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Organic Syntheses

Synthesis of 4-Methylbenzoate(2',4',6'-trimethoxyphenyl)iodonium Tosylate

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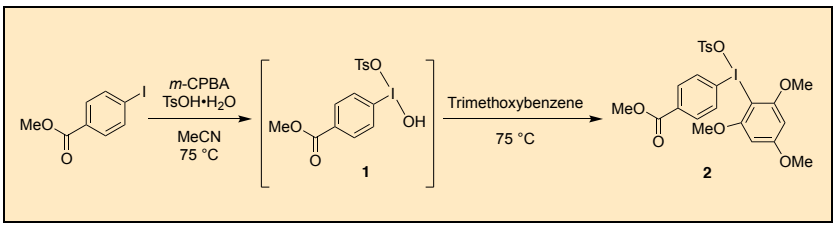
Checked by Zhaobin Han and Kuiling Ding



Procedure (Note 1)

A. *(4-Methylbenzoate)(2',4',6'-trimethoxyphenyl)iodonium tosylate* (**2**). A 2-necked (24/40) 500-mL round-bottomed flask containing a cylindrical teflon-coated magnetic stir bar (5×0.8 cm) (Note 2) is charged with methyl-4-iodobenzoate (Note 3) (13.1 g, 50.0 mmol, 1 equiv) and *p*-toluenesulfonic acid monohydrate (Note 4) (9.5 g, 50 mmol, 1 equiv). The flask is fitted with a water-cooled reflux condenser and clamped above an oil bath on a digitally controlled hot-plate/stirrer, which is on a support jack (Figure 1A). Acetonitrile (Note 5) (40 mL) is added to the reaction flask resulting in a turbid suspension. The support jack is used to raise the oil bath and stirring is commenced with a stir rate of ~250 rpm (Figure 1). *m*-Chloroperoxybenzoic acid (*m*-CPBA) (Note 6) (11.7 g, 67.8 mmol, 1.36 equiv) is added to the reaction flask in one portion, via a powder funnel inserted in the side neck, followed by additional acetonitrile (10 mL); the

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resulting reaction mixture is an off-white suspension (Figure 1B). The side neck is sealed with a rubber septum and heating is commenced; the oil bath temperature is increased from 24 °C to 75 °C (oil bath temperature) over a period of 20 min (rate of increase ~ 1.25 °C/min) (Note 7). The reaction temperature is maintained at 75 °C for an additional 30 min.

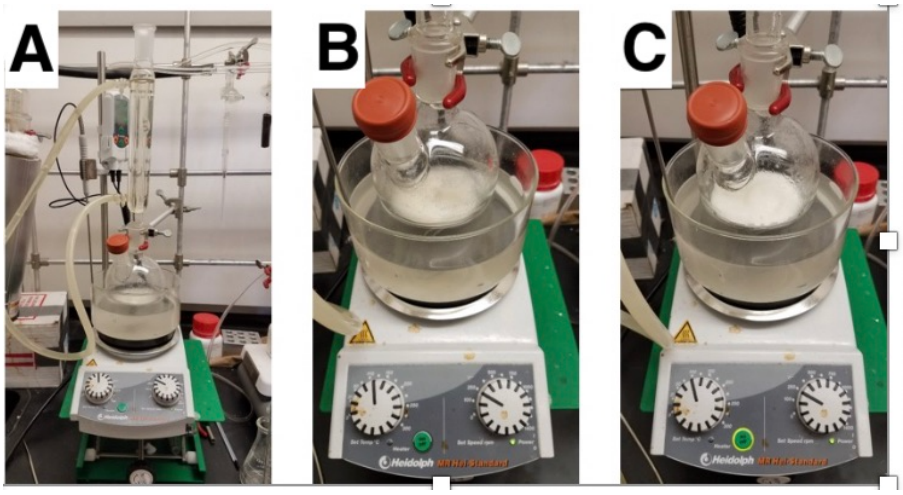


Figure 1. A) Reaction set-up; B) Reaction mixture after addition of *m*-CPBA at 25 °C; C) Reaction mixture at ~50 °C (Note 7).

The septum is removed from the side neck and 1,3,5-trimethoxybenzene (Note 8) (8.4 g, 50 mmol, 1 equiv) is added to the flask through a powder funnel, followed by additional acetonitrile (10 mL). The reaction mixture immediately becomes homogenous and the color changes from white to light orange (Figure 2A). The reaction is stirred for 5 min at 75 °C. The oil bath is lowered via the support jack and the reaction mixture allowed to cool for 30 min. Methyl *tert*-butyl ether (MTBE) (Note 9) (300 mL) is added to the reaction flask and a white precipitate forms immediately (Figure 2B); the heterogeneous mixture is stirred at room temperature for an additional 30 min. The precipitate is collected by vacuum filtration through a filter paper using a 8.5 cm diameter Büchner funnel. Additional MTBE (3×50 mL) is used to transfer residual solid from the reaction flask to the filter funnel. The resulting solid is air-dried at room temperature for 30 min. Compound **2** is isolated as a free-flowing off-white powder (26.3 g, 43.8 mmol, 88%)

(Notes 10 and 11) (Figure 2C). The purity of **2** was determined to be 98.7 wt % by qNMR (Notes 12 and 13).

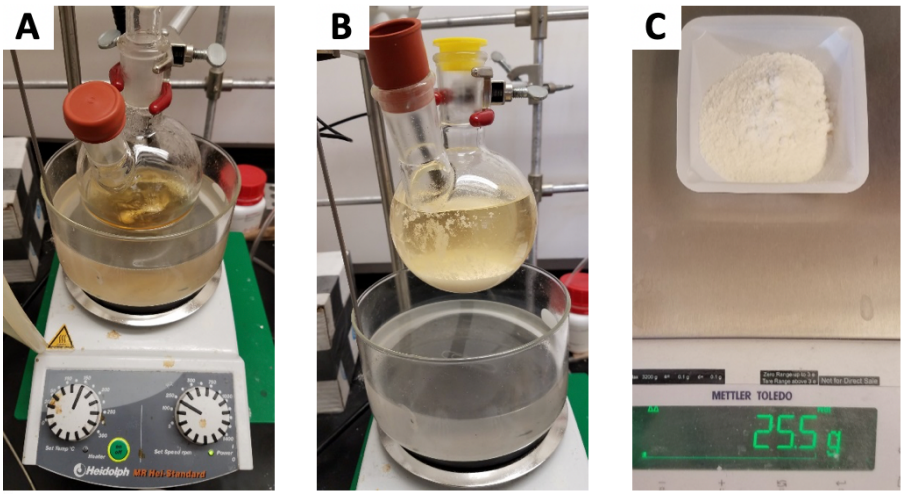


Figure 2. A) Reaction mixture after addition of 1,3,5-trimethoxybenzene; B) trituration with TBME; C) isolated product 2.

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) methyl-4-iodobenzoate, *p*-toluenesulfonic acid monohydrate, acetonitrile, *m*-chloroperoxybenzoic acid, 1,3,5-trimethoxybenzene, *tert*-butyl methyl ether, 4,4'-dihydroxybiphenyl, and dimethyl sulfoxide-d_6. *Caution! Reactions and subsequent operations involving peracids and peroxy compounds should be run behind a safety shield. For relatively fast reactions, the rate of addition of the peroxy compound should be slow enough so that it reacts rapidly and no significant unreacted excess is allowed to build up. The reaction mixture should be stirred efficiently while the peroxy compound is being added, and cooling should generally be provided and maintained since many reactions of peroxy compounds are exothermic. New or unfamiliar reactions, particularly those run at elevated temperatures, should be run first on a small scale. Reaction products should never be recovered from the final reaction mixture by distillation until all residual active oxygen compounds (including unreacted peroxy compounds) have been destroyed. Decomposition of active oxygen compounds may be accomplished by the procedure described in Korach, M.; Nielsen, D. R.; Rideout, W. H. Org. Synth.* ***1962****, 42, 50 (Org. Synth.* ***1973****, Coll. Vol. 5, 414).* See the discussion for details.

2. Stir-bar size/shape is an important factor for efficient mixing as a thick slurry forms in the reaction. Smaller, or "football" shaped, stir bars resulted in poor mixing and inconsistent yields.
3. Methyl-4-iodobenzoate was purchased from Oakwood Chemicals (99%) and used as received. The checkers purchased methyl-4-iodobenzoate (99%) from Acros Organics and used the material as received.
4. *p*-Toluenesulfonic acid monohydrate was purchased from Sigma-Aldrich (T35920, ≥ 98%) and used as received. The checkers purchased *p*-toluenesulfonic acid monohydrate (>98.5%) from Alfa Aesar and used the material as received.
5. Acetonitrile was purchased from Oakwood (4 L) and used as received. The checkers purchased acetonitrile (99.5% pure) from Alfa Aesar and used the material as received.
6. *m*-Chloroperoxybenzoic acid (*m*-CPBA) was purchased from Aldrich (≤ 77%). The *m*-CPBA was titrated iodometrically by the submitters and determined to contain 74 wt. % active oxidant.[2] The checkers purchased *m*-chloroperoxybenzoic acid (*m*-CPBA, ⩽77%) from Aldrich and used the material as received.
7. When the oil bath reached 50–55 °C a thick white slurry is formed (Figure 1C).

8. 1,3,5-Trimethoxybenzene was purchased from Oakwood and used as received. The checkers purchased 1,3,5-trimethoxybenzene (99%) from Alfa Aesar and used the material as received.
9. Methyl *tert*-butyl ether (MTBE) was purchased from Fisher Scientific (Acros Organics, 99.9% pure) and used as received.
10. A second reaction on identical scale provided 26.6 g (89%) of the product **2**.
11. Characterization of **2**: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.28 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 3.94 (s, 6H), 6.48 (s, 2H), 7.11 (d, J = 7.6 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.97 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.8 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 20.83, 52.70, 56.26, 57.43, 87.07, 92.16, 121.10, 125.53, 128.13, 131.78, 132.09, 134.67, 137.78, 145.53, 159.47, 165.21, 166.37. FT-IR (film): 3083, 1720, 1581, 1212, 1168, 1115, 680, 566 cm^{-1}. HRMS (ESI$^+$): Calculated for $C_{17}H_{18}IO_5^+$ [M - OTs]$^+$: 429.0193; Observed 429.0192. mp 192 – 194 °C (dark brown liquid at 194 °C).
12. The purity of **2** (MW 600.42; 14.9 mg) was determined by qNMR in DMSO-d_6 as solvent and 4,4'-dihydroxybiphenyl (> 99 wt% purity; MW 186.21; 11.8 mg) as internal standard; the relaxation time (D1) was set to 30 seconds.
13. 4,4'-Dihydroxybiphenyl was purchased from TCI America (> 99%) and used as received.

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.

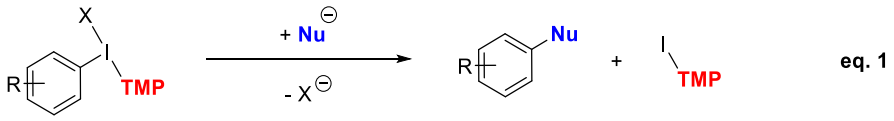
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant

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

Hypervalent iodine continues to intrigue organic chemists with its diverse breadth of reactivity.[3] The use of diaryliodonium salts[4] as aryl-transfer reagents has increased dramatically in the past decade as they have become more available by the development of efficient "one-pot" synthesis methods.[2,5] Unsymmetrical diaryliodonium salts that selectively, and predictably, transfer one aryl group over the other are particularly desirable reagents, especially for the transfer of elaborate aryl groups to nucleophilic moieties. While the mesityl (Mes; 2,4,6-trimethylphenyl) group effectively serves as a general auxiliary in metal-catalyzed reactions of diaryliodonium salts,[4a] a broadly applicable auxiliary has not been adopted in metal-free reactions. Despite chemoselectivity studies[6,7] that provide structural insight for auxiliary development few, if any, auxiliaries are in wide-spread use for metal-free nucleophile arylation reactions.[8] We have been exploring the use of 2,4,6-trimethoxyphenyl (TMP) group as a spectator auxiliary of unsymmetrical aryl(TMP)iodonium salts toward this end and recently developed general one-pot syntheses of the tosylate and trifluoroacetate salts.[9] On the basis of our continuing efforts[9a,10] to develop and promote the use of aryl(TMP)iodonium salts in metal-free aryl transfer reactions (equation 1), we describe here a decagram scale synthesis of one member in this class of reagent.

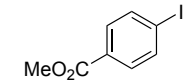
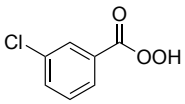
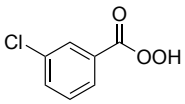
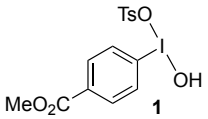
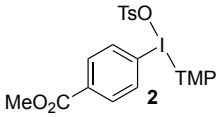


eq. 1

Based on limited safety information on hypervalent iodine in the literature[11] and the potential for exothermic events that have been suggested in a related diaryliodonium salt synthesis,[12] we conducted a safety evaluation during the development of this procedure. We specifically focused on the potential thermal hazards of *I*-oxidation with *m*-CPBA and the thermal stability of the hypervalent iodine species (intermediate **1** and product **2**). We employed differential scanning calorimetry (DSC) to determine the onset temperature and magnitude of exothermic decomposition events for the reagents, intermediate and product (see Table 1). Additionally, we employed reaction calorimetry to determine the heat of reaction for each stage. The starting methyl-4-iodobenzoate does not exhibit exothermic decomposition, but has a clean melt that begins at 105 °C (Table 1). "Wet" (commercial) *m*-CPBA and "dried" (under vacuum) *m*-CPBA[2,13] both exhibited a large exotherm (~ 1000 J/g) (Table 1). The decomposition of "dried" *m*-CPBA is more vigorous than "wet" *m*-CPBA, which warranted the use of "wet" reagent in this procedure. An isolated sample of solid [hydroxy(tosyloxy)iodo]aryl intermediate **1**[13] displays an exothermic decomposition of 295 J/g at 139 °C (Table 1). The thermal risk of **1** is mitigated by the boiling point (82 °C) of the acetonitrile solvent and the maximum reaction temperature (75 °C) being significantly lower than the onset temperature. Notably, analysis of the "reaction slurry" after the oxidation stage (Figure 1C) revealed a comparable onset temperature of 142 °C but a lower exotherm size of 23 J/g (Table 1). The product **2**, isolated and dried, displayed an exotherm of 188 J/g that occurred at 182 °C, following a broad melt. Reaction calorimetry revealed the oxidation was exothermic (stage 1; ~ 121 kJ/mol), and the addition of trimethoxybenzene was slightly endothermic (stage 2). Related reaction sequences conducted in a flow reactor have been reported to have an exothermic heat of reaction of 160-180 kJ/mol.[14] Notably, despite the heat generated in the present case, the internal temperature did not exceed the target of 75 °C due to efficient heat transfer. The following conclusions contributed to the procedure described above. 1) *m*-CPBA is the most energetic compound in the reaction but can be safely used by employing the "wet" commercial reagent and gradually heating the reaction mixture in stage 1. 2) The hypervalent iodine

intermediate **1** and product **2**, have smaller exothermic decompositions as isolated solids compared to *m*-CPBA, and onset temperatures well above the operating reaction temperature (75 °C); the reaction slurry has an almost negligible exotherm. 3) Isothermal aging of **2** (neat) at 130 °C displayed autocatalytic decomposition after 3 hours and therefore prolonged heating of the neat solid **2** should be avoided.

Table 1. Thermal stability of reagents, 1, and 2 by DSC[a]

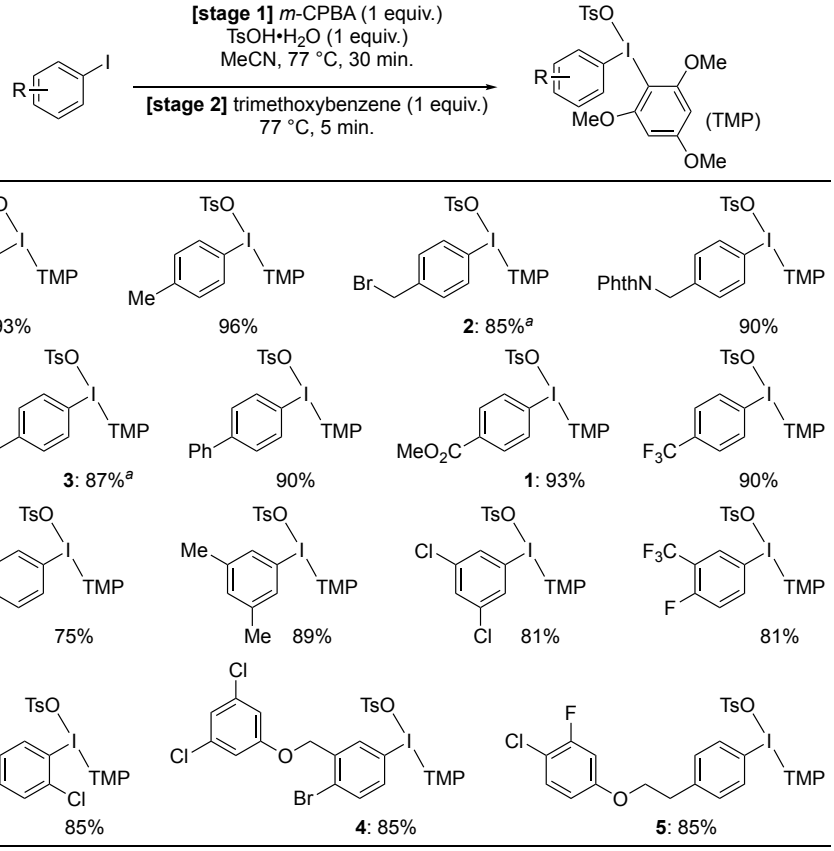
Structure (name)	Melting point (°C)	Exotherm onset temp. (°C)	Exotherm (J/g)
 methyl-4-iodobenzoate	105 (onset)	N/A	N/A
 "wet" *m*-CPBA	N/A	62	992
 "dried" *m*-CPBA	N/A	86	1065
 **1**	N/A	139	295
Reaction slurry after stage 1 (Fig. 1C)	N/A	142	23
 **2**	163-182 (DSC) 170-188 (capiliary)	182	188

[a] Scan from ambient to 350 °C at 5K/min.

We have previously described 25 examples of aryl(TMP)iodonium tosylates with isolated yields ranging from 67-96% (88% average).[8a] Selected examples are presented here, which highlight the functional groups and substitution patterns that are compatible on the aryl group (Table 2). Electrophilic (i.e., benzyl bromide) and oxidizable (i.e., benzyl alcohol)

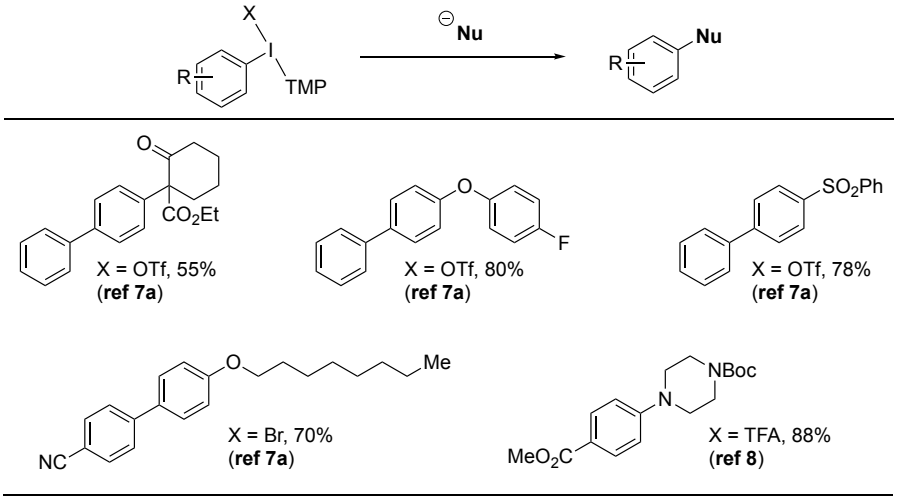
functional groups are tolerated at more mild temperature (room temp). *Ortho*-, *meta*-, and *para*-substitution is tolerated on the aryl moiety and the synthesis of aryl(TMP)iodonium salts with elaborate aryl groups support the use of unsymmetrical iodonium salts. We have also found that aryl(TMP)iodonium tosylates undergo facile anion exchange with other anions under aqueous conditions to generate the corresponding aryl(TMP)iodonium bromides, iodide, trifluoroacetates, triflates, tetrafluoroborates, and hexafluorophosphates.[8a] Finally, we have demonstrated that aryl(TMP)iodonium salts are useful reagents for *C*-, *N*-, *O*-, *S*-nucleophiles (Table 3);[8,9] we, and others, are continuing to investigate novel arylation reactions with these reagents.

Table 2. Selected scope of aryl(TMP)iodonium salts



[a]Reaction conducted at room temperature over both stages.

Table 3. Synthetic applications of aryl(TMP)iodonium salts



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Appendix
Chemical Abstracts Nomenclature (Registry Number)

Methyl 4-iodobenzoate (619-44-3)
p-Toluenesulfonic acid monohydrate (6192-52-5)
Acetonitrile (75-05-8)
m-Chloroperbenzoic acid (937-14-4)
1,3,5-Trimethoxybenzene (621-23-8)
tert-Butyl methyl ether (1634-04-4)
4,4'-Dihydroxybiphenyl (92-88-6)

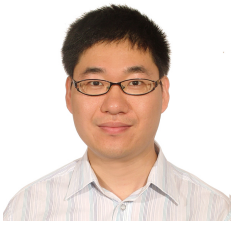
David Stuart was born and raised in Victoria, British Columbia, Canada. He obtained a B.Sc. (Honors) degree from the University of Victoria in 2005 and a Ph.D. from the University of Ottawa in 2010 under the supervision of Prof. Keith Fagnou. Dave was an NSERC Postdoctoral Fellow with Prof. Eric Jacobsen at Harvard from 2010-2012. He began his independent career in the Department of Chemistry at Portland State University in the fall of 2012. His research group focuses on the discovery and development of novel arylation reactions with unsymmetrical diaryliodonium salts.

Thomas L. Seidl was born in 1977 in Honolulu, Hawaii. He received his B.S. in chemistry from the University of Hawaii in 2000. Thomas moved to Oregon in 2005 and spent several years managing a coatings development group at Bayer Diabetes Care. In 2012 Thomas joined the doctoral program at Portland State University and his thesis focused on the development of reagents and reactions that use hypervalent iodine. He graduated in 2017. Thomas is currently the Chief Scientific Officer of Pacific Diabetes Technologies.

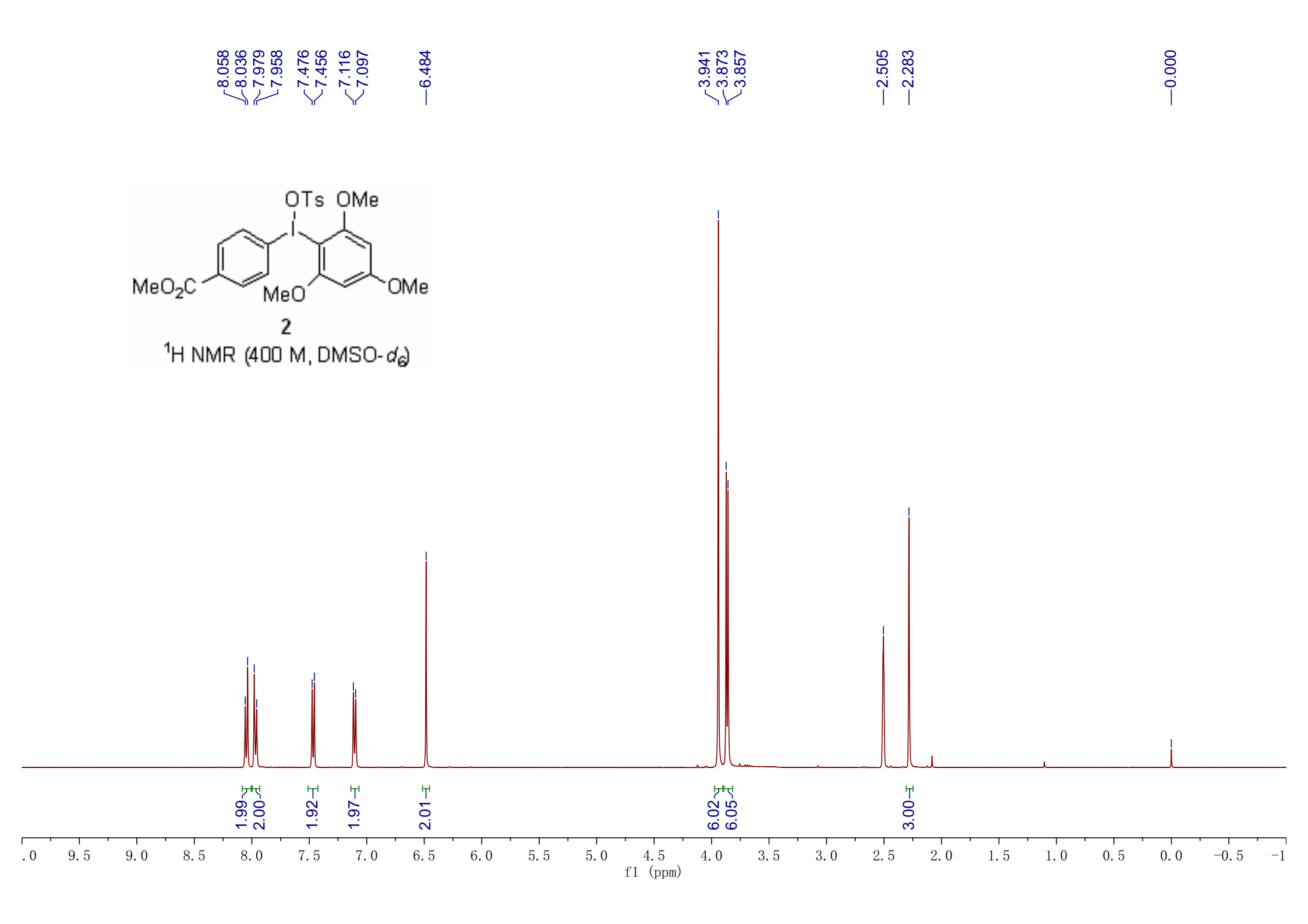
Aaron Moment worked for DuPont Pharmaceuticals as a research engineer for one year before joining Merck & Co., Inc., Rahway, NJ, USA in 2001, where he worked for 17 years. During his industrial career, he focused on the scale up, development, and commercialization of small molecule active ingredients. Aaron recently joined Columbia University as a Professor of Practice in Chemical Engineering, where he is teaching undergraduates and also developing graduate level courses in the area of pharmaceutical process development. He may be contacted at ajm2293@columbia.edu.

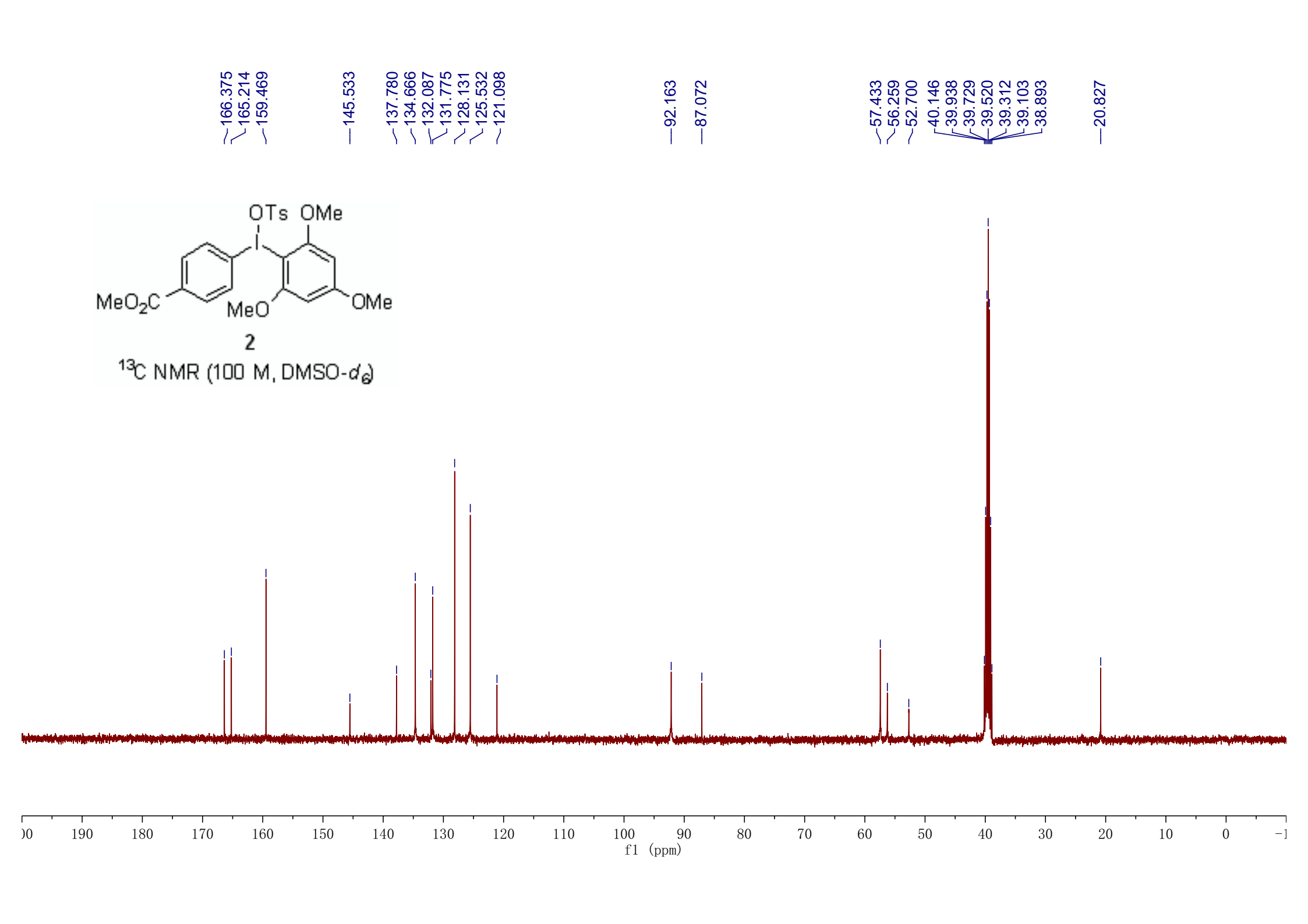
Chuck Orella received a B.S. from UC Santa Barbara, a M.S. from the University of Delaware, and a Ph.D. from the University of Virginia in Chemical Engineering. During his career in pharmaceutical development, characterization, scale up, and technology transfer he has had a lead role in bringing 5 API's and 2 vaccines to market. He currently leads a group that uses thermal and pressure analysis for evaluating the process safety of pharmaceuticals in development and commercial production.

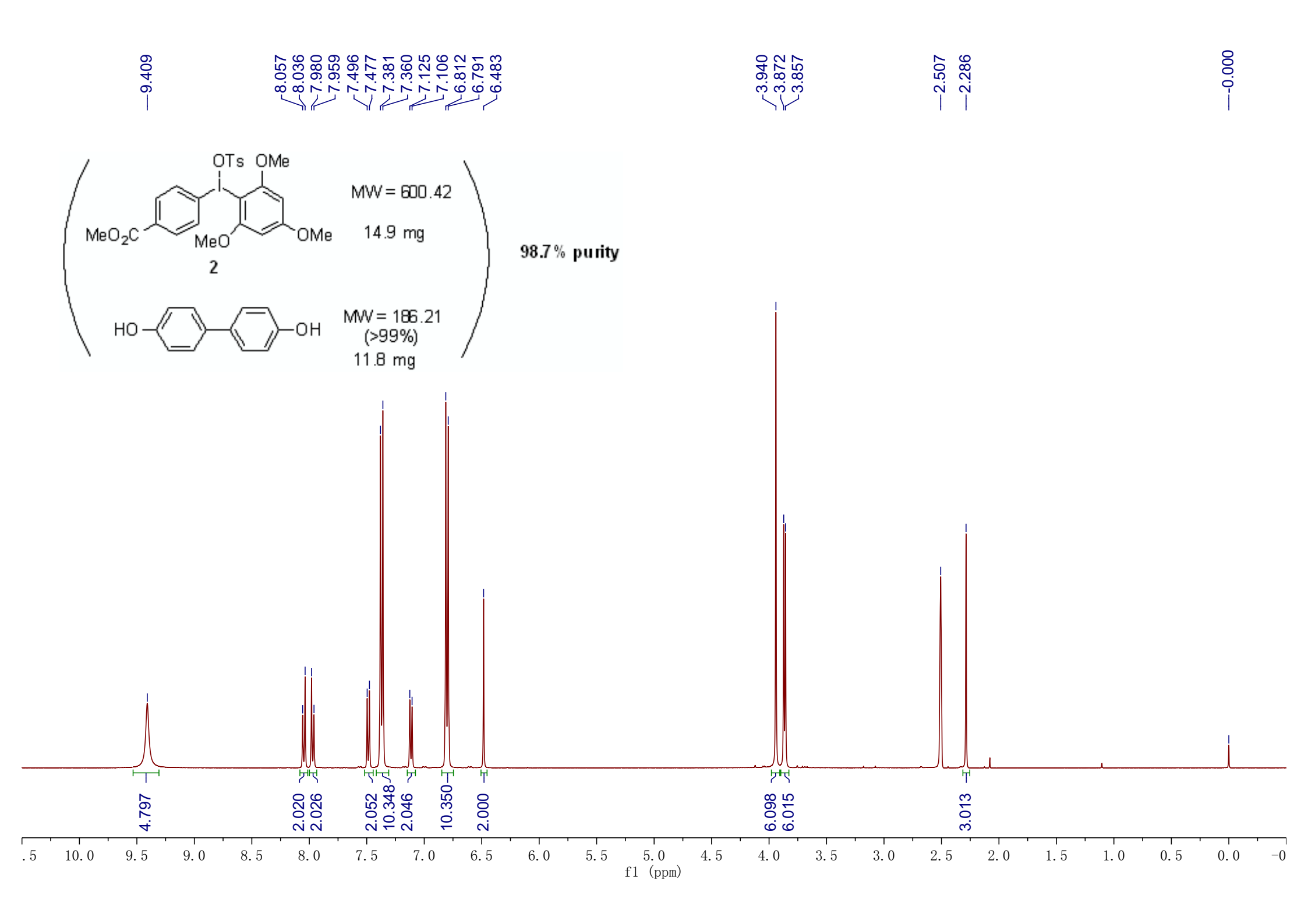
Thomas Vickery was born in Boston MA in 1959, and grew up outside Philadelphia. He graduated from Carnegie-Mellon in 1986 with a B.S. in Chemical Engineering. He has worked in process safety and reaction calorimetry from 1989 to present, initially at FMC Corporation, and from 1994 to present at Merck & Co., Inc., Rahway, NJ, USA. There he has made major contributions in the areas of corrosion, reaction calorimetry, understanding exothermic decompositions, electrochemistry and laboratory reaction safety management. He has several published articles on a variety of process safety topics.



Dr. Zhaobin Han received his B.S. degree in chemistry from Nanjing University in 2003. He received his Ph.D. degree from Shanghai Institute of Organic Chemistry under the supervision of Prof. Kuiling Ding and Prof. Xumu Zhang in 2009, working on development of novel chiral ligands for asymmetric catalysis. He is now an Associate Professor in the same institute and his current research interests focus on the development of efficient catalytic methods based on homogeneous catalysis.


8.058
8.036
7.979
7.958
7.476
7.456
7.116
7.097
6.484
3.941
3.873
3.857
2.505
2.283
0.000
OTs
OMe
I
MeO2C
MeO
OMe
2
1H NMR (400 M, DMSO-d6)
1.99
2.00
1.92
1.97
2.01
6.02
6.05
3.00
f1 (ppm)


166.375
165.214
159.469
145.533
137.780
134.666
132.087
131.775
128.131
125.532
121.098
92.163
87.072
57.433
56.259
52.700
40.146
39.938
39.729
39.520
39.312
39.103
38.893
20.827
OTs OMe
MeO2C
MeO
OMe
2
13C NMR (100 M, DMSO-d6)
f1 (ppm)


9.409
8.057
8.036
7.980
7.959
7.496
7.477
7.381
7.360
7.125
7.106
6.812
6.791
6.483
3.940
3.872
3.857
2.507
2.286
0.000
OTs
OMe
MeO2C
MeO
OMe
2
MW = 600.42
14.9 mg
98.7 % purity
HO
OH
MW = 186.21
(>99%)
11.8 mg
4.797
2.020
2.026
2.052
10.348
2.046
10.350
2.000
6.098
6.015
3.013
f1 (ppm)