Organic Syntheses

Photochemical Benzannulation of *N*-Phosphoryl Ynamides and α-Diazo Ketones in Continuous Flow

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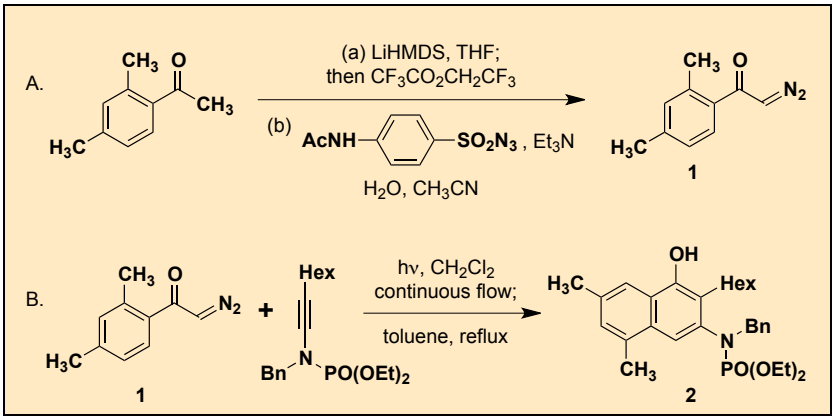

Procedure

A. *2-Diazo-1-(2,4-dimethylphenyl)ethan-1-one (**1**).* A 250-mL, three-necked, round-bottomed flask (Note 1) equipped with a 25 x 10 mm, Teflon-coated, octagonal magnetic stir bar is placed in a glove box. Solid LiHMDS (1.81 g, 13.5 mmol, 1.1 equiv) (Note 2) was weighed out in the glove box, added to the flask, and three septa are attached. The flask is removed from the glove box and equipped with an argon inlet adapter and a 50-mL pressure-equalizing addition funnel fitted with a rubber septum. The third septum is fitted with a thermocouple temperature probe. Tetrahydrofuran (35 mL) (Note 3) is added by syringe and the solution cooled to –78 °C in a

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dry ice-acetone bath (Note 4). A solution of 2′,4′-dimethylacetophenone (1.82 mL, 1.81 g, 12.2 mmol, 1.0 equiv) (Note 5) in 27 mL of THF is added via the addition funnel over 15 min while the internal temperature of the reaction mixture is kept below -70 °C. The addition funnel is rinsed with two 5-mL portions of THF. The reaction mixture is stirred at -78 °C for 1 h and then 2,2,2-trifluoroethyl trifluoroacetate (1.97 mL, 2.88 g, 14.7 mmol, 1.2 equiv) (Note 6) is added rapidly in one portion via syringe. After 30 min, the yellow solution is poured into a 500-mL separatory funnel containing 120 mL of diethyl ether and 120 mL of 5% aqueous HCl solution. The aqueous layer is separated and extracted with two 60-mL portions of diethyl ether. The combined organic layers are washed with 120 mL of saturated NaCl solution, dried over 10 g of anhydrous $MgSO_4$, and filtered through a 30-mL sintered glass Büchner funnel (medium porosity, 30 mm diameter). The $MgSO_4$ is washed with diethyl ether (3 x 10 mL) and the combined filtrate is concentrated by rotary evaporation (20 °C, 20 mmHg) to afford 4 g of a yellow oil. This material is immediately dissolved in 15 mL of acetonitrile and transferred via glass funnel (9 cm diameter) to a 250-mL single-necked, round-bottomed flask equipped with a 25 x 10 mm, Teflon-coated, octagonal magnetic stir bar (Note 7). The original flask is rinsed with acetonitrile (2 x 5 mL), which is transferred via glass funnel (9 cm diameter) to the 250-mL flask. Water (0.22 mL, 12.2 mmol, 1.0 equiv) and triethylamine (2.56 mL, 1.86 g, 18.4 mmol, 1.5 equiv) (Note 8) are added via syringe. A 50-mL pressure-equalizing addition funnel is attached. A solution of 4-acetamidobenzenesulfonyl azide (4.41 g, 18.4 mmol, 1.5 equiv) (Note 9) in 25 mL of acetonitrile is then added via the addition funnel over 15 min. The addition funnel is rinsed with 5 mL of acetonitrile and the reaction flask is wrapped with aluminum foil. The resulting dark yellow solution is stirred at room temperature for 2 h, during which time a white precipitate appears (Figure 1).

The solution is then concentrated by rotary evaporation (40 °C, 20 mmHg) to provide 10.7-16.6 g of a thick yellow suspension. This material is diluted with 1:1 diethyl ether-hexanes (100 mL) and filtered through 5 g of Celite in a 30-mL sintered glass funnel (medium porosity, 30 mm diameter) into a 250-mL, round-bottomed flask. The solid material is washed with 1:1 diethyl ether-hexanes (3 x 15 mL), and the filtrate is then concentrated by rotary evaporation (20 °C, 20 mmHg) to yield 2.8-4.7 g of a dark yellow oil.

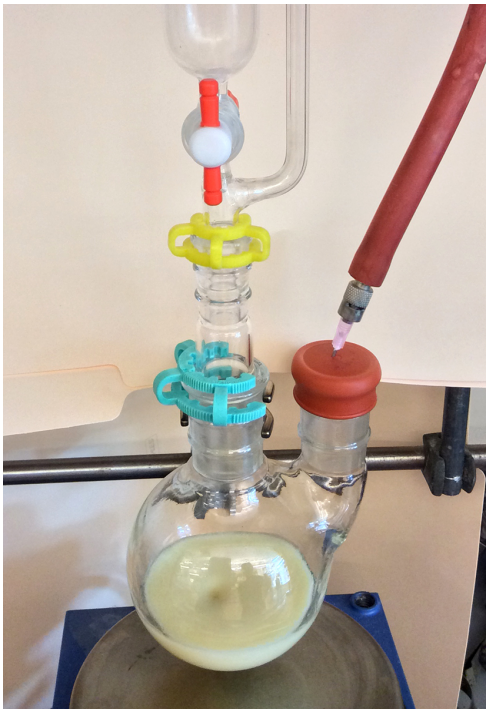

Figure 1. White precipitate formed in Step A

This material is dissolved in a minimum amount of 1:7 ethyl acetate-hexanes (ca. 6 mL) and loaded onto a column (64 mm diameter) of 200 g of silica gel (Note 10) prepared as a slurry in 1:7 ethyl acetate-hexanes. Elution with 1:7 ethyl acetate-hexanes (35 mL fractions collected in 20 x 150 mm test tubes) affords the product in fractions 21-57. These fractions are combined and the solvent is removed by rotary evaporation (20 °C, 20 mmHg). Further concentration at room temperature, 0.05 mmHg for 1 h provides 1.77 g (83%) of diazo ketone **1** as a yellow crystalline solid (Notes 11 and 12).

B. *Diethyl benzyl(3-hexyl-4-hydroxy-6,8-dimethylnaphthalen-2-yl)phosphoramidate* (**2**). Figure 2 shows the continuous flow photochemical reactor employed for this reaction. Fluorinated ethylene propylene (FEP) tubing, o.d. = 1.59 mm, i.d. = 0.76 mm, length = 1520 cm (Note 13), is wrapped around a quartz immersion well in tightly packed coils leaving 90 cm of tubing free at each end. The length of tubing wrapped around the well is 1340 cm (internal volume = 6.1 mL). The ends of the tubing are secured to

the well with Teflon tape. The top end of the tubing is fitted with a nut, ferrule, and a thread to a female Luer adapter for attachment to a syringe as shown in Figure 2. The bottom end of the tubing is connected

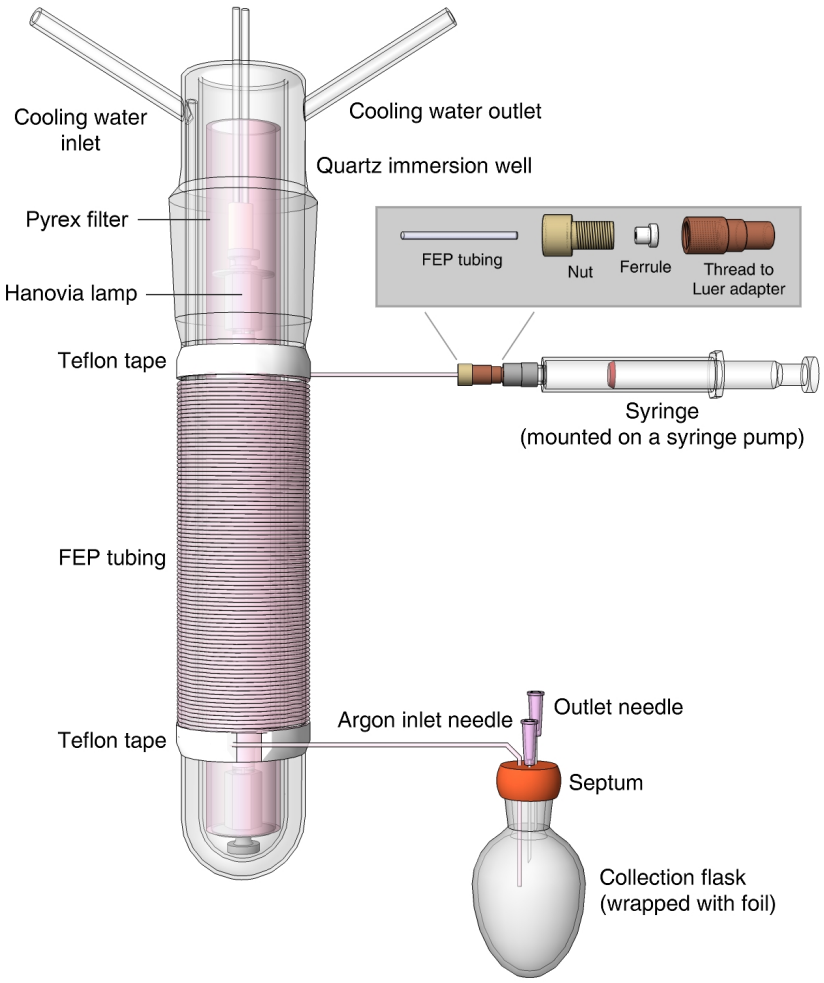

Figure 2. Continuous Flow Reactor for Photochemical Benzannulation

through a rubber septum to a 100-mL, round-bottomed flask equipped with an argon inlet needle and a needle vent. The receiving flask is wrapped in aluminum foil (Figure 3). The immersion well is connected to recirculating tap water via PVC tubing. A Pyrex filter and a Hanovia 450 W medium-pressure mercury lamp are placed inside the immersion well (Note 14).

Figure 3. Photograph of Continuous Flow Reactor

A 100-mL pear flask equipped with a rubber septum and argon inlet needle is charged with 2-diazo-1-(2,4-dimethylphenyl)ethan-1-one (**1**) (1.56 g, 8.90 mmol, 1.2 equiv), diethyl benzyl(oct-1-yn-1-yl)phosphoramidate[2] (2.63 g, 7.48 mmol, 1.0 equiv), and CH_2Cl_2 (30 mL) (Notes 15 and 16). The yellow solution is degassed via three freeze-pump-thaw (–196 °C, 0.05 mmHg) cycles. A 20-mL plastic syringe is charged with 5 mL of CH_2Cl_2, the syringe is connected to the Luer adapter, the lamp is turned on (Note 17), and the 5 mL of CH_2Cl_2 is pumped through the system at a rate of 0.58 mL/min (Note 18). Approximately one-half of the reaction

mixture is transferred to a 20-mL plastic syringe and pumped through the system at a rate of 0.58 mL/min (calculated residence time = 10.4 min). The syringe is charged with the other half of the reaction solution which is then pumped through the system. The total time required for the injection of the 30-mL reaction solution is 50 min. The 100-mL pear flask is then rinsed with two 0.6-mL portions and one 9 mL portion of CH_2Cl_2 with each portion pumped through the tubing at a rate of 0.58 mL/min. The lamp is turned off, the aluminum foil on the 100-mL collection flask is removed, and the orange solution is concentrated by rotary evaporation (20 °C, 20 mmHg) to afford 3.97 g of dark orange oil (Note 19). This material is dissolved in 50 mL of toluene (Note 20) and the flask is equipped with a 20 x 10 mm, Teflon-coated, oval magnetic stir bar and an 11-cm Liebig condenser fitted with an argon inlet adapter. The orange solution is heated at reflux in an oil bath for 5 h and then concentrated to afford 3.70 g of orange solid (Note 21). This material is dissolved in 15 mL of CH_2Cl_2 and concentrated onto 10 g of silica gel. The resulting free-flowing powder is deposited onto a column (80 mm diameter) of 300 g of silica gel prepared as a slurry in 1:2 ethyl acetate-hexanes. Elution is carried out with a gradient of 1:2 to 4:1 ethyl acetate-hexanes, with a ratio of 1:2 EtOAc-hexanes used for fractions 1-81, 1:1 for fractions 82-121, 2:1 for fractions 122-151, and 4:1 for the remaining fractions. Fractions (35 mL) are collected in 20 x 150 mm test tubes. The desired product is obtained in fractions 70-164. These fractions are combined and the solvent is removed by rotary evaporation (20 °C, 20 mmHg). Further concentration at room temperature, 0.1 mmHg for 10 h provides 3.15 g (88%) of **2** as a pale yellow solid (Notes 22 and 23) (Figure 4).

Figure 4. Product of Step B

Notes

1. Glassware was flame-dried under vacuum (0.1 mmHg), back-filled with argon while hot, and then maintained under the inert atmosphere during the course of the reaction.
2. Solid LiHMDS (98%) was purchased from Aldrich-Fine Chemicals and used as received.
3. Tetrahydrofuran (low water HPLC grade) was purchased from J. T. Baker and purified by pressure filtration through activated alumina immediately prior to use.
4. The submitters prepared a solution of LiHMDS from hexamethyldisilazane (98+%, purchased from Alfa Aesar and distilled at 124-125 °C from CaH_2 prior to use) and butyllithium (purchased from Alfa Aesar and titrated according to the method of Watson and Eastham[3]). The reaction flask was charged via syringe with hexamethyldisilazane (2.81 mL, 2.17 g, 13.5 mmol, 1.1 equiv) and 35 mL of THF. The flask was cooled in an ice/water bath and a solution of *n*-butyllithium (5.20 mL, 2.59 M in hexane, 13.5 mmol, 1.1 equiv) was added dropwise via syringe over 10 min. The reaction mixture was stirred for an additional 10 min and then cooled to -78 °C.
5. 2′,4′-Dimethylacetophenone (97%) was purchased from Alfa Aesar and was used as received.
6. 2,2,2-Trifluoroethyl trifluoroacetate (98%) was purchased from Alfa Aesar and distilled (bp 53-55 °C) from CaH_2 prior to use.
7. Acetonitrile was purchased from Aldrich Chemical Company and distilled (bp 80-81 °C) from CaH_2 prior to use. The submitters employed a 250-mL, two-necked flask for this stage of the reaction.
8. Triethylamine was purchased from J. T. Baker and distilled (bp 87-88.5 °C) from CaH_2 prior to use.
9. 4-Acetamidobenzenesulfonyl azide was purchased from Alfa Aesar and used without purification.
10. The submitters employed silica gel (40-63 μm) that was purchased from Sorbent Technologies and was used as received. The checkers used high purity grade silica gel with a pore size of 60 Å and a 230-400 mesh particle size purchased from Fluka.
11. 2-Diazo-1-(2,4-dimethylphenyl)ethan-1-one (**1**) has the following physical and spectroscopic properties: R_f = 0.20 (1:7 ethyl acetate-

hexanes; Agela silica gel plate); mp 40–41 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.36 (s, 3H), 2.52 (s, 3H), 5.66 (s, 1H), 7.08 – 7.03 (m, 2H), 7.31 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 20.2, 21.2, 55.9, 126.3, 127.4, 132.3, 134.5, 136.9, 141.2, 189.6; HRMS (EI) calculated for $C_{10}H_{10}N_2O$ $[M]^+$ 174.0788, found 174.0788; IR (film): 3108, 2924, 2095, 1613, 1448, 1343, 1220, 1150, 1008, 853, 824, 753 cm^{-1}; Anal. calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.85; H, 5.70; N, 15.92.

12. A second run of Step A provided 1.83 g (86%) of the product.
13. FEP tubing (Catalog No. 1520xL), nut (P-235), ferrule (P-200Nx), and thread to Luer adapter (P-678) were obtained from IDEX Health and Science. The tubing was dried in an oven at 160 °C overnight, allowed to cool in a dessicator, and flushed with argon prior to the assembly of the photochemical flow reactor. It is essential to thoroughly dry the FEP tubing since any residual water will intercept the ketene intermediates resulting in a lower yield of the benzannulation product.
14. The Hanovia 450 W medium-pressure mercury lamp was obtained from Ace Glass Inc. (Catalog No. 7825-34). A double-walled quartz immersion well (Catalog No. 7854-25) was employed with the dimensions o.d. of outer joint = 53 mm, length above joint = 76 mm, distance from bottom of well to joint = 220 mm. The Pyrex filter sleeve was obtained from Ace Glass Inc. (Catalog No. 7835-44).
15. Dichloromethane (HPLC grade) was purchased from J. T. Baker and purified by pressure filtration through activated alumina immediately prior to use.
16. Water-free starting materials are necessary for the reaction; thus the checkers azeotropically dried the diazo ketone with benzene (evaporated 3 x 50 mL from benzene at 20 °C/20 mmHg). The submitters did not report this precaution as being necessary, although they have on occasion observed related diazo ketones to pick up small amounts of water during purification by column chromatography on silica gel.
17. UV light can be damaging to eyesight. The photochemical reactor should be surrounded by an appropriate shield to protect researchers from exposure to UV radiation. The Submitters carried out the reaction in a fume hood with windows covered in aluminum foil secured by tape. UVEX safety glasses were worn for eye protection as an additional precaution when the mercury lamp was in operation.

18. The Submitters employed a Harvard Apparatus PHD 2000 Programmable syringe pump for the reaction. It is advisable to use a plastic syringe since glass syringes sometimes may leak. If a glass syringe is used, then a matching set of syringe barrel and plunger should be chosen and the syringe pump should be kept level to minimize leaking.
19. Alternatively, the next stage of the reaction can be carried out the following day. In this case, the solution from the photolysis should be degassed with a stream of argon for 5 min and then stored under argon at 5 °C.
20. Toluene (Baker analyzed, ACS reagent) was purchased from J. T. Baker and purified by pressure filtration through activated alumina immediately prior to use.
21. TLC analysis was performed with silica gel plates (2 cm x 5 cm, glass backed, purchased from Agela Technologies) with 1:2 ethyl acetate-hexanes as eluent and visualization with Seebach's stain (2.5 g of phosphomolybdic acid, 1 g of $Ce(SO_4)_2$, 6 mL of conc H_2SO_4, and 94 mL of H_2O). Diazo ketone **1**: R_f = 0.58, diethyl benzyl(oct-1-yn-1-yl)phosphoramidate: R_f = 0.40, vinylcyclobutenone intermediate: R_f = 0.49, naphthol benzannulation product **2**: R_f = 0.26.
22. Diethyl benzyl(3-hexyl-4-hydroxy-6,8-dimethylnaphthalen-2-yl)phosphoramidate (**2**) has the following physical and spectroscopic properties: mp 121–123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.90 (t, *J* = 6.8 Hz, 3H), 1.25–1.39 (m, 13H), 1.69 (bs, 1H), 2.33 (s, 3H), 2.40 (s, 3H), 2.66– 2.81 (m, 2H), 4.05–4.26 (m, 5H), 4.77–4.82 (m, 1H), 6.29 (s, 1H), 6.98 (d, *J* = 8.3 Hz, 2H), 7.13–7.21 (m, 5H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 14.3, 16.4 (d, *J* = 7.2 Hz), 19.3, 21.9, 22.9, 26.2, 29.2, 30.4, 31.9, 55.8 (*J* = 5.7 Hz), 63.0 (d, *J* = 13.9 Hz), 118.4, 118.6 (d, *J* = 2.9 Hz), 123.0 (d, *J* = 3.8 Hz), 124.2, 127.6, 128.0, 128.5, 129.6 (d, *J* = 1.6 Hz), 130.0, 133.6, 134.2, 137.0 (d, *J* = 3.3 Hz), 137.8 (d, *J* = 2.4 Hz), 150.4; HRMS (ESI) calculated for $C_{29}H_{40}NO_4P$ $[M+H]^+$ 498.2768, found 498.2765; IR (film): 3271, 2954, 2930, 2870, 2850, 1605, 1571, 1498, 1456, 1413, 1394, 1367, 1334, 1248, 1182, 1154, 1126, 1050, 1023, 962, 915, 891, 864, 817, 807, 738, 719, 702, 599 cm^{-1}; Anal. calcd for $C_{29}H_{40}NO_4P$: C, 70.00; H, 8.10; N, 2.81. Found: C, 69.75; H, 8.12; N, 2.75.
23. A second run of Step B provided 3.16 g (88%) of the product.

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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.

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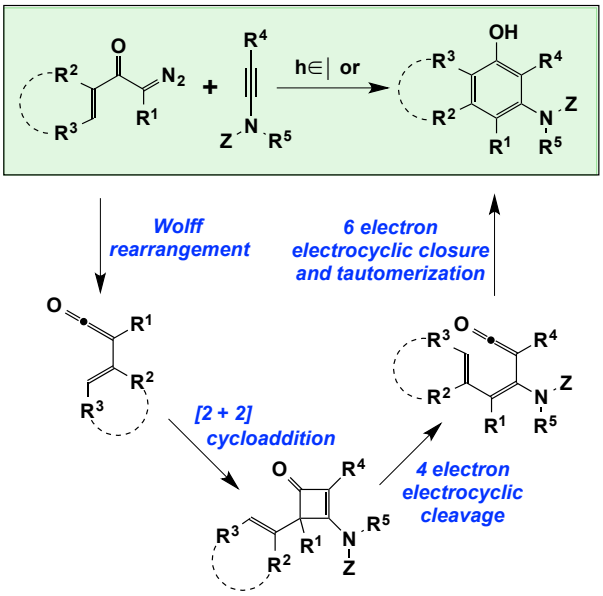
Discussion

Benzannulation is an important ring-forming process in which a benzenoid ring system is assembled from two or more precursors in a single step with all or most substituents in place.[4] For many highly substituted aromatic and heteroaromatic target molecules, benzannulation provides the most efficient and attractive synthetic route.

Previously we have developed a benzannulation strategy based on the reaction of activated alkynes with vinylketenes[5] and this chemistry has been applied by our laboratory and others for the synthesis of a number of biologically interesting natural products.[6] A recent variant of this method employs ynamide derivatives as the alkyne reaction partner,[7] enabling the regioselective synthesis of highly substituted anilines which are versatile precursors to multiply substituted indoles and other benzofused nitrogen heterocyclic systems.[8]

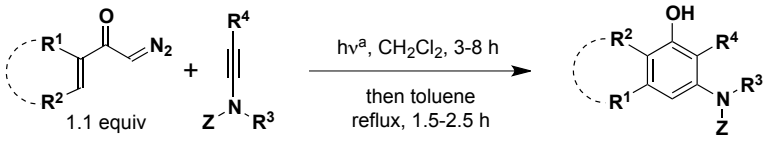
The key transformation reported in the present article is an example of the "second-generation" version of the benzannulation developed in our laboratory. In the original version of the benzannulation, vinylketenes are generated via the 4-electron electrocyclic ring opening of cyclobutenones. For the synthesis of polycyclic aromatic and heteroaromatic compounds, however, a superior approach employs α-diazo ketones as the vinylketene precursors. Upon irradiation or thermolysis, α-diazo ketones undergo Wolff rearrangement[9] to generate the key vinylketene intermediates, thereby triggering a cascade involving a series of pericyclic transformations. As outlined in Scheme 1, the highly reactive vinylketene first undergoes rapid [2 + 2] cycloaddition with the ynamide benzannulation partner to yield a vinylcyclobutenone intermediate. Reversible 4-electron electrocyclic cleavage initiated by heat or light then furnishes a dienylketene intermediate, and 6-π electrocyclic ring closure and tautomerization finally generates the highly substituted benzenoid aromatic product.

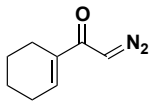
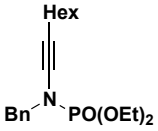
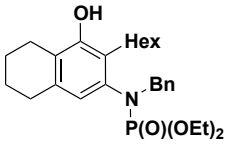
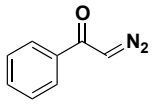
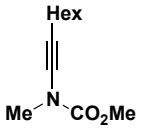
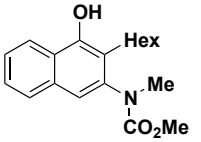
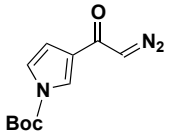
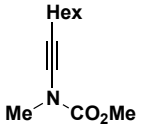
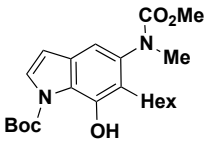
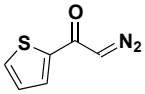
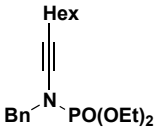
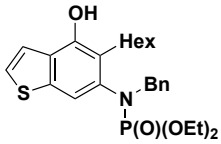


Scheme 1. Mechanism of Benzannulations Based on Diazo Ketones with Ynamides as Reaction Partners

An attractive feature of this "second-generation" version of the benzannulation is that a variety of alkenyl, aryl, and hetaryl α-diazo ketones are readily available, providing access to a wide range of polycyclic aromatic and heteroaromatic compounds. Representative examples of the "second generation" benzannulation with ynamides as reaction partners are presented in Table 1.[10] The benzannulations shown here are best conducted as a two-stage process. As in the case of a number of other "second generation" benzannulations we have studied, a mixture of the desired aromatic product and the intermediate vinylcyclobutenone is isolated after the photochemical phase of the benzannulation. In such cases, heating the crude reaction mixture for several hours serves to complete the conversion of the vinylcyclobutenone to phenol.

Table 1. Selected Examples of Photochemical Benzannulations



Entry	Diazo ketone	Ynamide	Product	Yield (%)[b]
1				66
2				64-76
3				40
4				78

[a] Batch processes with irradiation using a Hanovia 450 W medium-pressure mercury lamp. [b] Isolated yield of products purified by column chromatography.

The benzannulation described in the present article features the use of an *N*-phosphoryl ynamide as the alkyne reaction partner. We have reported that *N*-phosphoryl ynamides exhibit significantly greater ketenophilicity than *N*-sulfonyl and *N*-carbonyl ynamides, with [2 + 2] cycloadditions taking place nearly an order of magnitude faster with *N*-phosphoryl ynamides as compared to the corresponding carbamates.[10] *N*-Phosphoryl ynamides are conveniently prepared via the copper-catalyzed

alkynylation method reported by Hsung and coworkers,[11] and we have reported a detailed procedure for the synthesis of the ynamide employed in the present article.[2]

α-Diazo ketones function as the vinylketene precursor in the "second generation" version of the benzannulation. Many α-diazo ketones are conveniently prepared by the reaction of diazomethane (or TMS-diazomethane) with carboxylic acid derivatives such as acyl chlorides and certain mixed anhydrides. Alternatively, diazo ketones can also be generated from the corresponding ketones by reaction with sulfonyl azides ("diazo transfer").[12] For the benzannulation described in this article, diazo ketone **1** was synthesized via the detrifluoroacetylative diazo transfer developed in our laboratory.[13] The use of 4-acetamidobenzenesulfonyl azide[14] as the diazo transfer agent in this reaction enables the separation of most of sulfonamide byproduct by filtration and simplifies the purification of the diazo ketone via column chromatography.

Recently we reported that the "second generation" photo-Wolff-based benzannulation can be successfully accomplished under conditions of continuous flow.[10] Continuous flow photochemical reactors provide significant advantages over traditional "batch" reactors.[15] Photochemical reactions carried out in batch are relatively inefficient because light does not penetrate into the bulk of the solution. In contrast, flow reactions can be carried out in narrow gauge tubing with a relatively high surface-to-volume ratio allowing for efficient and uniform irradiation of the reaction mixture. A second important advantage is that photochemical flow reactions often proceed in higher yield. This is due to the fact that side reactions involving the photochemical decomposition of the desired products is minimized with the continuous removal of products from further irradiation in the reactor. Finally, reactions conducted in continuous flow reactors are independent of scale and thus can be scaled up without the need for re-optimization of reaction parameters. In our previous study, we found that the benzannulations shown in Table 1 could each be carried out under conditions of continuous flow with yields equal or superior to those obtained in batch reactions.[10]

The flow photochemical reactor used in this article is based on the design described by Booker-Milburn and coworkers.[16,17] A very attractive feature of this design is its simplicity and the fact that all of the necessary equipment is generally already available in laboratories set up for

performing conventional photochemical reactions. For the flow reaction described in the present article, transparent fluorinated ethylene-propylene (FEP) tubing (0.76 mm i.d., 1.59 mm o.d.) is tightly wound around a quartz immersion well cooled with circulating tap water as shown in Figure 1 above. A 450-W medium pressure mercury lamp is placed inside the immersion well with a Pyrex filter sleeve to suppress polymer buildup inside the tubing. A syringe pump is used to drive the reaction mixture (ca. 0.25 M in ynamide and diazo ketone) through the tubing. We have found that this simple apparatus allows preparative photochemical benzannulations to be achieved in excellent yield and with results sometimes superior to that observed in batch reactions.

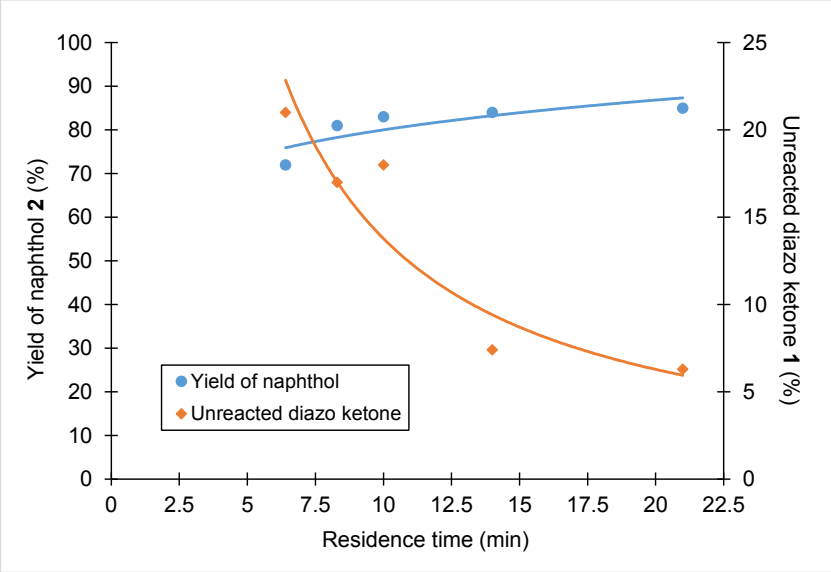
A key reaction parameter in optimizing photochemical flow reactions is residence time in the irradiation zone of the reactor. We employed a reactor with a shorter length of tubing (internal volume ca. 1.2 mL) for optimization of the residence time for this continuous flow benzannulation. Experiments were conducted at one-tenth of the projected full scale using a small (20%) excess of the diazo ketone. Aliquots of the reaction mixture were analyzed by ^{1}H NMR against 1,3,5-trimethoxybenzene as internal standard to determine the amount of unreacted diazo ketone after irradiation for different periods of time. After heating for 5 h to complete the benzannulation, the product of each run was purified by column chromatography and analyzed by ^{1}H NMR vs. 1,3,5-trimethoxybenze to determine the yield of naphthol produced in the reaction.

Table 2 summarizes the results of our optimization experiments. As expected, faster flow rates (shorter residence times) result in the recovery of larger amounts of unreacted diazo ketone. For our optimal procedure, we chose to employ 1.2 equiv of diazo ketone which allows for efficient reaction even with residence times on the order of 10 min. This residence time corresponds to an excellent throughput of 10.5 mmol/h for the "preparative scale" photochemical flow reactor employed in the procedure described in this article. It should be noted, however, that if desired, the benzannulation can be carried out in comparable overall yield using only 1.05 equiv of diazo ketone simply by increasing the residence time as indicated in Table 2.

Table 2. Optimization of Residence Time for Flow Benzannulation

flow rate (mL/min)	residence time (min)[a]	yield (%)	unreacted diazo ketone (%)
0.057	21	85[b]	6.3
0.086	14	84[b]	7.4
0.115	10	83	18
0.144	8.3	81	17
0.188	6.4	72	21

[a] Residence time = volume of irradiated tubing (mL) / flow rate (mL/min). [b] Average of two runs.



In the case of the benzannulation described in this article, a residence time of 10.4 min was employed with 50 min then required to pump the reaction solution containing 7.3 mmol of ynamide through the photochemical reactor. For comparison, irradiation for 8 h was necessary to achieve complete photo-Wolff rearrangement when the same benzannulation was carried out in batch mode, though the yield in this case (81-90% on 0.3 mmol scale) was comparable to that obtained under condtions of continuous flow. We have previously reported that it is also

possible to effect the entire benzannulation cascade by heating, i.e. without the need for irradiation.[10] In this case, however, reaction of the ynamide with 1.2 equiv of diazo ketone **1** in toluene at reflux required 7.5 for complete reaction and produced the desired naphthol **2** in only moderate (55%) yield.

In summary, the "second-generation" benzannulation based on vinylketenes can be conveniently performed under conditions of continuous flow using readily available photochemical equipment and a syringe pump. The high throughput of this reactor allows the benzannulation to be carried out on a multigram scale with reaction times on the order of several hours.

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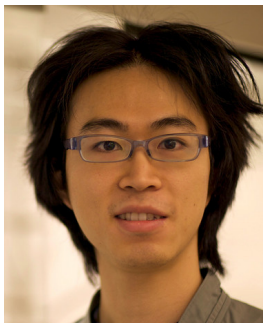
Appendix
Chemical Abstracts Nomenclature (Registry Number)

4-Acetamidobenzenesulfonyl azide; (2158-14-7)
2,2,2-Trifluoroethyl trifluoroacetate; (407-38-5)
LiHMDS: Lithium bis(trimethylsilyl)amide; (4039-32-1)
2′,4′-Dimethylacetophenone; (89-74-7)
Diethyl benzyl(oct-1-yn-1-yl)phosphoramidate: Phosphoramidic acid, *N*-1-octyn-1-yl-*N*-(phenylmethyl)-, diethyl ester; (1332480-36-0)
2-Diazo-1-(2,4-dimethylphenyl)ethan-1-one; (23722-51-2)

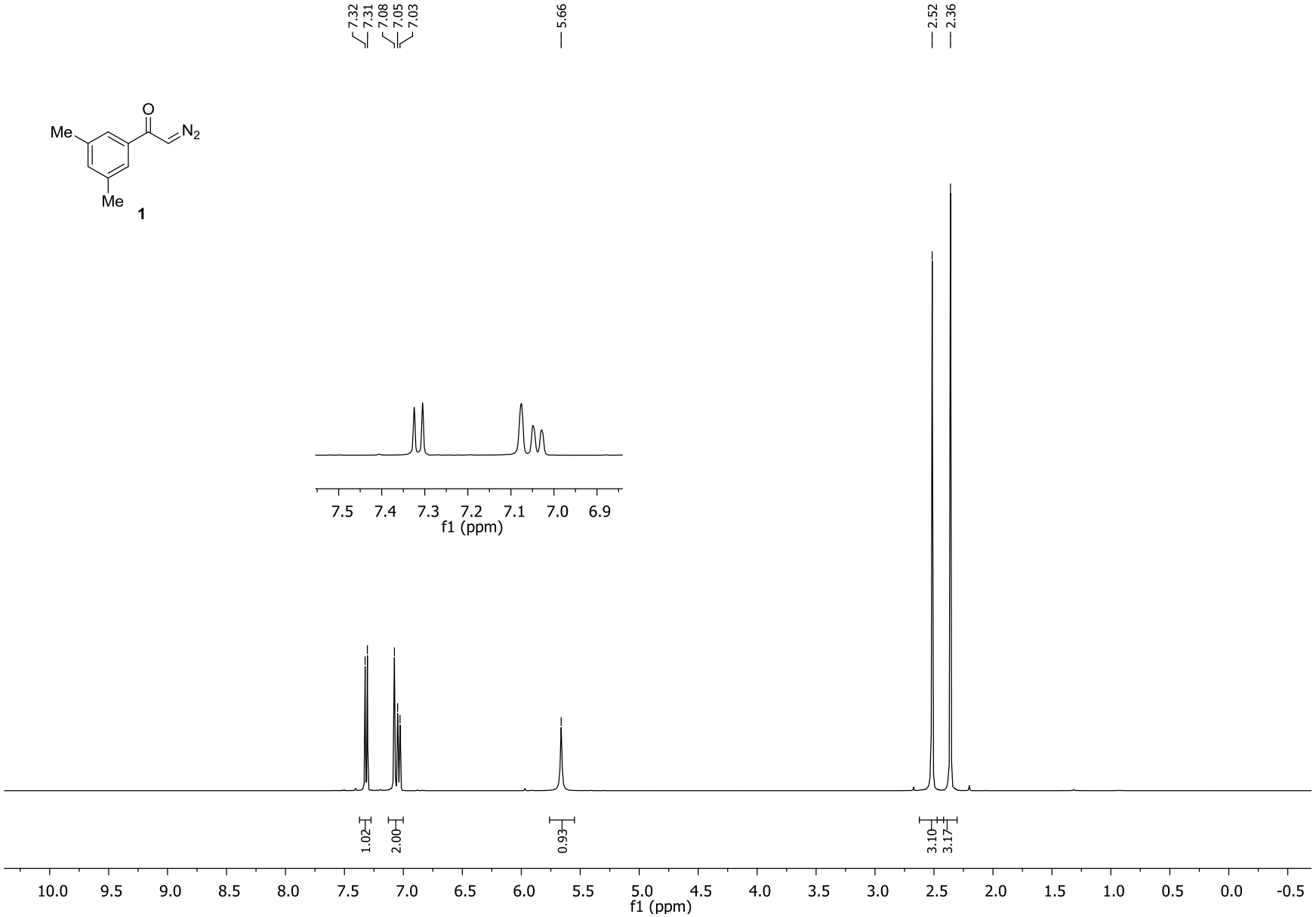
John M. Read was born in Laredo, Texas, in 1994. He is currently an undergraduate at the Massachusetts Institute of Technology and expects to receive his B.S. degree in chemistry in 2016. John joined the laboratory of Professor Rick Danheiser in 2013, and his research has focused on the synthesis of highly substituted polycyclic compounds and requisite precursors



Yu-Pu Wang was born in Taipei, Taiwan. He received a B.S. degree in Chemistry in 2009 from Rice University working in the laboratory of Professor James M. Tour. He received his Ph.D. degree at the Massachusetts Institute of Technology in 2015 working in the research group of Professor Rick L. Danheiser on the development of new methods for the synthesis of highly substituted indoles and their application to the synthesis of natural products and polycyclic systems with interesting electronic properties.

Rick L. Danheiser received his undergraduate education at Columbia where he carried out research in the laboratory of Professor Gilbert Stork. He received his Ph.D. at Harvard in 1978 working under the direction of E. J. Corey on the total synthesis of gibberellic acid. Dr. Danheiser is the A. C. Cope Professor of Chemistry at MIT where his research focuses on the design and invention of new annulation and cycloaddition reactions, and their application in the total synthesis of biologically active compounds.

Christian Ebner was born in southern Germany. During his undergraduate studies at ETH Zurich, Switzerland, he moved to the Scripps Research Institute in La Jolla, USA to conduct his master thesis in the laboratory of Professor K. C. Nicolaou involving the development of a novel macroheterocyclization. Since June 2012, he has been a doctoral student in the group of Professor Erick M. Carreira, working on the total synthesis of terpenoid natural products.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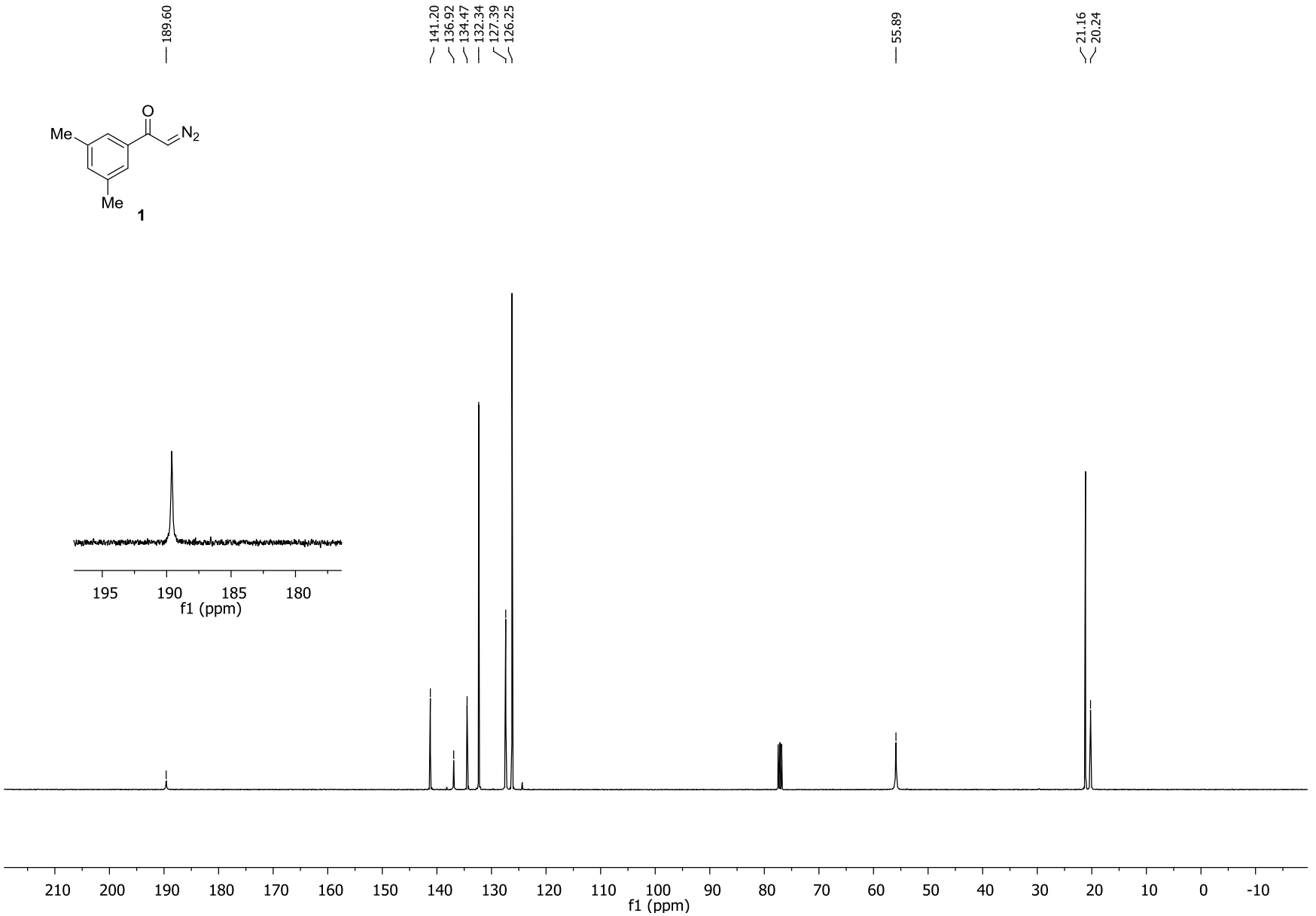
2.00
0.93
3.10
3.17
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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f1 (ppm)
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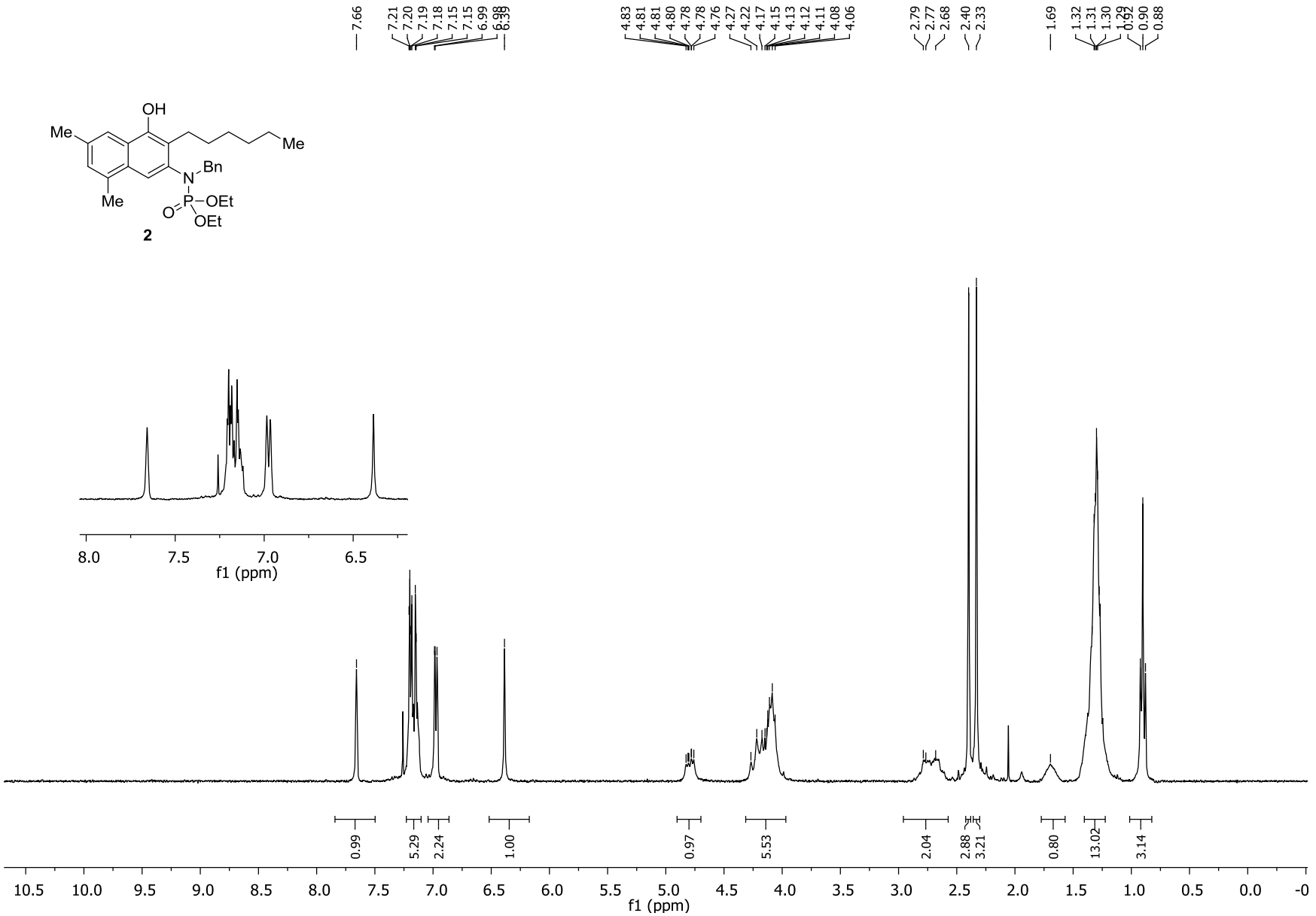
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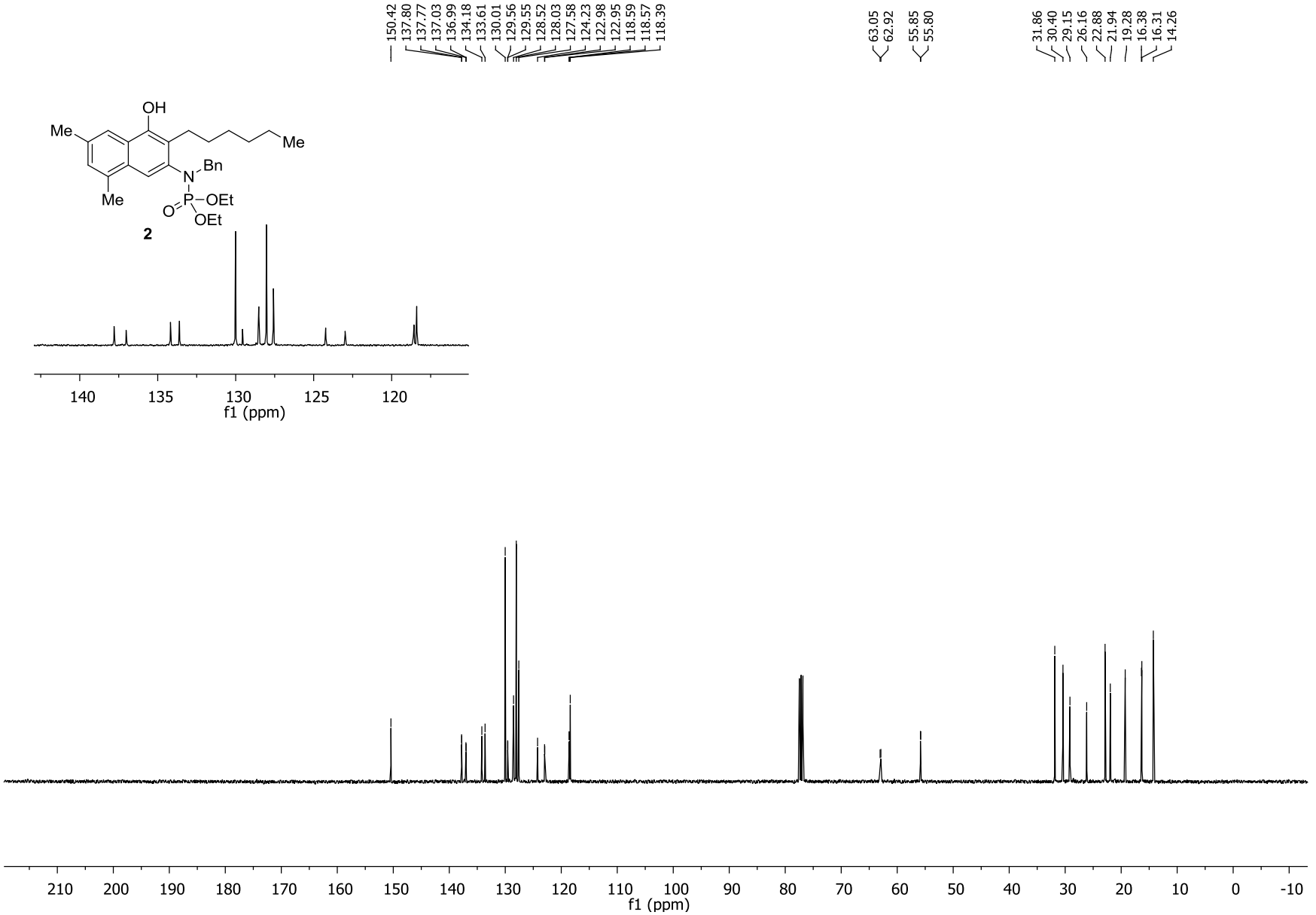
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