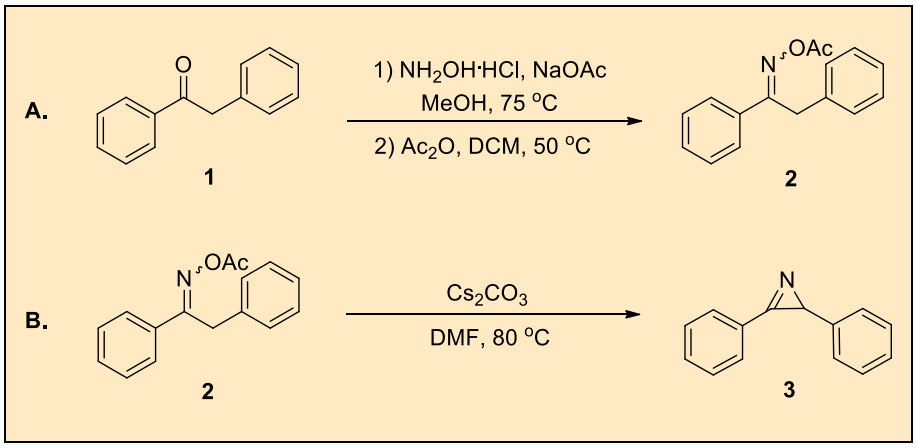
Organic Syntheses

Synthesis of 2,3-Diaryl-2*H*-azirines via Cs_2CO_3-Mediated Cyclization of Ketoxime Acetates

Mi-Na Zhao and Zheng-Hui Guan[1]*

Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of Ministry of Education, Department of Chemistry & Materials Science, Northwest University, Xi'an 710127, P. R. China

Checked by Dirk Trauner and Julius R. Reyes



Procedure (Note 1)

A. *1,2-Diphenylethanone O-acetyl oxime (**2**)*. A 250 mL single-necked, 24/40 recovery flask equipped with a 3.5 x 1.5 cm egg-shaped Teflon-coated magnetic stir bar is charged with 1,2-diphenylethanone (11.76 g, 59.9 mmol, 1.0 equiv) (Note 2), anhydrous methanol (100 mL) (Note 3), hydroxylamine hydrochloride (5.00 g, 72.0 mmol, 1.2 equiv) (Note 4), and sodium acetate anhydrous (7.38 g, 90.0 mmol, 1.50 equiv) (Note 5). The flask is then fitted with a Findenser and placed under a positive pressure of N_2 (Note 6). The resulting white, milky slurry is brought to a gentle reflux by placement onto a pre-heated 75 °C oil bath for 2 h (Figure 1A). During this time, the reaction

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remained a slurry (Notes 7 and 8). Upon cooling to 25 °C, the reaction is directly concentrated on a rotary evaporator under reduced pressure (40 °C, 110 mmHg). Water (80 mL) is added, and the mixture is extracted with ethyl acetate (3 x 60 mL) using a 250-mL separatory funnel. The combined organic layers are combined, dried over anhydrous Na_2SO_4 (40 g), and filtered through a cotton plug. The filtrate is concentrated on a rotary evaporator under reduced pressure (40 °C, 90 mmHg) and placed under high vacuum for 30 min to yield the crude oxime as a light yellow crystalline solid (12.89 g, crude quant. yield), which was used directly without purification (Notes 9) (Figure 1B).

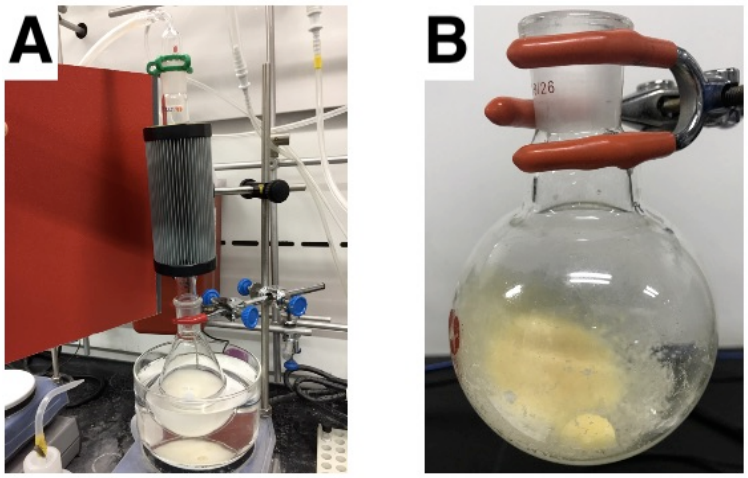


Figure 1. A) Reaction setup for Step A (1,2-diphenylethanone oxime) (photo provided by checkers); B) Crude product of 1,2-diphenylethanone oxime (photo provided by the submitters)

A 250 mL single-necked, 24/40 recovery flask equipped with a 3.5 x 1.5 cm egg-shaped Teflon-coated magnetic stir bar is charged with the crude oxime, dichloromethane (50 mL) (Note 10) and acetic anhydride (12.3 g, 120 mmol, 2.0 equiv) (Note 11). The flask is then fitted with a Findenser and placed under a positive pressure of N_2, and the resulting yellow solution is brought to a gentle reflux for 2 h by placement onto a preheated 50 °C oil bath (Notes 12 and 13) (Figure 2A). Upon cooling to 25 °C, the reaction is partitioned between water (50 mL) and dichloromethane (50 mL) in 250-mL separatory funnel. The layers are separated, and the aqueous layer is further extracted with dichloromethane

(2 x 50 mL). The combined organic layers are dried over anhydrous Na_2SO_4 (30 g), filtered through a cotton plug, and concentrated on a rotary evaporator (40 °C, 300 mmHg) (Note 14). The crude residue is purified by column chromatography on silica gel to afford 1,2-diphenylethanone *O*-acetyl oxime (**2**) as a light yellow solid (14.50 g, 57.2 mmol, 96%) (Figure 2B) (Notes 15, 16, 17, 18, and 19).

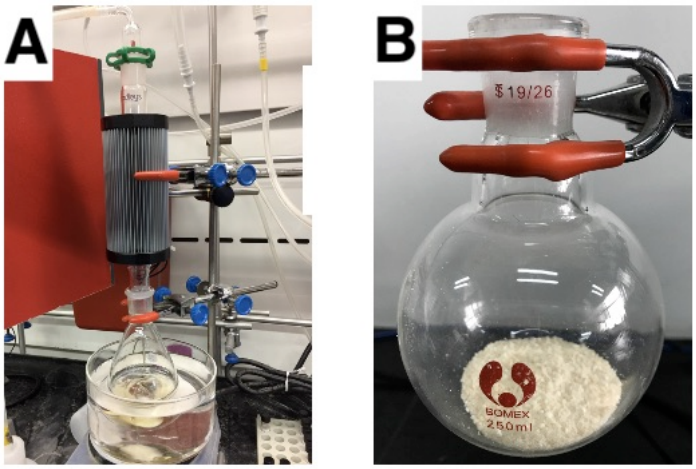


Figure 2. A) Reaction setup for Step A (1,2-diphenylethanone *O*-acetyl oxime (photo provided by checkers); B) Compound 1,2-diphenylethanone *O*-acetyl oxime (2) (photo provided by the submitters)

B. *2,3-Diphenyl-2H-azirine (**3**)*. A 250 mL single-necked, 24/40 recovery flask equipped with a 3.5 x 1.5 cm egg-shaped Teflon-coated magnetic stir bar is charged with **2** (8.44 g, 33.32 mmol, 1.0 equiv) and *N*,*N*-dimethylformamide (DMF) (100 mL) (Note 20), and the resulting colorless solution is treated with cesium carbonate (15.64 g, 48.0 mmol, 1.4 equiv) (Note 21) without appreciable change in appearance. The flask is evacuated and backfilled with N_2 three times, and the mixture is placed onto an 80 °C pre-heated oil bath under N_2 for 1 h (Notes 22 and 23) (Figure 3). During this time the reaction remained a mixture, and a color change from colorless to yellow is observed during the course of the reaction (Note 24). Upon cooling to ambient temperature, the reaction mixture is diluted with water

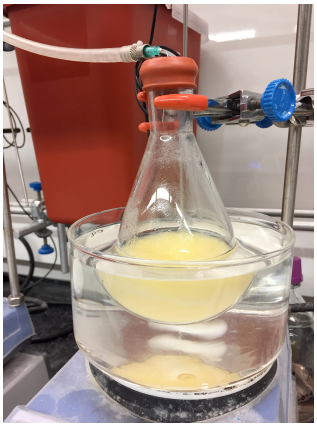


Figure 3. Reaction setup for Step B (photo provided by checkers)

(200 mL) and extracted with 10% EtOAc in hexanes (3 x 100 mL) in a 1 L separatory funnel. The combined organic layers are then washed with water (2 x 100 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 (45 g), and filtered through a cotton plug. Following concentration on a rotary evaporator under reduced pressure (40 °C, 200 mmHg). The residual yellow oil is purified by column chromatography to afford 2,3-diphenyl-2*H*-azirine (**3**) as yellow liquid that eventually solidified (5.12 g, 26.49 mmol, 79%) (Figure 4) (Notes 25, 26, 27, and 28).

Figure 4. 2,3-Diphenyl-2*H*-azirine (3) (photo provided by the submitters)

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 1,2-diphenylethanone, hydroxylamine hydrochloride, sodium acetate anhydrous, methanol, ethyl acetate, dichloromethane, acetic anhydride, hexanes, cesium carbonate, and *N*,*N*-dimethylformamide.
2. The submitters purchased 1,2-diphenylethanone (98%) from Bide Pharmatech Ltd and used as received. The checkers purchased 1,2-diphenylethanone (98%) from Oakwood Chemical and used the material as received.
3. The submitters purchased anhydrous methanol from Tianjin Yongda Chemical Reagent Company Limited and used the material as received. The checkers purchased "Extra Dry" methanol (99.9%) from Acros and used it as received.
4. The submitters purchased hydroxylamine hydrochloride (98.5%) from Guangzhou Jinhuada Chemical Reagent Company Limited and used it as received. The checkers purchased hydroxylamine hydrochloride (ACS grade, 99%) from Oakwood Chemical and used the material as received.
5. The submitters purchased sodium acetate anhydrous (99%) from Sinopharm Chemical Reagent Company Limited and used the material

as received. The checkers purchased sodium acetate (anhydrous, 99%) from Oakwood Chemical and used it as received.

6. Radleys Findensers were purchased from Heidolph Instruments.
7. A 700 mL oil bath was used and stirring was performed at 500 rpm. The submitters observed during heating that a pale yellow solution was obtained and that no color change was observed over the course of the reaction.
8. The submitters monitored the reaction by TLC analysis on silica using hexanes/ethyl acetate (8:1). R_f of **1** = 0.72, R_f of 1,2-diphenylethanone oxime = 0.48. The checkers, due to the heterogeneity of the mixture, monitored the reaction by NMR analysis of a reaction aliquot worked up as indicated in the procedure.
9. The submitters obtained the following characterization data of the non-purified 1,2-diphenylethanone oxime: yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.24 (s, 2H), 7.26-7.27 (m, 5H), 7.34-7.36 (m, 3H), 7.60-7.62 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 32.5, 126.4, 126.6, 128.6, 129.4, 130.2, 133.5, 135.4, 136.3, 157.5. HRMS calcd (ESI) *m*/*z* for $C_{14}H_{13}NNaO$: $[M+Na]^+$ 234.0889. Found: 234.0892.
10. The submitters purchased dichloromethane from Tianjin Yongda Chemical Reagent Company Limited and used the solvent as received. The checkers purchased "Extra Dry" dichloromethane (99.8%) from Acros and used the solvent as received.
11. The submitters purchased acetic anhydride (98.5%) from Sinopharm Chemical Reagent Company Limited and used the material as received. The checkers purchased acetic anhydride (ACS grade, 99%) from Oakwood Chemical and used the material as received.
12. A 700 mL oil bath and stirring was performed at 500 rpm. The submitters noted that during the reflux a yellow solution was obtained and no color change was observed over the course of the reaction.
13. The submitters monitored the reaction by TLC analysis on silica using hexanes/ethyl acetate (10:1). R_f of 1,2-diphenylethanone oxime = 0.27, R_f of **2** = 0.23. The checkers monitored the reaction by ^{1}H NMR analysis of a reaction aliquot worked up as indicated in the procedure.
14. Upon cooling to −20 °C, the submitters were able to obtain the crude oxime as a yellow solid (ca. 13 g) containing some residual solvents. The checkers did not obtain a crystalline solid. Purification by column chromatography on silica gel (Note 16) and cooling purified **2** to −15 °C also did not induce solidification.

15. The submitters recrystallized the crude oxime as follows: Ethyl acetate (3 mL) and hexanes (60 mL) was added to the crude residue and the flask equipped with a condenser. The mixture was heated until all the solids were dissolved. The solution was cooled to room temperature and then placed in an ice bath at 0 °C to induce formation of pale yellow solids. The solid was collected by filtration through a Büchner funnel and washed with ice-cold hexanes (2 × 15 mL).
16. The checkers purchased Merck Geduran Si 60 (0.040−0.063 mm) silica gel. Using 84 g of silica gel, a wet-packed column of 5.5 cm in diameter and 8 cm in height is obtained. The product was eluted using a gradient from 5% to 20% EtOAc in hexanes, and a total of 69 20-mL fractions were collected. The product was found by TLC analysis to be in fractions 33 to 58, which were concentrated under reduced pressure and placed under high vacuum (7×10^{-2} mmHg) for 30 min.
17. The checkers obtained the following characterization data for **2**: light yellow liquid (isomer ratio > 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.23 (s, 3H), 4.24 (s, 2H), 7.17−7.24 (m, 3H), 7.24−7.31 (m, 2H), 7.32−7.44 (m, 3H), 7.70−7.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.0, 34.5, 126.9, 127.7, 128.5, 128.8, 129.0, 130.8, 134.2, 135.4, 163.8, 168.8; IR (ATR): 3029, 1766, 1601, 1495, 1445, 1366, 1199, 1000, 952, 922, 898, 762 cm^{-1}; HRMS calcd (APCI) *m*/*z* for $C_{16}H_{15}NO_2$ $[M+Na]^+$: 276.0995, found 276.1008.
18. The checkers determined the purity of **2** to be 98%, as determined by quantitative NMR using 23.2 mg of 1,3,5-trimethoxybenzene (99%) as an internal standard and 33.7 mg of **2**.
19. On half-scale (6.00 g of **1**), the checkers obtained a 94% yield of **2**, with a purity of 98% (31.6 mg **2**, 21.2 mg 1,3,5-trimethoxybenzene).
20. The submitters purchased *N*,*N*-dimethylformamide from Guangzhou Jinhuada Chemical Reagent Company Limited and used the solvent as received. The checkers purchased from *N*,*N*-dimethylformamide (ACS grade, 99.8%) from Oakwood Chemical and used the solvent as received.
21. The submitters purchased cesium carbonate (99.9%) from Adamas, which was used the material as received, and used the cesium carbonate in fewer equivalents (1.2 equiv) as base. The checkers purchased cesium carbonate (99%) from Oakwood Chemical and used it as received.
22. A 700-mL oil bath was used with stirring performed at 860 rpm.
23. The submitters monitored the reaction mixture by TLC analysis on silica gel using hexanes/ethyl acetate (8:1): R_f of **2** = 0.40, R_f of **3** = 0.73. The

checkers monitored the reaction mixture by TLC analysis on silica gel using 10% EtOAc in hexanes: R_f of **2** = 0.19, 0.13 and R_f of **3** = 0.47.

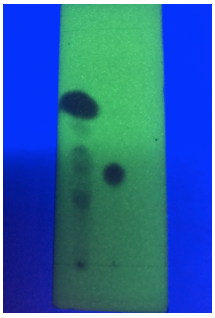


Figure 5. Crude product TLC after Step B obtained by submitters

24. The submitters observed during heating that a pale yellow solution was obtained and that no color change was observed over the course of the reaction.
25. The checkers used 30 g of silica gel to obtain a wet-packed column of 4 cm in diameter and 5 cm in height. The product was eluted using 5% EtOAc in hexanes, and a total of 39 12-mL fractions were collected. The product was found by TLC analysis to be in fractions 6 to 19, which were concentrated under reduced pressure and placed under high vacuum (8×10^{-2} mmHg) for 22 h.
26. The checkers obtained the following characterization data for **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.33 (s, 1H), 7.13−7.19 (m, 2H), 7.22−7.32 (m, 3H), 7.51−7.65 (m, 3H), 7.86−7.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.6, 124.3, 126.2, 127.2, 128.4, 129.4, 130.0, 133.3, 141.0, 163.6; IR (ATR): 3029, 1741, 1601, 1495, 1450, 1321, 989, 758 cm^{-1}; HRMS calcd (APCI) *m*/*z* for $C_{14}H_{11}N$ $[M+H]^+$: 196.0964, found 196.0966.
27. The checkers found **3** to have only moderate stability toward sílica gel and determined the purity of **3** to be 92%, as determined by quantitative NMR using 31.4 mg of 1,3,5-trimethoxybenzene as an internal standard and 32.9 mg of **3**.
28. On half-scale (4.23 g of **2**) the checkers obtained an 85% yield of **3** with a purity of 95% (28.9 mg **3**, 25.6 mg 1,3,5-trimethoxybenzene).

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.

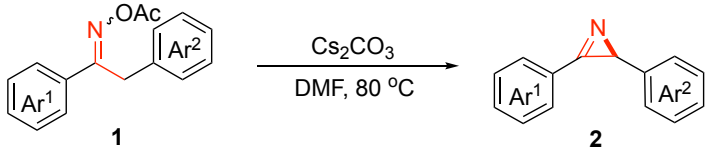
Discussion

2*H*-Azirines, the smallest azaheterocycles, are fundamental and prevalent structure in many natural products, medicines, and antibiotic molecules, including azirinomycin, dysidazirine, and antazirine.[2] Conventionally, synthetic approach to 2*H*-azirines is relied on thermal/photochemical rearrangement of vinyl azides or Neber reaction (nucleophilic cyclization of ketoxime tosylates).[3] However, these conventional methods are mainly limited to the synthesis of 2-carboxylates-

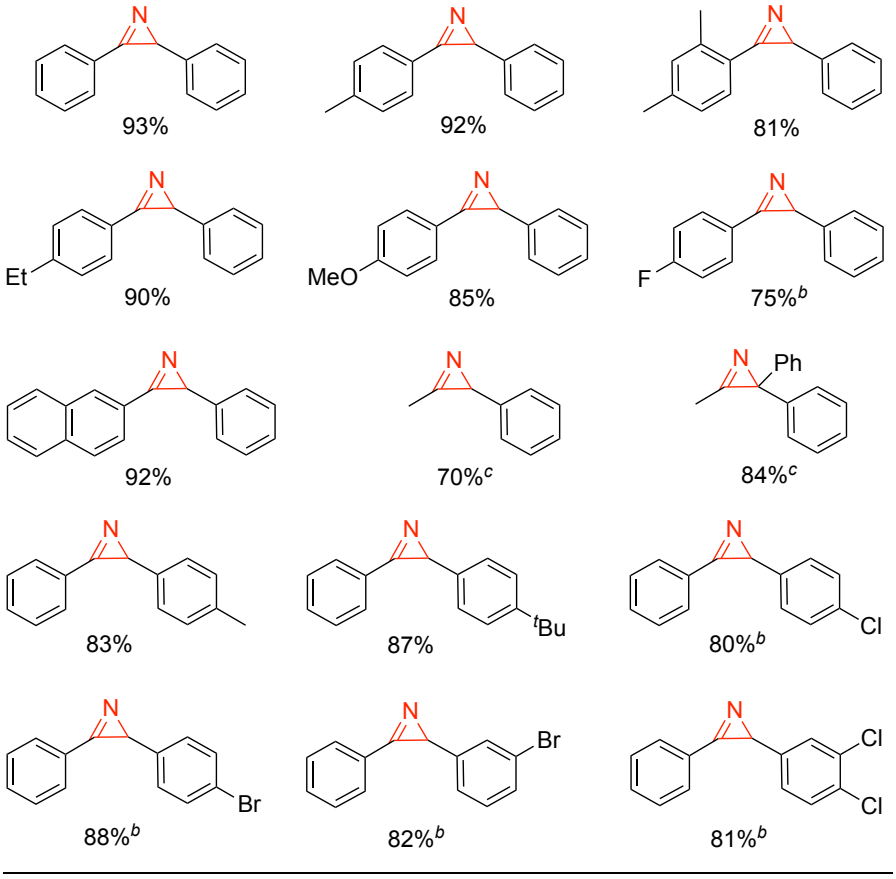
substituted 2*H*-azirines and 2,2-unsubstituted 2*H*-azirines in high efficiency. The 2,3-diaryl-2*H*-azirines synthesis by these methods generally results in low yields.[4] Although new synthetic strategies, such as the oxidation of enamines,[5] Wolff rearrangement of *α*-diazo oxime ethers,[6] and decarboxylative ring contraction of isoxazol-5(4*H*)-ones,[7] have been developed for the synthesis of 2*H*-azirines in recently, there is still lacking efficient method for the synthesis of 2,3-diaryl-2*H*-azirines. In view of their broad utility of 2,3-diaryl-2*H*-azirines in the synthesis of bioactive azaheterocycles including pyrroles, oxazines, dibenzocarbazole, azepines and pyridines,[8] the development of efficient and practical method for the synthesis of 2,3-diaryl-2*H*-azirines remains highly desirable.

Ketoximes and their derivatives are versatile building blocks in organic synthesis because of their ready accessibility and high reactivity.[9] In recent years, organic transformations of ketoxime carboxylates via N-O bond cleavage for the construction of azaheterocycles is an active area of research.[10] Given our long-term endeavor in the development of azaheterocycles synthesis from ketoximes,[11] herein, we describe a practical and efficient Cs_2CO_3-mediated cyclization of ketoxime acetates for the synthesis of 2,3-diaryl-2*H*-azirines.[12] The salient features of this method include easily available starting materials, broad functional group compatibility, and mild reaction conditions (Table 1).

Table 1. Selected Scope of 2,3-Diaryl-2*H*-azirines[a]



1 **2**



[a]Reaction condition: ketoxime acetates **1** (0.2 mmol), Cs_2CO_3 (0.24 mmol), DMF (1 mL), 80 °C, Ar; isolated yield. [b]Cs_2CO_3 (20 mol%). [c]60 °C.

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References

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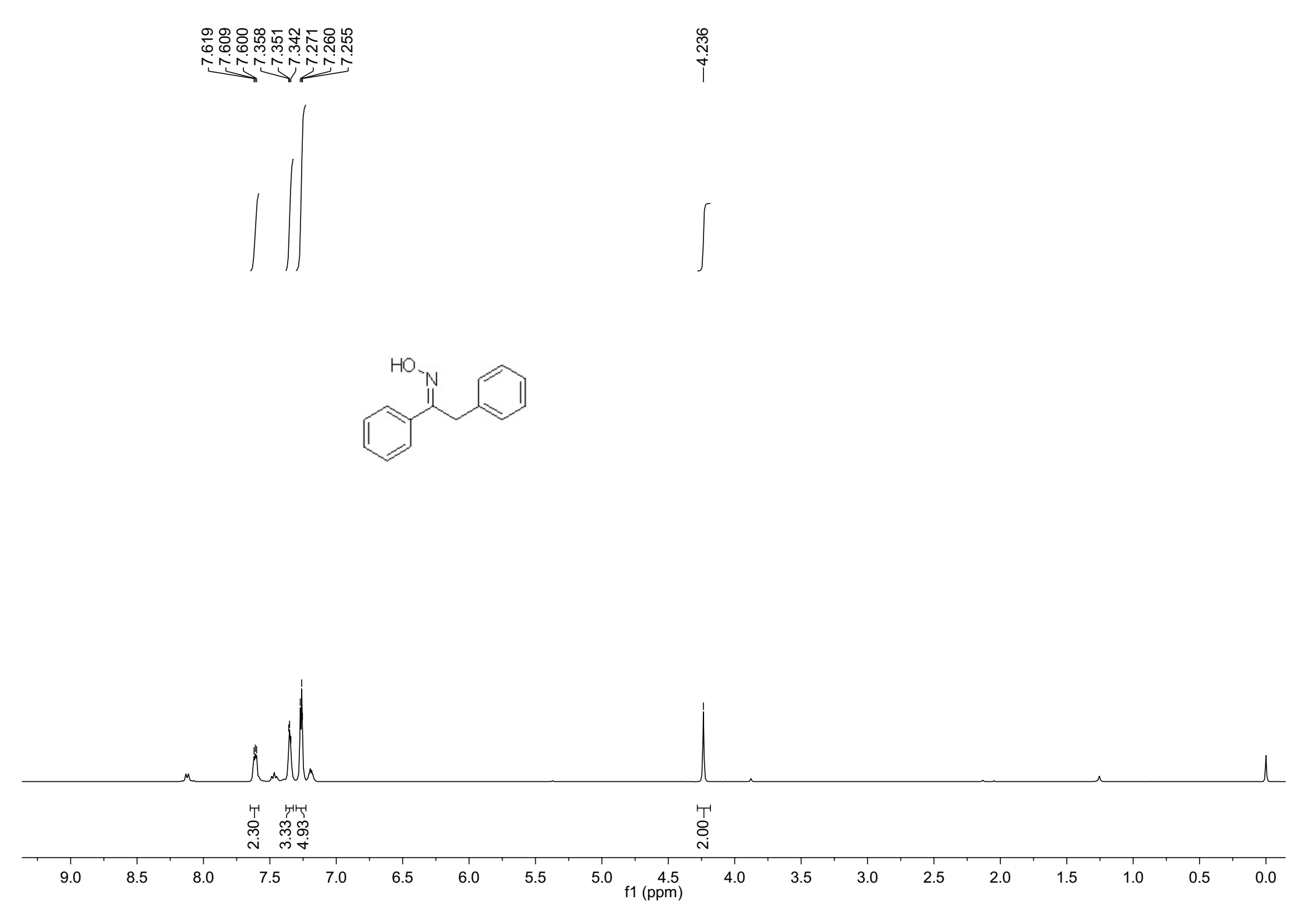
Appendix
Chemical Abstracts Nomenclature (Registry Number)

1,2-Diphenylethanone: 2-Phenylacetophenone; (451-40-1)
Hydroxylamine hydrochloride: Hydroxylamine hydrochloride; (5470-11-1)
Sodium acetate anhydrous: Sodium acetate; (127-09-3)
Acetic anhydride: Acetic anhydride; (108-24-7)
Cesium carbonate: Cesium carbonate; (534-17-8)

Mi-Na Zhao received her B.Sc. degree in chemistry at Xinzhou Normal University in 2006 and obtained her Ph.D. degree under the guidance of Prof. Zheng-Hui Guan from Northwest University in 2016. After a two-year postdoctoral research in the same group, she has worked at the Baoji University of Arts and Sciences. Her research focused on the development of transition metal-catalyzed cyclization reaction of ketoxime acetates or enamides.

Zheng-Hui Guan received his B.Sc. and Ph.D. degrees from Lanzhou University in 2004 and 2009, respectively, supervised by Prof. Yong-Min Liang. From 2007 to 2008, he was a visiting scholar, supervised by Prof. Xumu Zhang, at Rutgers University. In 2009, he joined Northwest University to start his independent career as an associate professor and was promoted to full professor in 2014. His research interests currently focus on the development of novel and practical synthetic methodologies. He has published over 70 research papers. He was awarded Chinese Chemical Society (CCS) Prize for Young Scientists (2015), and Thieme Chemistry Journals Award (2016).

Julius R. Reyes obtained B.S. in 2010 from the University of California, Berkeley under the supervision of Professors Andrew Streitwieser and Richmond Sarpong. He subsequently joined the labs of Professor Viresh Rawal at the University of Chicago, where his doctoral studies concerned the synthesis welwitindolinone B isothiocyanate. In 2016, he then moved to the University of Munich as an Alexander von Humboldt postdoctoral fellow and then to New York University with Professor Dirk Trauner studying the synthesis of complex cytochalasans.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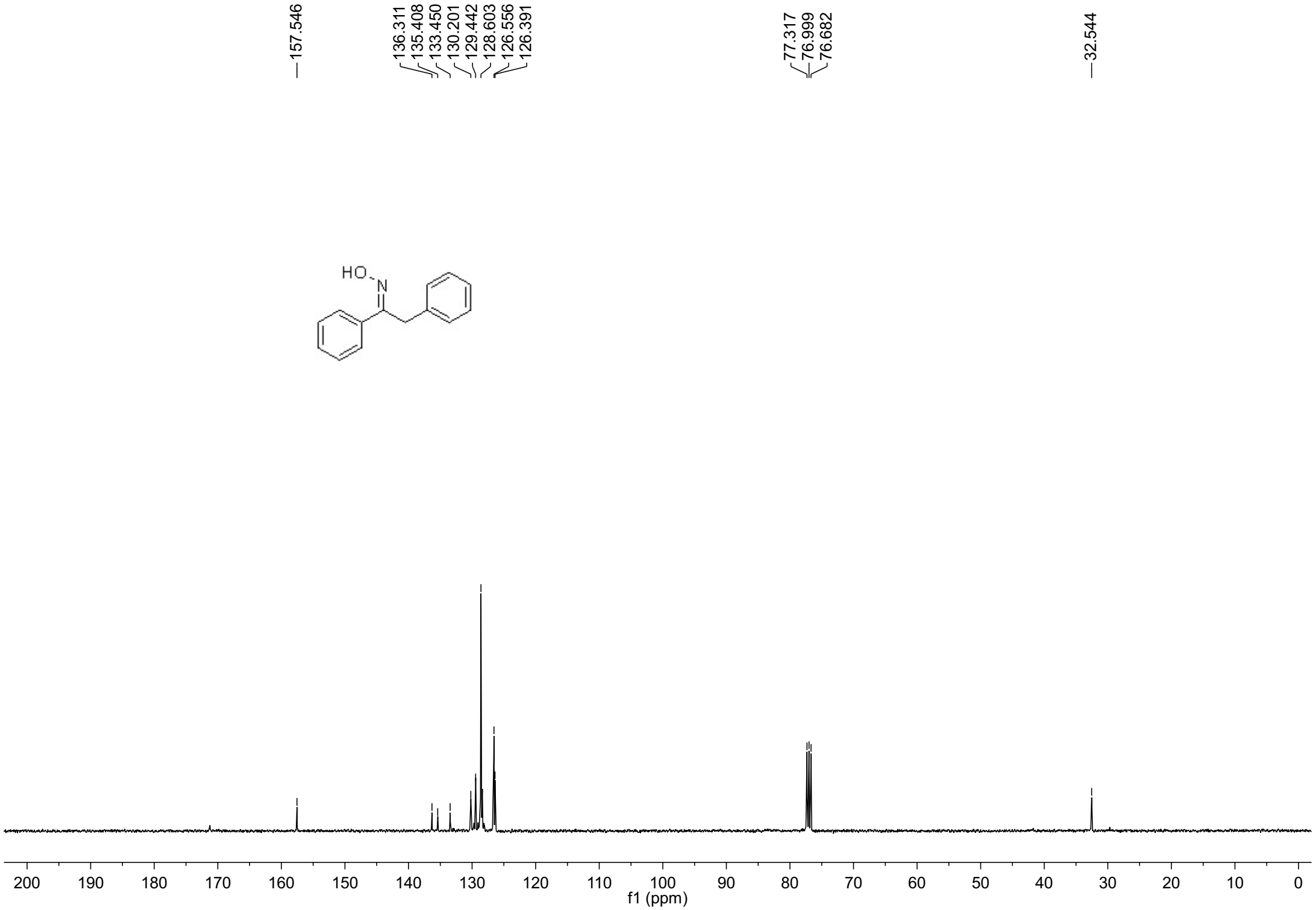
7.600
7.358
7.351
7.342
7.271
7.260
7.255
4.236
HO
N
2.30
3.33
4.93
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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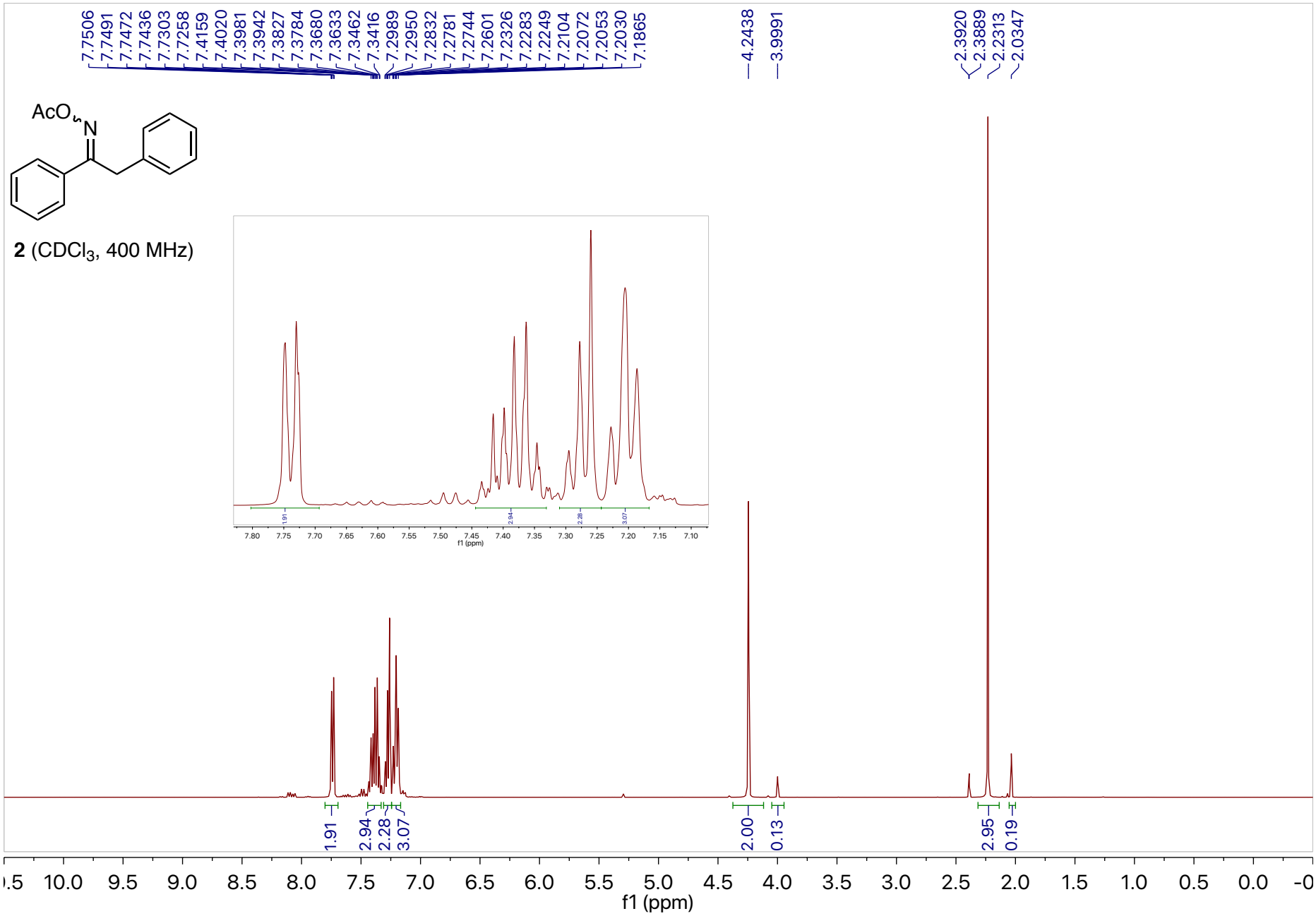
136.311
135.408
133.450
130.201
129.442
128.603
126.556
126.391
77.317
76.999
76.682
32.544
HO
N
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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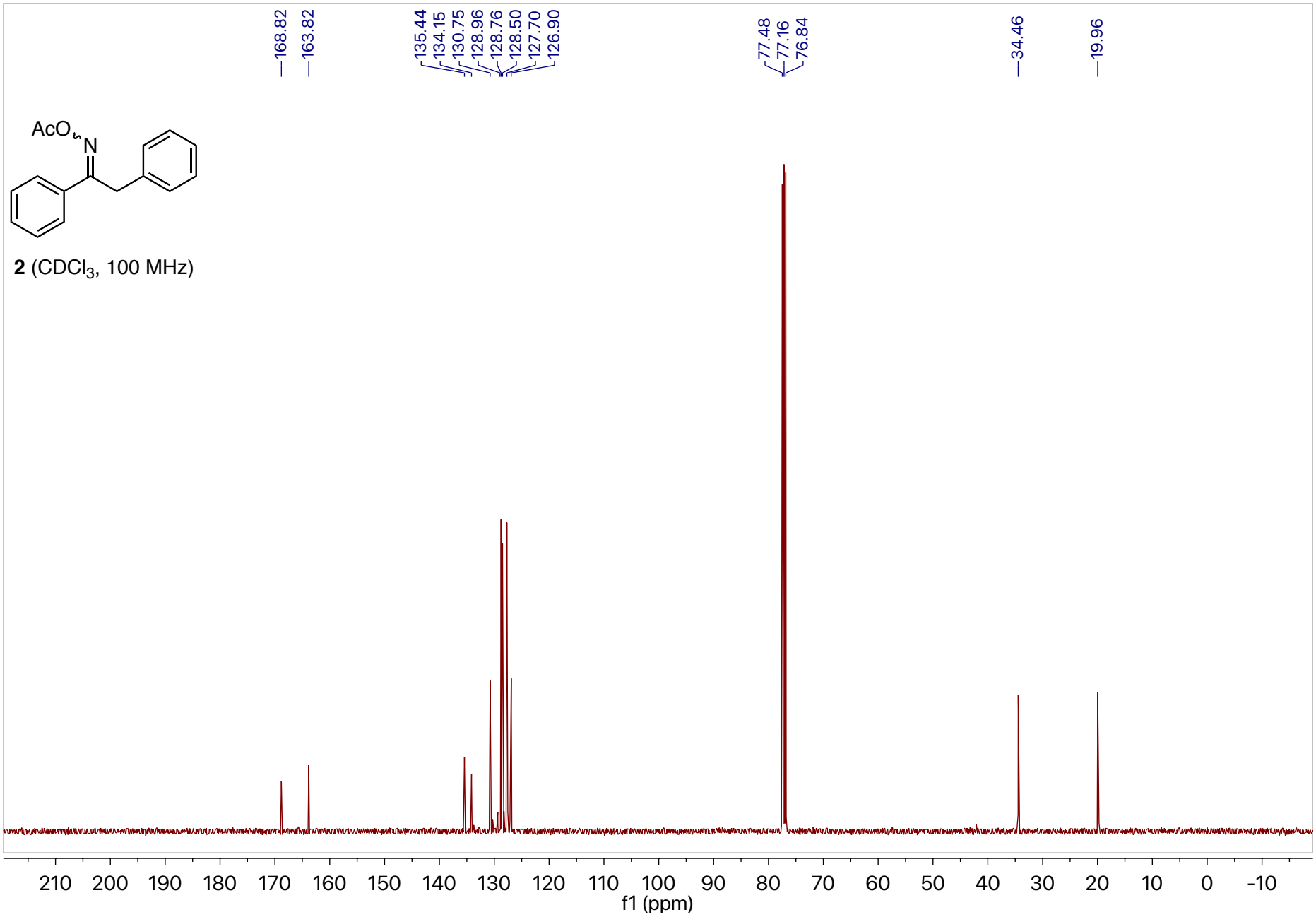
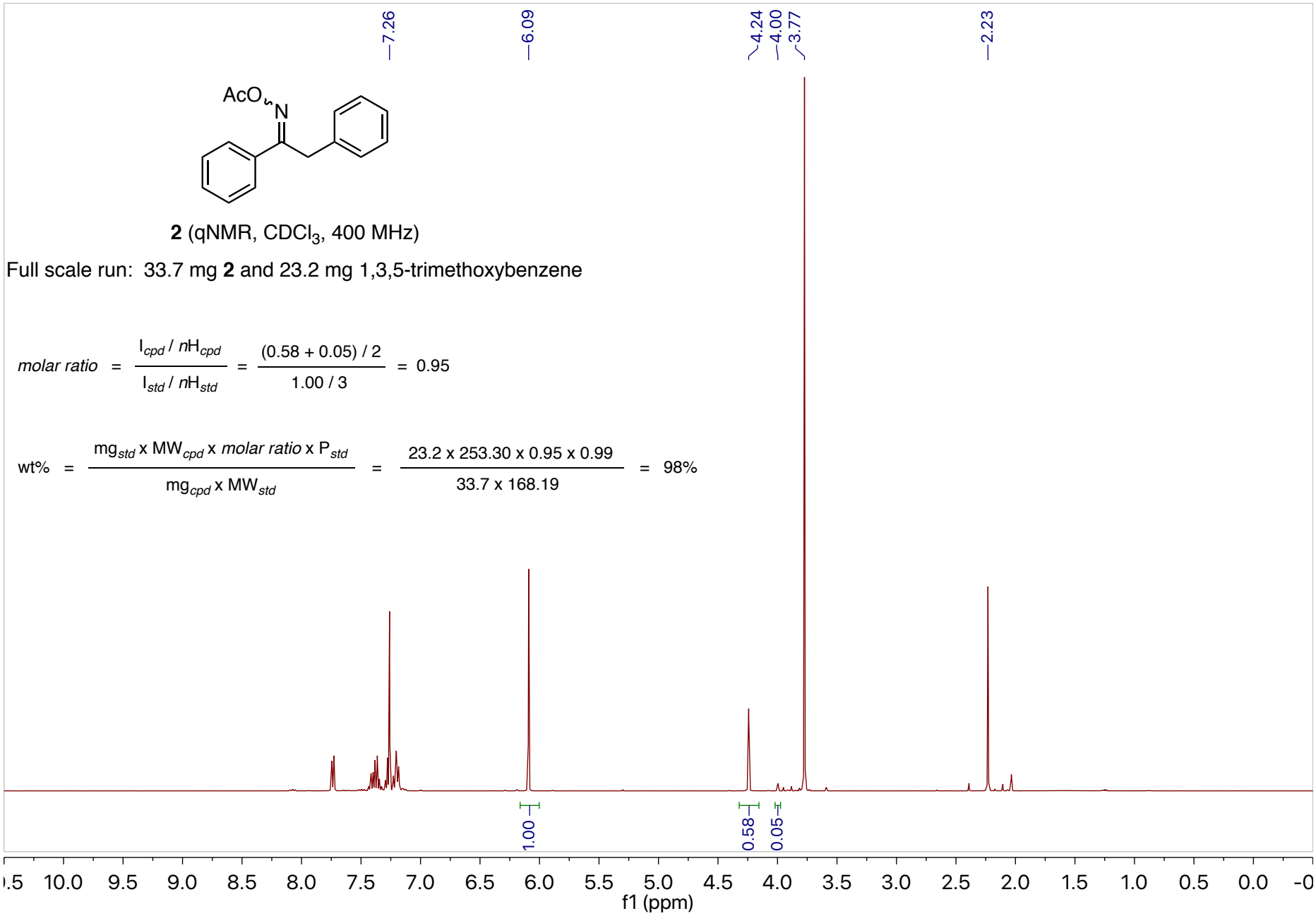
7.7491
7.7472
7.7436
7.7303
7.7258
7.4159
7.4020
7.3981
7.3942
7.3827
7.3784
7.3680
7.3633
7.3462
7.3416
7.2989
7.2950
7.2832
7.2781
7.2744
7.2601
7.2326
7.2283
7.2249
7.2104
7.2072
7.2053
7.2030
7.1865
4.2438
3.9991
2.3920
2.3889
2.2313
2.0347
AcO
N
2 (CDCl3, 400 MHz)
1.91
2.94
2.28
3.07
2.00
0.13
2.95
0.19
f1 (ppm)


168.82
163.82
135.44
134.15
130.75
128.96
128.76
128.50
127.70
126.90
77.48
77.16
76.84
34.46
19.96
AcO
N
2 (CDCl3, 100 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

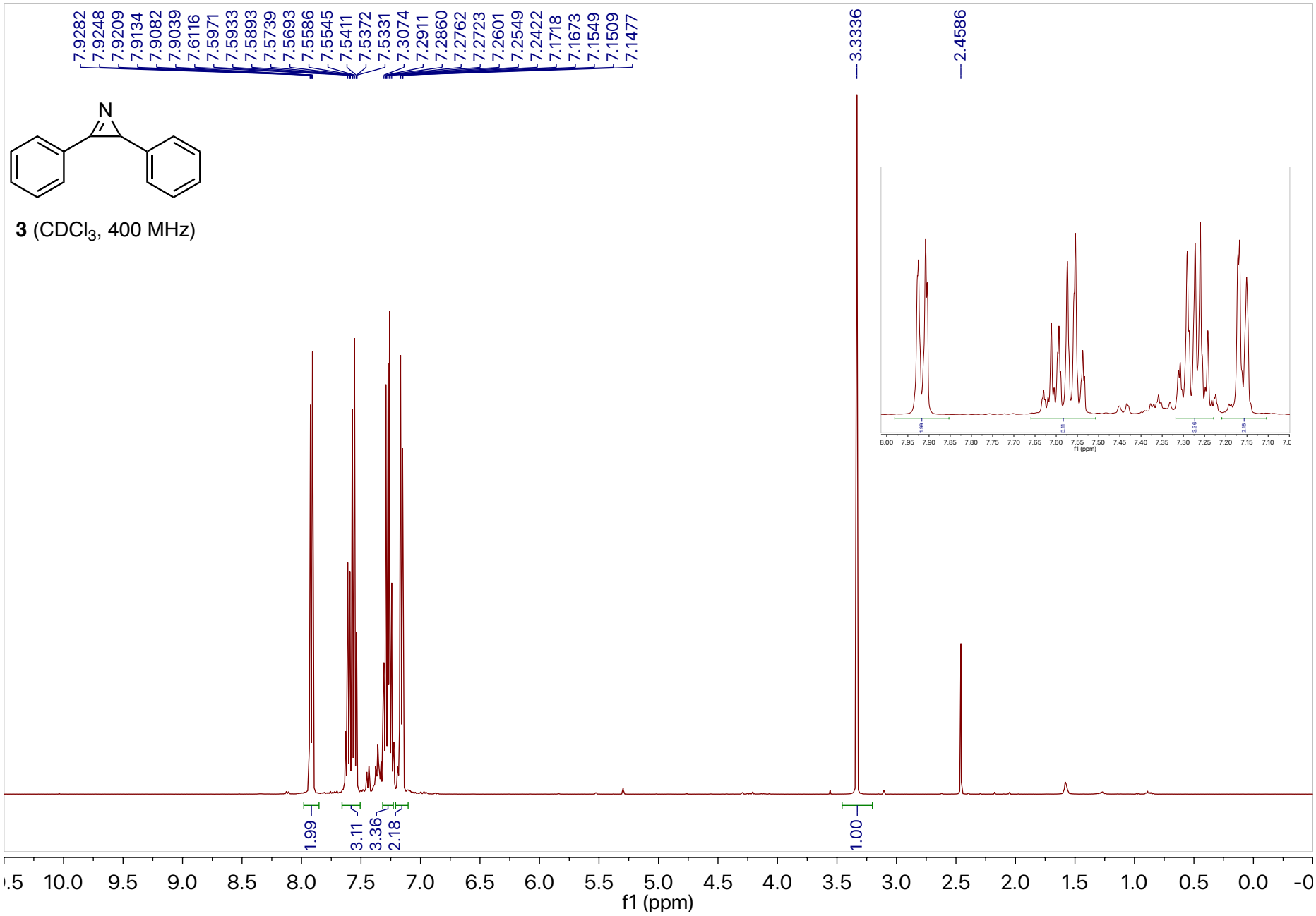


2 (qNMR, $CDCl_3$, 400 MHz)

Full scale run: 33.7 mg **2** and 23.2 mg 1,3,5-trimethoxybenzene

$$\textit{molar ratio} = \frac{I_{cpd} / n\mathrm{H}_{cpd}}{I_{std} / n\mathrm{H}_{std}} = \frac{(0.58 + 0.05) / 2}{1.00 / 3} = 0.95$$

$$\text{wt\%} = \frac{\mathrm{mg}_{std} \times \mathrm{MW}_{cpd} \times \textit{molar ratio} \times \mathrm{P}_{std}}{\mathrm{mg}_{cpd} \times \mathrm{MW}_{std}} = \frac{23.2 \times 253.30 \times 0.95 \times 0.99}{33.7 \times 168.19} = 98\%$$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7.9082
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7.6116
7.5971
7.5933
7.5893
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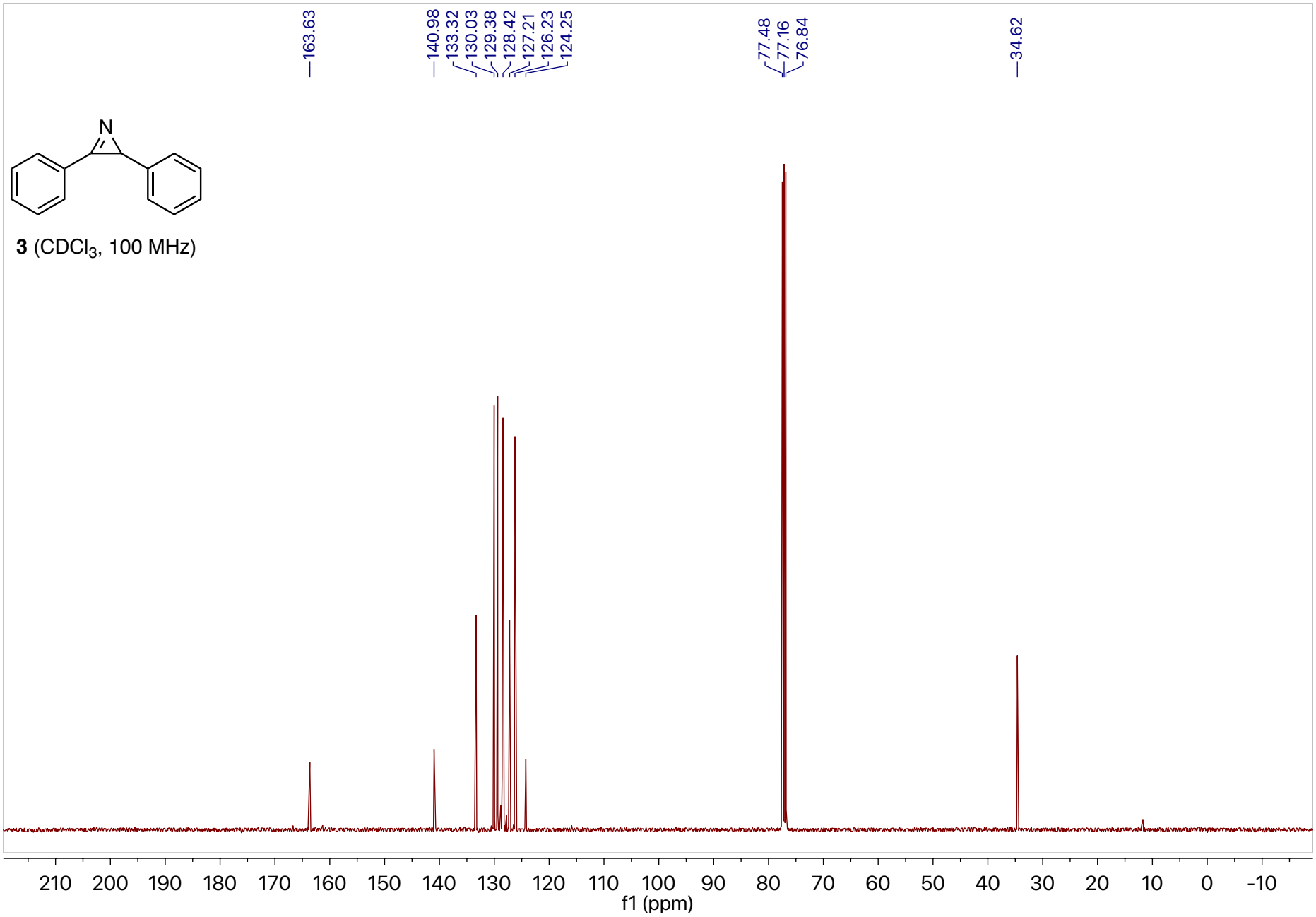
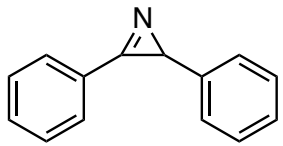
7.5693
7.5586
7.5545
7.5411
7.5372
7.5331
7.3074
7.2911
7.2860
7.2762
7.2723
7.2601
7.2549
7.2422
7.1718
7.1673
7.1549
7.1509
7.1477
3.3336
2.4586
N
3 (CDCl3, 400 MHz)
1.99
3.11
3.36
2.18
1.00
f1 (ppm)


163.63
140.98
133.32
130.03
129.38
128.42
127.21
126.23
124.25
77.48
77.16
76.84
34.62
N
3 (CDCl3, 100 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



3 (qNMR, $CDCl_3$, 400 MHz)

Full scale run: 32.9 mg **3** and 31.4 mg 1,3,5-trimethoxybenzene

$$\textit{molar ratio} = \frac{I_{cpd} / nH_{cpd}}{I_{std} / nH_{std}} = \frac{1.00 / 1}{3.53 / 3} = 0.85$$

$$\text{wt\%} = \frac{mg_{std} \times MW_{cpd} \times \textit{molar ratio} \times P_{std}}{mg_{cpd} \times MW_{std}} = \frac{31.4 \times 193.25 \times 0.85 \times 0.99}{32.9 \times 168.19} = 92\%$$