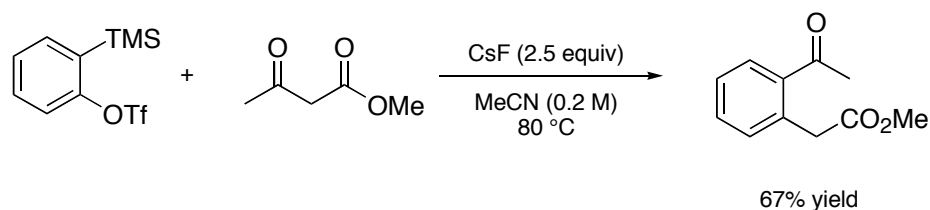# Organic Syntheses

# 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.

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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

# THE DIRECT ACYL-ALKYLATION OF ARYNES.
# PREPARATION OF METHYL 2-(2-ACETYLPHENYL)ACETATE.



67% yield

Submitted by David C. Ebner, Uttam K. Tambar, and Brian M. Stoltz.[1]
Checked by Morten Storgaard, Nathan D. Ide, John A. Ragan, and Jonathan A. Ellman.

Discussion Addendum *Org. Synth.* **2019**, *96*, 80

## 1. Procedure

*Methyl 2-(2-acetylphenyl)acetate*. An oven-dried (Note 1) 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stir bar, and cesium fluoride (19.7 g, 130 mmol, 2.5 equiv) (Note 2) is added. The flask is fitted with a reflux condenser in the middle neck, an adaptor equipped with a thermometer in one of the side necks, and a septum in the other side neck. The condenser is equipped with a vacuum adaptor connected to a Schlenk line (nitrogen/vacuum manifold). The connected glassware is evacuated under high vacuum (0.025 mmHg) and carefully back-filled with nitrogen. This procedure is repeated twice to secure an oxygen-free atmosphere in the flask. Dry MeCN (260 mL) (Note 3) is added to the flask via a syringe through the septum. While stirring the reaction mixture, methyl acetoacetate (5.60 mL, 6.01 g, 51.8 mmol, 1.00 equiv) (Note 4) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (15.7 mL, 19.3 g, 64.7 mmol, 1.25 equiv) (Note 5) are added through the septum via syringes. The flask is submerged in an oil bath (100 °C) and the reaction mixture is heated to reflux (internal temperature: 78–81 °C, reached after 15 min). The mixture is stirred at reflux temperature for 40 min (Note 6). Initially, the reaction mixture is a white opaque suspension, but during heating it changes color to yellow and upon reflux the color changes to orange. As the reaction progresses the opaque solution becomes transparent and the color changes back to yellow. Throughout the entire time a white precipitate is present in the flask. The reaction flask is removed from the oil bath and allowed to cool to ambient temperature (23 °C) over the course of 1 h. The flask is

disconnected from the condenser and the nitrogen inlet, and the reaction mixture is diluted with saturated aqueous NaCl solution (200 mL) (Note 7). This mixture is carefully poured into a 1-L separatory funnel (Note 8). After the layers are separated, the aqueous layer is extracted with $Et_2O$ ($3 \times 200$ mL) (Notes 9 and 10). The combined organic layers are dried over anhydrous $Na_2SO_4$ (Note 11) and filtered (Note 12). Concentration of the dried organic layers is effected by rotary evaporation (35 °C, 45 mmHg) which affords an orange, viscous oil. Partial purification is achieved by flash chromatography ($4.5 \times 24$ cm, 170 g silica gel) (Note 13) using a gradient of hexanes to 40% $Et_2O$ in hexanes. The crude product is loaded on the column with benzene (20 mL) (Note 14). Fraction collection (50 mL fractions) is begun as the crude product is eluted first with 100 mL of hexanes (Note 15), followed by 1500 mL of 9:1 hexanes:$Et_2O$, 2000 mL of 4:1 hexanes:$Et_2O$, 1000 mL of 7:3 hexanes:$Et_2O$ and finally 750 mL of 3:2 hexanes:$Et_2O$. Fractions 38–85 are concentrated by rotary evaporation (30–35 °C, 45 mmHg) to afford 7.96 g (80%) of a slightly yellow solid (Note 16). The partially purified product is further purified by bulb-to-bulb distillation (Note 17) at 124–130 °C (0.75 mmHg) (Note 18) which affords 6.63 g (67%) of the title compound as an off-white, crystalline solid (Notes 19, 20, 21, 22 and 23).

## 2. Notes

1.    The glassware and magnetic stir bar are dried in an oven (150 °C) overnight before use and assembled while still hot and cooled to ambient temperature (23 °C) under high vacuum (0.025 mmHg).

2.    Cesium fluoride (CsF) (99.9%) was purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI. The submitters used the reagent directly as received, but the checkers found that it may be important to dry CsF prior to use. The CsF is dried in a desiccator in high vacuum (0.025 mmHg) overnight at room temperature (23 °C) in the presence of $P_2O_5$.

3.    The submitters used acetonitrile (MeCN) that was dried by passage through an activated alumina column under argon. The checkers used acetonitrile (HPLC grade, 0.2 micron filtered) from Fisher Scientific Chemicals that was distilled over $CaH_2$ under nitrogen atmosphere prior to use.

4. Methyl acetoacetate (99%) was purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI. The reagent was used as received without further purification.

5. 2-(Trimethylsilyl)phenyl trifluoromethanesulfonate (97%) was purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI. The reagent was used as received without further purification. Submitters reported that the reagent can be prepared alternatively by a method of Peña and coworkers.[2]

6. The progress of the reaction is followed by thin-layer chromatography (TLC) analysis on E. Merck silica gel 60 F254 precoated plates (0.25 mm) (used by submitters) or Dynamic Adsorbents, Inc. glass plates coated with 250 mm F-254 silica gel (used by checkers) with 1:4 EtOAc:hexanes as the eluent. The plates are visualized by UV and *p*-anisaldehyde staining (0.5 mL *p*-anisaldehyde in 50 mL glacial acetic acid and 1 mL 97% $H_2SO_4$). The title compound and a side product identified as methyl 2-(2-acetylphenyl)-2-phenylacetate both have very similar $R_f$ values; 0.43 and 0.53, respectively. Both compounds are visible in UV and with *p*-anisaldehyde staining. The title compound stains reddish brown and the side product stains pale brown. The completion of the reaction is determined by disappearance of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate, which has a $R_f = 0.91$ visualized by UV. This starting material cannot be visualized with *p*-anisaldehyde staining. To clarify the disappearance, cross-spotting with pure 2-(trimethylsilyl)phenyl trifluoromethanesulfonate is used since many by-products are formed nearby the diagnostic spot.

7. Sodium chloride (NaCl), crystalline, was purchased from Fisher Scientific Chemicals.

8. The remaining solids in the flask are not transferred to the separatory funnel to avoid clogging of the stopcock. Instead, the solids are washed with the portions of $Et_2O$ before the solvent is transferred to the separatory funnel for extraction.

9. Ethyl ether ($Et_2O$) anhydrous, stabilized, HPLC grade, was purchased from Fisher Scientific Chemicals and was used without further purification.

10. Extraction with $Et_2O$ forms a white, opaque emulsion that only slowly separates.

11. Sodium sulfate ($Na_2SO_4$) anhydrous, powder, was purchased from EMD Chemicals Inc.

12. Removal of the drying agent was carried out by using a Wilmad Labglass (60 mL, size M) sintered glass funnel by vacuum filtration.

13. The submitters used ICN silica gel (particle size 0.032–0.063 mm) and the checkers used silica gel 60 (0.040–0.063 mm), 230–400 mesh ASTM purchased from Merck KGaA.

14. Benzene was purchased from EMD Chemicals Inc.

15. Hexanes, HPLC grade, were purchased from Fisher Scientific.

16. Purification by flash chromatography gives a mixture of the title compound and a side product, methyl 2-(2-acetylphenyl)-2-phenylacetate,[3] in an 87:13 ratio as determined by ^{1}H NMR. This side product was obtained pure by the submitters using preparative thin-layer chromatography (3:2 hexanes:$Et_2O$ eluent) and exhibits the following spectroscopic properties: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.56 (s, 3 H), 3.71 (s, 3 H), 5.76 (s, 1 H), 7.04–7.09 (m, 1 H), 7.18–7.25 (m, 2 H), 7.25–7.40 (m, 5 H), 7.73–7.77 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.3, 52.2, 53.7, 127.0, 127.3, 128.7, 129.3, 129.6, 130.6, 131.8, 137.1, 138.1, 138.7, 173.3, 202.0. IR (thin film) υ 1735, 1681, 1254, 1201, 1161 $cm^{-1}$. HRMS (EI[+]) calcd for $[C_{17}H_{16}O_3]^+$: *m/z* 268.1100, found 268.1105.

17. Bulb-to-bulb distillation was performed with a Büchi Glass Oven B-585 Kugelrohr by the submitters. The checkers used an oven from Aldrich with an internal thermometer installed. The temperature is controlled by a variable autotransformer from Staco Engery Products Co. model 3PN1010B (in: 120 V, 50/60 Hz, out: 0 – 140 V, 10 apm, 1.4 KVA). The bulbs are connected to a Trico-Folberth air pressure wiper and the entire instrument is connected to a mercury manometer from Kontes Scientific Glassware Instruments. The receiving bulb is cooled with an acetone/dry ice bath.

18. The submitters reported a boiling point at 159–165 °C (1.1 mmHg).

19. The yellow solid melts at 70–80 °C. When 100 °C is reached the receiving bulb is exchanged with a new one to avoid contamination with low-boiling impurities. Initially, the product distillate is a colorless oil, which solidifies as the distillation proceeds. The distillation stops when 59% of the title compound is recovered leaving a residue (2.00 g) containing a 50:50 mixture of the title compound and the side product. This residue is transferred from a 250-mL round-bottomed flask to a 50-mL round-bottom flask and is resubjected to distillation to afford an additional 762 mg (8%) of the title compound. The brown distillation residue (1.08 g) primarily

contains the side product and contains less than 5 mol% of the title compound.

20. The title compound contains 2–3% of methyl 2-(2-acetylphenyl)-2-phenylacetate, as determined by ^{1}H NMR.

21. The title product exhibits the following properties: mp 53–55 °C (lit.[4] mp 57–59 °C). MS (ES+) $m/z$ 193 (100%, M + H$^+$). IR (neat) υ 3004, 2954, 1732, 1674, 1217, 1168 cm$^{-1}$. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 2.54 (s, 3 H), 3.64 (s, 3 H), 3.91 (s, 2 H), 7.21 (d, $J = 7.3$ Hz, 1 H), 7.32 – 7.43 (m, 2 H), 7.78 (d, $J = 7.6$ Hz, 1 H). ^{13}C NMR (100 MHz, CDCl$_3$) δ: 28.2, 39.6, 51.3, 127.0, 129.6, 131.6, 132.2, 133.9, 136.6, 171.4, 200.6. Anal. calcd for C$_{11}$H$_{12}$O$_3$: C, 68.74; H, 6.29; found: C, 68.65; H, 6.55.

22. The submitters also suggest an alternative procedure for the final purification: After chromatography the material can be purified by crystallization. To 8.00 g of the yellow solid is added 1200 mL of pentane. The mixture is warmed to dissolve the solid. The yellow solution is allowed to cool to room temperature before cooling to –20 °C in a freezer. After 9 h, the off-white solid that has formed is collected by vacuum filtration through a Büchner funnel. The solid is washed with cold pentane (2 × 25 mL) and dried under vacuum to afford 5.12 g (51% yield) of the title compound. This material contains 2.4% of the side product by ^{1}H NMR. Attempts by the initial checkers (Ide and Ragan) to perform this recrystallization gave variable results, with one run providing pure material in modest yield (43%), and another run providing material still containing 12% of the side product (57% recovery). The checkers noted that the product crystals were very dense spheres that were firmly attached to the sides of the flask, suggesting that the material may have initially come out of solution as oil droplets adhered to the flask wall, and then subsequently crystallized. Regardless of the explanation, distillation appears to provide a more robust purification.

23. The checkers discovered that the pure product slowly decomposed upon storage at room temperature. It is therefore recommended to store it in the freezer below –18 °C.
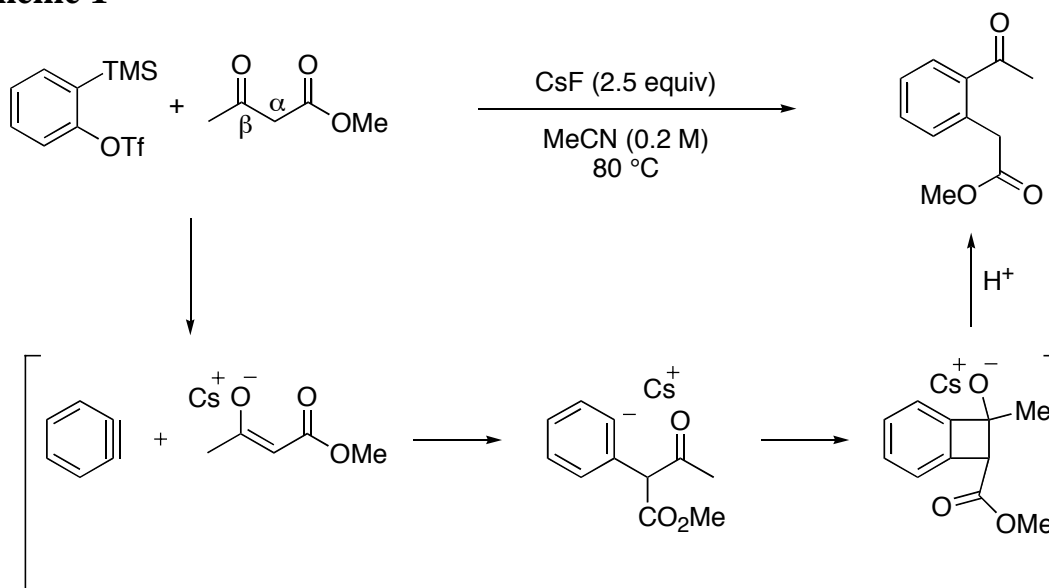
## Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

# 3. Discussion

While arynes have historically received attention from physical organic chemists, their use as reagents in synthetic organic chemistry is limited because of the harsh conditions needed to generate arynes, and the uncontrolled reactivity exhibited by these species. We have developed the acyl-alkylation of arynes, which is a mild and direct aryne insertion into a carbon-carbon bond.[5,6] With this reaction, two carbon-carbon bonds are formed in a single step, often with exquisite regiocontrol. The acyl-alkyation reaction is the net result of benzyne insertion into the α,β C–C single bond of the β-keto ester, presumably by a formal [2+2] cycloaddition/fragmentation cascade.[7]
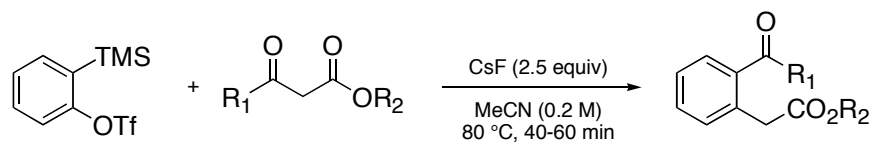
**Scheme 1**



The structures that are accessed by this methodology would otherwise require multi-step sequences for their preparation. The product was independently prepared according to a literature procedure.[8] The product obtained through our methodology was identical by all spectroscopic data to the compound prepared by this alternative method.

The reaction tolerates substitution at the γ-position (Table 1, entries 2-6), including aliphatic and aromatic groups. Heteroatoms may also be incorporated into the β-keto ester side chain, albeit in slightly lower yields (Table 1, entry 5). Additionally, the ester moiety can be varied while maintaining the efficiency of the reaction. For example, β-keto esters of

# Table 1. Acyl-Alkylation of Benzyne



| entry | substrate [a] | product | yield [b] |
|-------|---------------|---------|-----------|
| 1 | | | 67% |
| 2 | | | 78% |
| 3 | | | 84% |
| 4[c] | | | 85% |
| 5 | | | 53% |
| 6 | | | 99% |
| 7 | | | 72% |
| 8 | (R = C₆H₁₃) | (R = C₆H₁₃) | 75% |

[a] 1.25 equiv of aryne precursor relative to β-keto ester.  [b] Isolated yield.
[c] 2 equiv of aryne precursor relative to β-keto ester.

more complex alcohols such as menthol and cholesterol provide the desiredacyl-alkylation products in good yield (Table 1, entries 7 and 8). In general, the mild reaction conditions allow for a considerable degree of substitution on the β-keto ester subunit.

Substituted arynes can also be employed in this methodology. Methyl acetoacetate can react with arynes possessing mono-substitution at the *ortho*- and *meta*-positions (Table 2, entries 1-2) as well as disubstitution (Table 2, entry 3) to produce high yields of the corresponding acyl-alkylation products. Additionally, entries 1 and 3 demonstrate that heteroatom substituents are well tolerated.
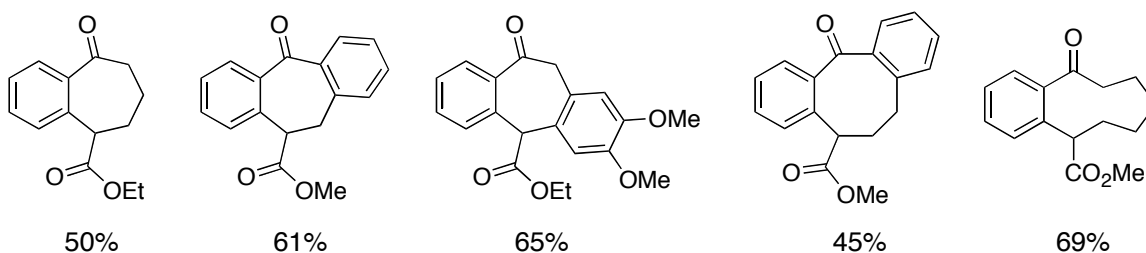
## Table 2. Acyl-Alkylation of Substituted Arynes



| entry | aryne precursor [a] | product | yield [b] |
|---|---|---|---|
| 1 |  |  | 95% |
| 2[c] |  |  | 82%[d] |
| 3 |  |  | 75% |

[a] 2 equiv of aryne precursor relative to β-keto ester. [b] Isolated yield. [c] 1.25 equiv of aryne precursor relative to β-keto ester. [d] Mixture of *meta*- and *para*- regioisomers (1.2 : 1).

Of particular note is the extension of this strategy toward the convergent synthesis of medium-sized carbocycles in a single step from simple starting materials. Recently this procedure for synthesizing

benzannulated carbocycles has been utilized in an enantioselective synthesis of the alkaloid (+)-amurensinine.[9]

**Figure 1. Medium-sized Carbocycles**



50%          61%          65%          45%          69%

1.  Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125.  Email: stoltz@caltech.edu.
2.  Peña, D.; Cobas, A.; Pérez, D.; Guitián, E. *Synthesis* **2002**, 1454-1458.
3.  Breslow, R.; Kivelevich, D. *J. Org. Chem.* **1961**, *26*, 679-681.
4.  Halford, J. O.; Raiford, R. W., Jr.; Weissmann, B. *J. Org. Chem.* **1961**, *26*, 1898-1901.
5.  Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340-5341.
6.  Subsequent to our report, similar aryne insertions into C-C bonds were disclosed: (a) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2005**, 3292-3294.  (b) Yoshida, H.; Watanabe, M.; Ohshita, F.; Kunai, A. *Tetrahedron Lett.* **2005**, *46*, 6729-6731.
7.  This mild method for generating benzyne from *ortho*-silyl aryl triflates was initially developed by Kobayashi: Himeshima, Y; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, *12*, 1211-1214.
8.  Cruces, J.; Estévez, J. C.; Castedo, L.; Estévez, R. J. *Tetrahedron Lett.* **2001**, *42*, 4825-4827.
9.  Tambar, U. K.; Ebner, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11752-11753.

### Appendix
### Chemical Abstracts Nomenclature; (Registry Number)

Methyl 2-(2-acetylphenyl)acetate: Benzeneacetic acid, 2-acetyl-, methyl ester; (16535-88-9)

Cesium fluoride; (13400-13-0)

Methyl acetoacetate: Butanoic acid, 3-oxo-, methyl ester; (105-45-3)

2-(Trimethylsilyl)phenyl trifluoromethanesulfonate: Methanesulfonic acid, 1,1,1-trifluoro-, 2-(trimethylsilyl)phenyl ester; (88284-48-4)

Brian M. Stoltz was born in Philadelphia, PA in 1970 and obtained his B.S. degree from the Indiana University of Pennsylvania in Indiana, PA. After graduate work at Yale University in the labs of John L. Wood and an NIH postdoctoral fellowship at Harvard in the Corey labs, he took a position at the California Institute of Technology. A member of the Caltech faculty since 2000, he currently is the Ethel Wilson Bowles and Robert Bowles Professor of Chemistry and a KAUST GRP Investigator. His research interests lie in the development of new methodology for general applications in synthetic chemistry.

David Ebner was born in 1980 in Stillwater, Minnesota. In 2000, he received his B.S. in chemistry and B.A. in mathematics at the University of St. Thomas, working with Tom Ippoliti. He subsequently began graduate studies at the California Institute of Technology under the direction of Brian Stoltz. After completing his Ph.D. on the palladium-catalyzed enantioselective oxidation of secondary alcohols in 2008, he began postdoctoral research in the laboratories of Erik Sorensen as an NIH Postdoctoral Fellow. His research interests include the development of novel synthetic methodology and the total synthesis of natural products.

Uttam Krishan Tambar was born on November 22, 1978 in Barnsley, England. In 2000, he obtained his A.B. in Chemistry and Physics at Harvard University, where he conducted research with Cynthia Friend and Stuart Schreiber. Uttam performed his Ph.D. studies in the laboratory of Brian Stoltz at the California Institute of Technology where he developed convergent methodologies for the synthesis of biologically active natural products. Since 2006, Uttam has been conducting research with James Leighton at Columbia University, where he has developed a general enantioselective aza-Diels-Alder reaction with acyclic dienes and an enantioselective [3+2] cycloaddition for the synthesis of heterocycles.

Morten Storgaard was born in Denmark in 1980. He graduated from Technical University of Denmark in 2006 with a M.Sc. degree in chemistry and in 2007 he continued as a Ph.D. student under the supervision of professor David Tanner and Dr. Bernd Peschke from Novo Nordisk. His research has mainly been focusing on palladium catalyzed coupling reactions towards the synthesis of biologically active compounds. In the summer and fall of 2008 he visited the group of Jonathan A. Ellman at University of California, Berkeley, working on the rhodium-catalyzed enantioselective synthesis of amines.

Nathan D. Ide was born in 1979 in Grand Haven, MI. In 2001, he obtained his B.S. in chemistry from Hope College in Holland, MI. While at Hope College, he worked with Stephen K. Taylor on the enzymatic resolution of γ- and δ-hydroxyamides. In 2001, he joined the research group of David Y. Gin at the University of Illinois in Urbana-Champaign, IL. His research efforts focused on the synthesis/reactivity of aziridine-containing peptides and the total synthesis (-)-crambidine. After obtaining his Ph.D. in 2006, he joined the Chemical Research & Development group at Pfizer in Groton, CT.