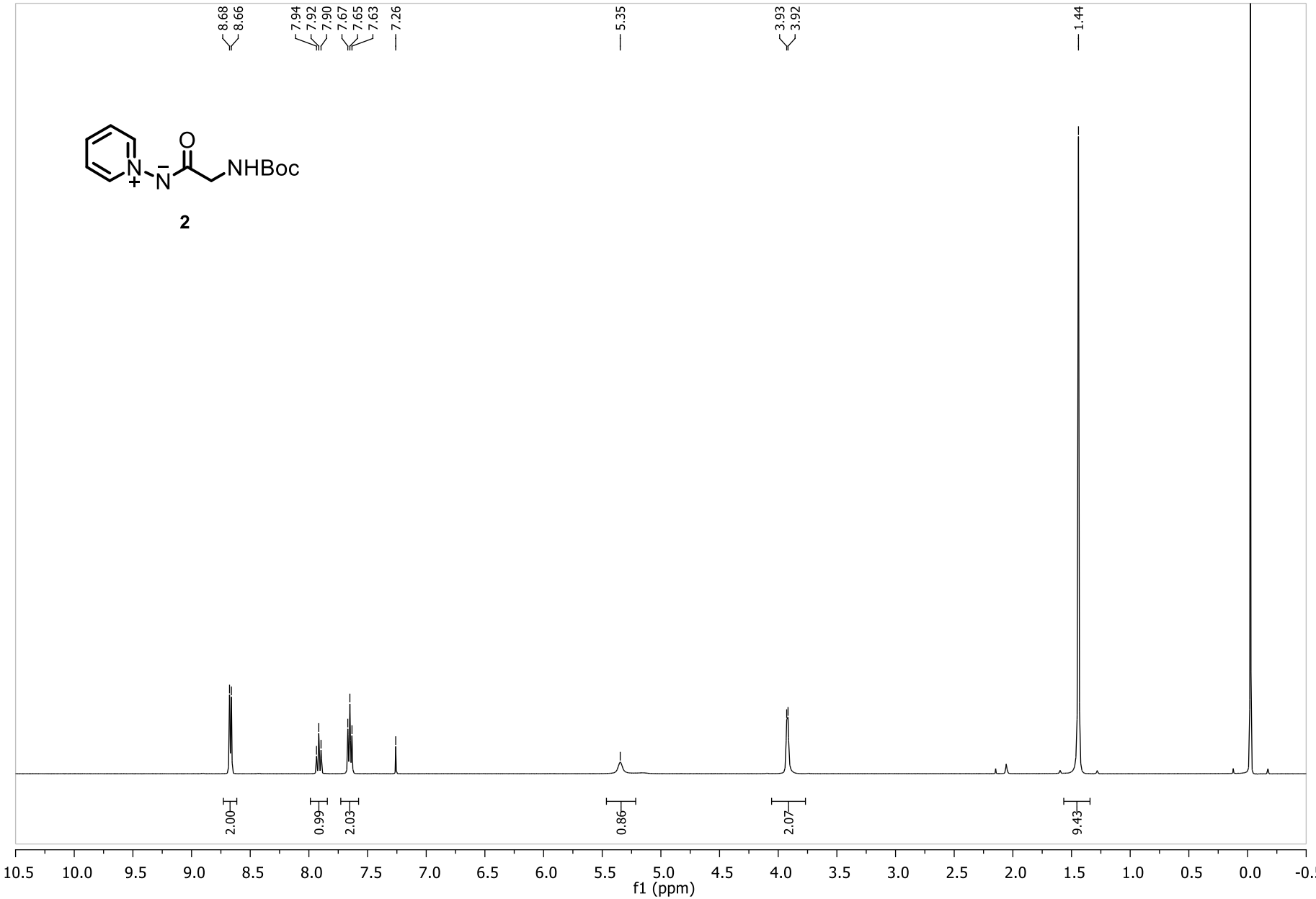
N-Benzyl-4-methyl-*N*-(phenylethynyl)benzenesulfonamide: Benzenesulfonamide, 4-methyl-*N*-(2-phenylethynyl)-*N*-(phenylmethyl)-; (609769-63-3)
Dichloro(2-pyridinecarboxylato) gold: Gold, dichloro(2-pyridinecarboxylato-κN^1,κO^2)-, (*SP*-4-3)-; (88215-41-2)

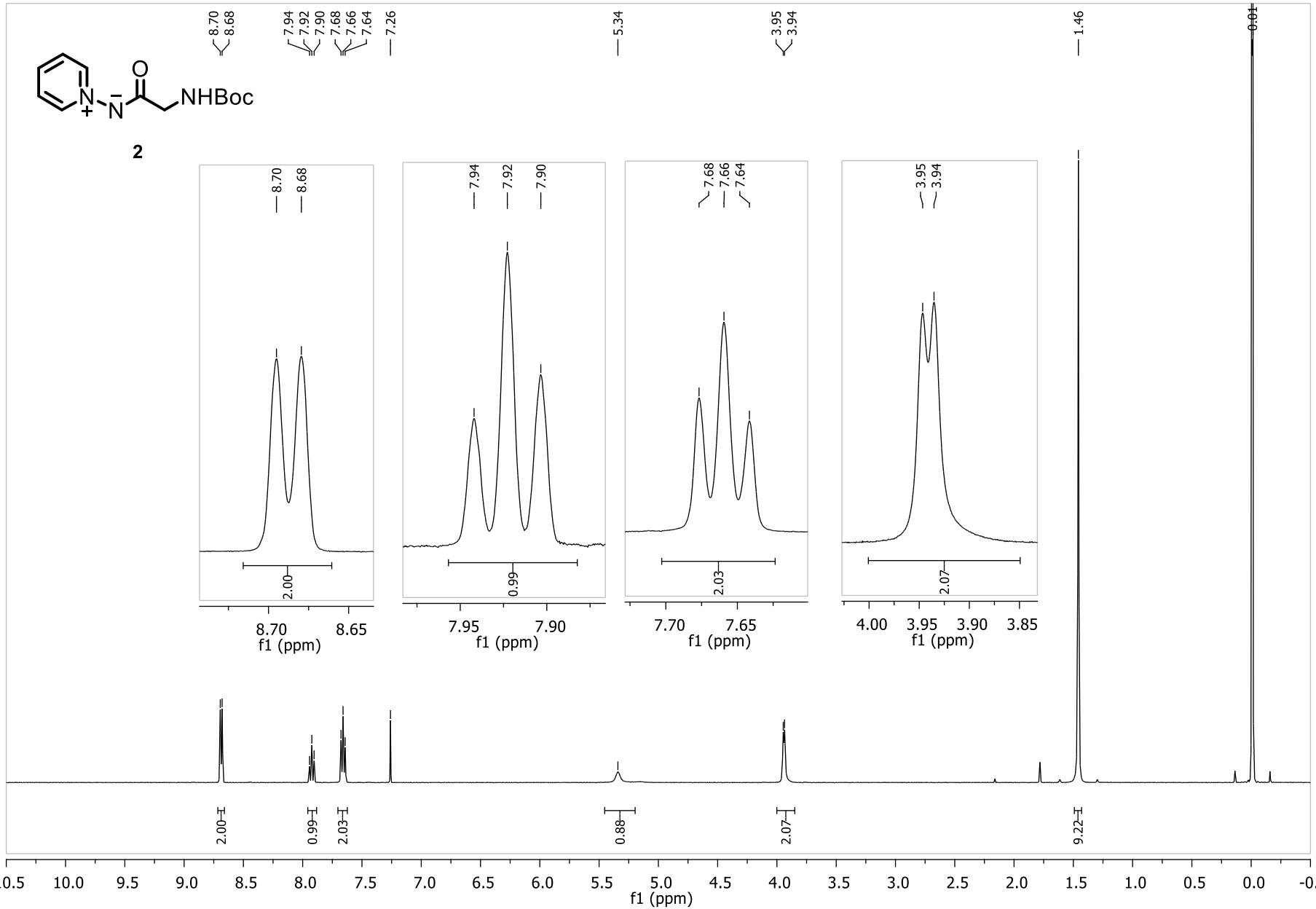
Matthew Ball-Jones studied for a MChem degree in Chemistry at the University of Reading. In 2013 he began his Ph.D. at the University of Birmingham to work under the supervision of Dr Paul Davies. His work involves the development of cascade reactions and the synthesis of polycyclic three-dimensional heterocycles.

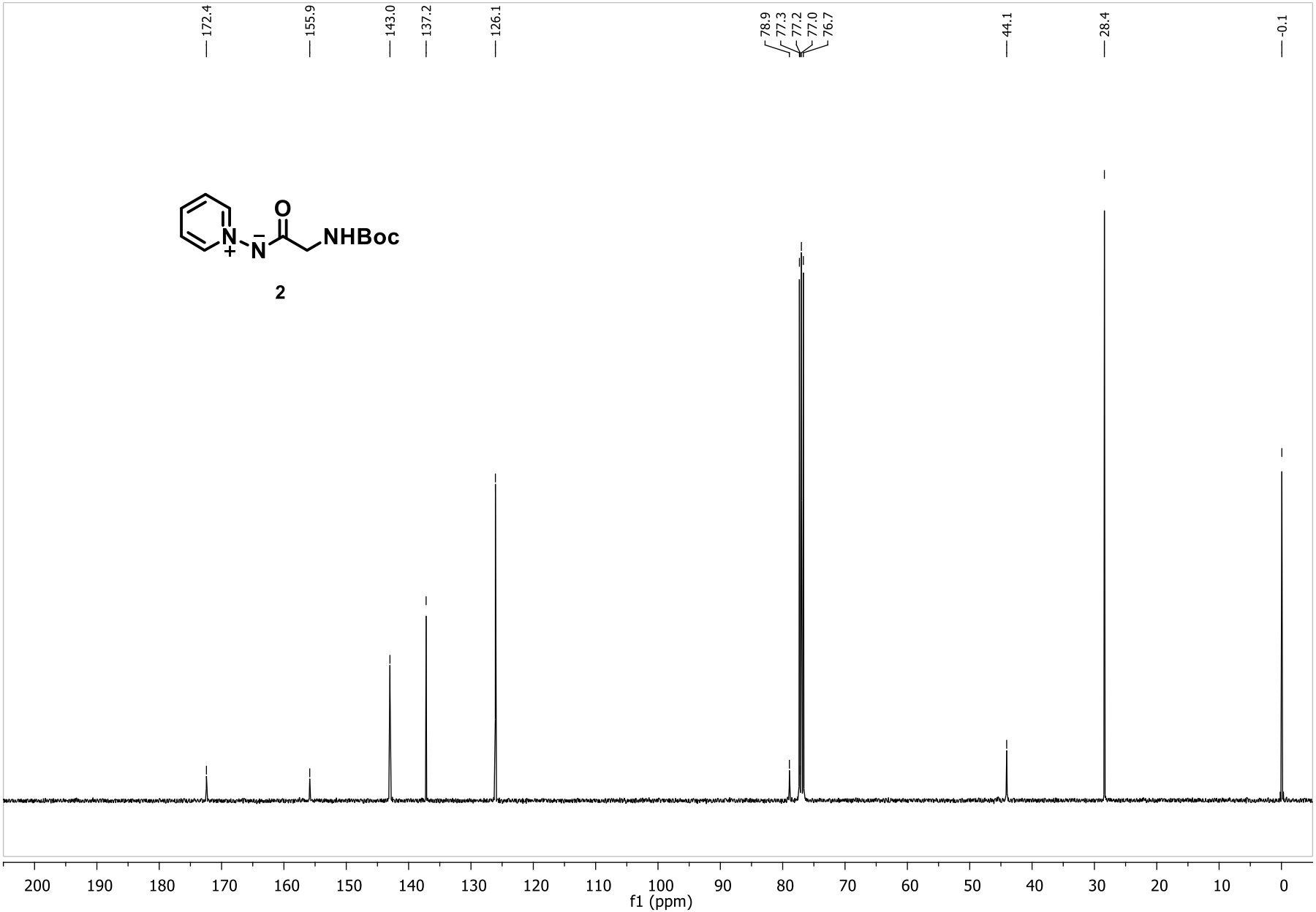
Paul Davies obtained his Ph.D. at the University of Bristol in 2003 with Prof. Varinder Aggarwal. After a postdoctoral stay at the Max Planck Institute fur Kohlenforschung with Prof. Alois Fürstner, he was appointed as a Lecturer and independent group leader in the School of Chemistry at the University of Birmingham in 2006, where he is now Senior Lecturer. His research interests focus on the discovery, development and application of new catalysis-based synthetic methods.

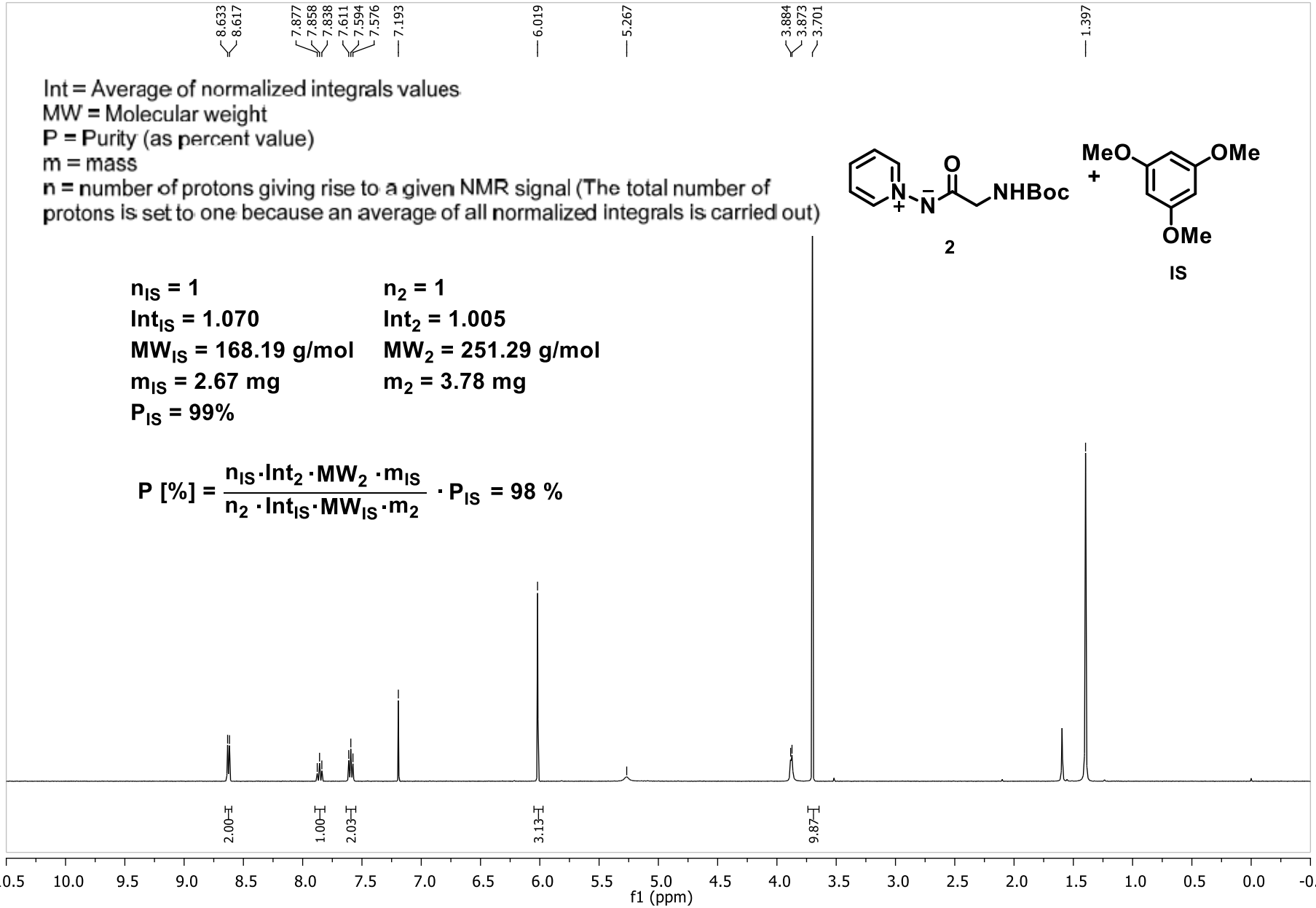
Manuela Brütsch completed her Master Degree in Chemistry in 2014 at the University of Zurich with Prof. Cristina Nevado. She then joined Prof. Jay S. Siegel's group at the Tianjin University in China to work as Research Assistant, followed by an appointment at the Scripps Research Institute in La Jolla with Prof. Dale Boger. In October 2016, she returned to the University of Zurich where she is working in Prof. Cristina Nevado's group.

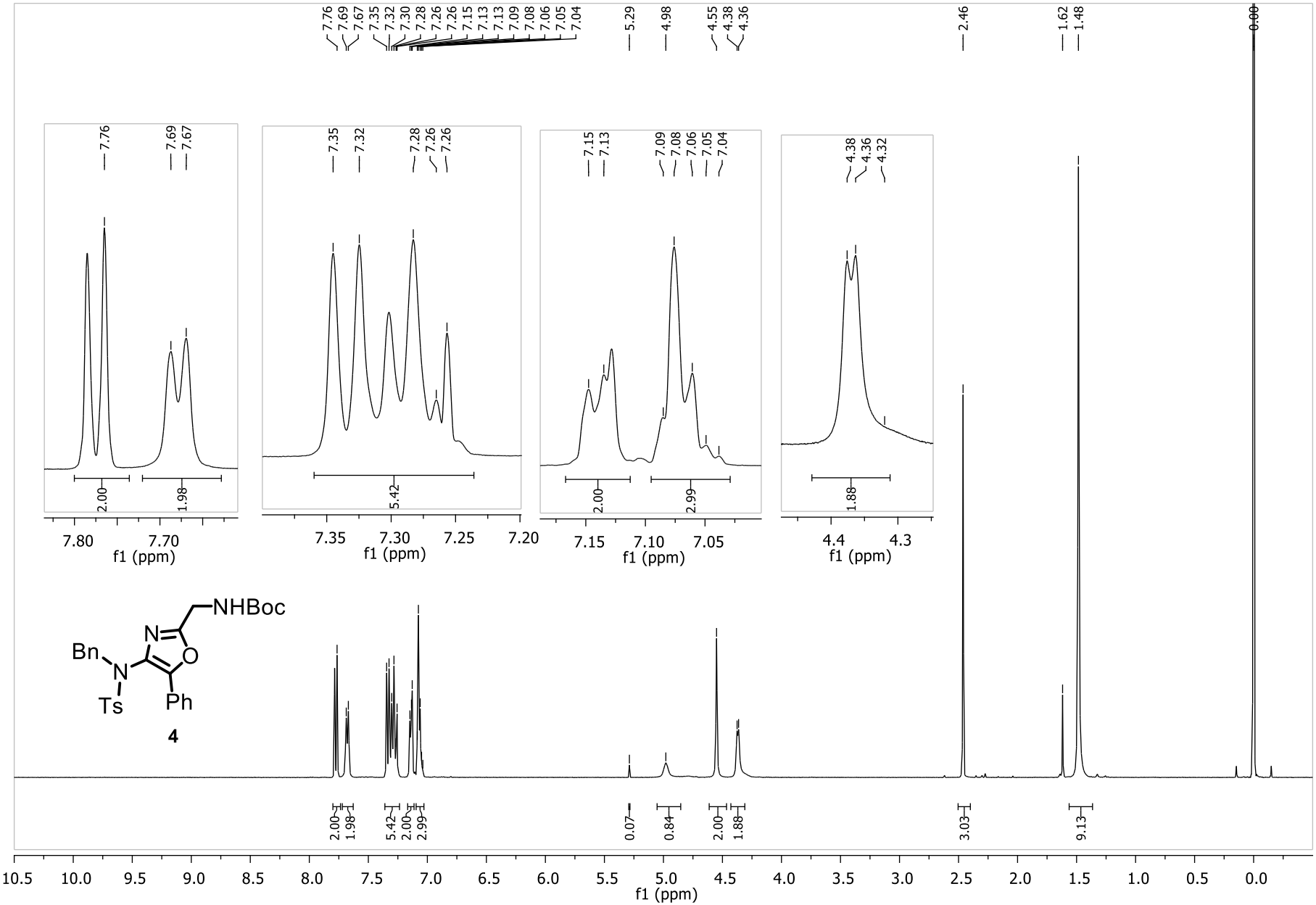
Estíbaliz Merino obtained her Ph.D. degree from the Autónoma University (Madrid-Spain). After a postdoctoral stay with Prof. Magnus Rueping at Goethe University Frankfurt and RWTH-Aachen University in Germany, she worked with Prof. Avelino Corma in Instituto de Tecnología Química-CSIC (Valencia) and Prof. Félix Sánchez in Instituto de Química Orgánica General-CSIC (Madrid) in Spain. At present, she is research associate in Prof. Cristina Nevado´s group in University of Zürich. She is interested in the synthesis of natural products using catalytic tools and in the development of new materials with application in heterogeneous catalysis.

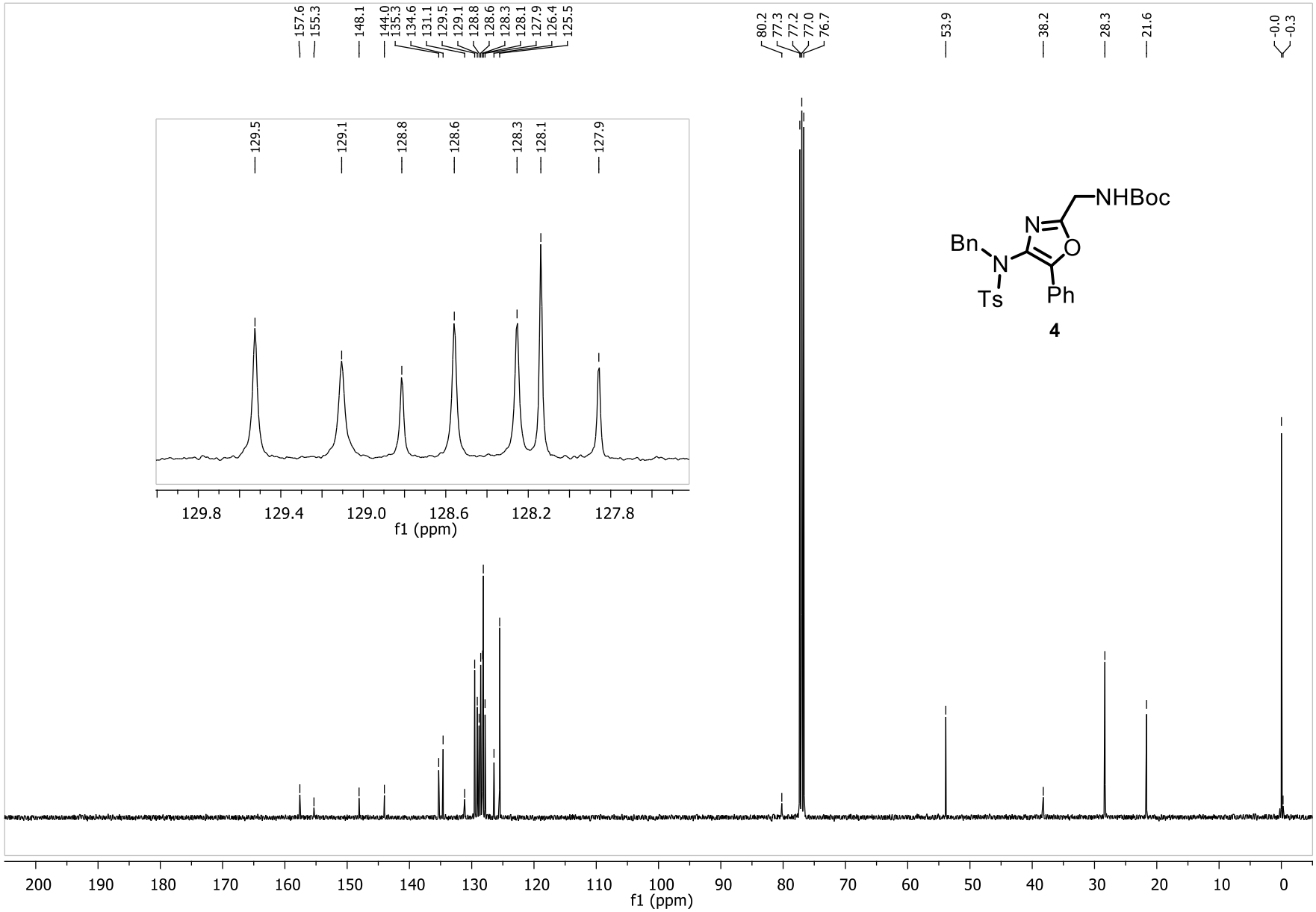

8.68
8.66
7.94
7.92
7.90
7.67
7.65
7.63
7.26
5.35
3.93
3.92
1.44
NHBoc
2
2.00
0.99
2.03
0.86
2.07
9.43
f1 (ppm)

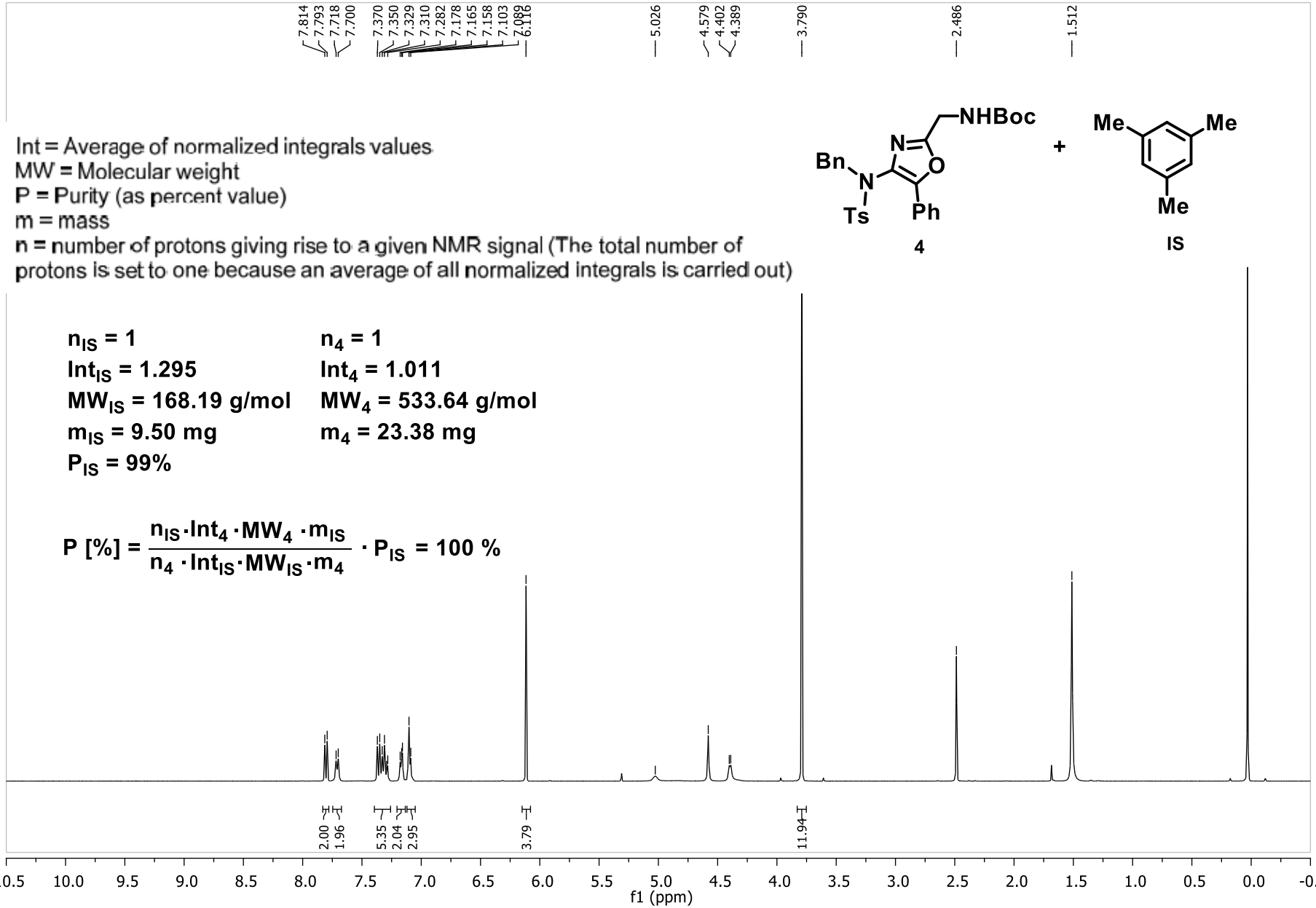

8.70
8.68
7.94
7.92
7.90
7.68
7.66
7.64
7.26
5.34
3.95
3.94
1.46
0.01
NHBoc
2
2.00
0.99
2.03
2.07
f1 (ppm)
0.88
9.22


172.4
155.9
143.0
137.2
126.1
78.9
77.3
77.2
77.0
76.7
44.1
28.4
-0.1
O
N
N
NHBoc
2
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.633
8.617
7.877
7.858
7.838
7.611
7.594
7.576
7.193
6.019
5.267
3.884
3.873
3.701
1.397
Int = Average of normalized integrals values
MW = Molecular weight
P = Purity (as percent value)
m = mass
n = number of protons giving rise to a given NMR signal (The total number of protons is set to one because an average of all normalized integrals is carried out)
NHBoc
2
MeO
OMe
OMe
IS
n_{IS} = 1
Int_{IS} = 1.070
MW_{IS} = 168.19 g/mol
m_{IS} = 2.67 mg
P_{IS} = 99%
n_2 = 1
Int_2 = 1.005
MW_2 = 251.29 g/mol
m_2 = 3.78 mg
$P\,[\%] = \frac{n_{IS} \cdot Int_2 \cdot MW_2 \cdot m_{IS}}{n_2 \cdot Int_{IS} \cdot MW_{IS} \cdot m_2} \cdot P_{IS} = 98\ \%$
2.00
1.00
2.03
3.13
9.87
10.5
10.0
9.5
9.0
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
0.0
-0.5
f1 (ppm)


7.76
7.69
7.67
7.35
7.32
7.30
7.28
7.26
7.15
7.13
7.13
7.09
7.08
7.06
7.05
7.04
5.29
4.98
4.55
4.38
4.36
2.46
1.62
1.48
0.00
2.00
1.98
5.42
2.00
2.99
1.88
f1 (ppm)
NHBoc
N
O
Bn
N
Ts
Ph
4
0.07
0.84
2.00
1.88
3.03
9.13


157.6
155.3
148.1
144.0
135.3
134.6
131.1
129.5
129.1
128.8
128.6
128.3
128.1
127.9
126.4
125.5
80.2
77.3
77.2
77.0
76.7
53.9
38.2
28.3
21.6
-0.0
-0.3
129.5
129.1
128.8
128.6
128.3
128.1
127.9
129.8
129.4
129.0
128.6
128.2
127.8
f1 (ppm)
NHBoc
N
O
Bn
N
Ts
Ph
4
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.814
7.793
7.718
7.700
7.370
7.350
7.329
7.310
7.282
7.178
7.165
7.158
7.103
7.089
6.116
5.026
4.579
4.402
4.389
3.790
2.486
1.512
Int = Average of normalized integrals values
MW = Molecular weight
P = Purity (as percent value)
m = mass
n = number of protons giving rise to a given NMR signal (The total number of protons is set to one because an average of all normalized integrals is carried out)
NHBoc
N
O
Bn
N
Ts
Ph
4
+
Me
Me
Me
IS
n_{IS} = 1
Int_{IS} = 1.295
MW_{IS} = 168.19 g/mol
m_{IS} = 9.50 mg
P_{IS} = 99%
n_4 = 1
Int_4 = 1.011
MW_4 = 533.64 g/mol
m_4 = 23.38 mg
$P\,[\%] = \frac{n_{IS} \cdot Int_4 \cdot MW_4 \cdot m_{IS}}{n_4 \cdot Int_{IS} \cdot MW_{IS} \cdot m_4} \cdot P_{IS} = 100\ \%$
2.00
1.96
5.35
2.04
2.95
3.79
11.94
10.5
10.0
9.5
9.0
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
0.0
-0.5
f1 (ppm)