Organic Syntheses

Palladium-Catalyzed Acetylation of Arylbromides

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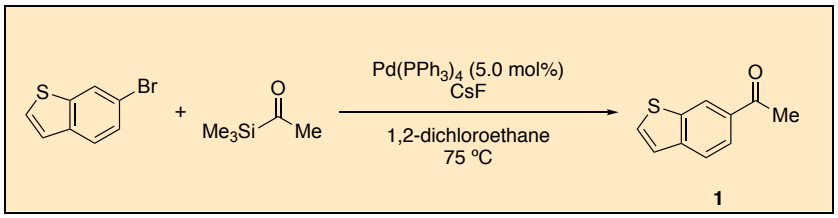


Procedure (Note 1)

*6-Acetylbenzothiophene (**1**).* A single-necked (24/40 joint) 250 mL round-bottomed flask is equipped with a Teflon-coated magnetic stir bar (4.0 x 1.5 cm, football-shaped). The apparatus is flame-dried under vacuum, then cooled to 23 ºC under an atmosphere of argon (Note 2). The flask is charged sequentially with 6-bromobenzothiophene (8.00 g, 37.5 mmol, 1 equiv) (Note 3), cesium fluoride (22.8 g, 150 mmol, 4 equiv) (Note 4), and tetrakis(triphenylphosphine)palladium(0) (2.17 g, 1.88 mmol, 0.05 equiv) (Note 4) through the neck of the flask in singular portions. The neck of the flask is then fit with a rubber septum. An argon inlet needle and a purge needle are placed in the rubber septum, and the flask is purged for 5 min (Figure 1A). After 5 min, the vent needle is removed, and acetyltrimethylsilane (10.8 mL, 75 mmol, 2 equiv) (Note 5) is added in one portion over 1 min via a plastic syringe fit with an 18 G x 1.5'' needle. 1,2-Dichloroethane (38 mL, 1 M) (Note 6) is then added to the flask via a plastic syringe fit with an 18 G x 6'' needle in a single portion over 1 min (Figure 1B). The rubber septum is quickly removed and replaced with a

DOI: 10.15227/orgsyn.098.0068 Published on the Web 3/28/2021

separately flame-dried air condenser with a 24/40 joint (Note 7). The reaction apparatus is then placed in an oil bath preheated to 75 ºC. The reaction mixture is stirred vigorously (800 RPM) for 24 h under positive argon pressure (Figure 1C).

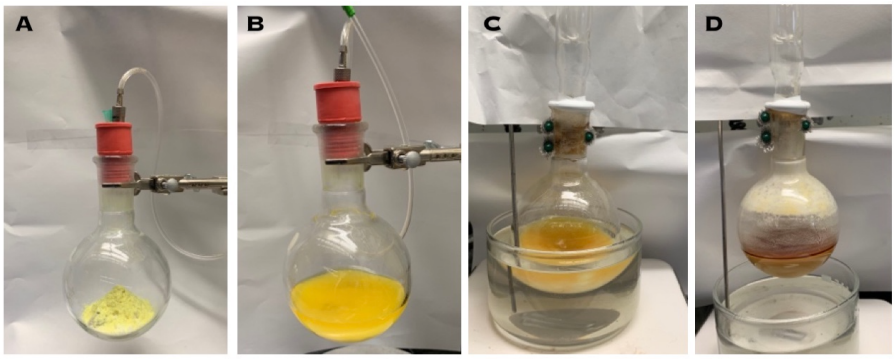


Figure 1. A) Reaction setup after flask is charged with solid reactants; B) Reaction setup after acetyltrimethylsilane; (2) and 1,2-dichloroethane addition; C) Reaction setup with air condenser and oil bath; D) Reaction mixture after stirring at 75 °C for 24 h (photos provided by submitters)

After 24 h (Note 8), the reaction flask is removed from the oil bath and allowed to cool to 23 ºC (Figure 1D). Once the reaction mixture is cooled to 23 ºC, the reflux condenser is removed, and the heterogeneous mixture is diluted with heptane (75 mL) (Note 9). The solution is then filtered through a plug of silica gel (50 g, pre-wetted with 100 mL ethyl acetate) (Note 10) in a fritted Büchner funnel (Note 11) into a 1000 mL round-bottomed flask using ethyl acetate as eluent (500 mL) (Notes 12 and 13). The filtrate is then concentrated under reduced pressure (31 °C, from 100 mmHg to 50 mmHg).

The resultant brown solid is purified via column chromatography using an OD 7.5 x 12 cm column of 250 g silica gel (Note 14) and eluted sequentially with 1400 mL 14:1 heptane:EtOAc and 2000 mL 9:1 heptane:EtOAc. The eluate is collected using 25 mL test tubes to provide the product in fractions 78–106 (Note 15). The fractions are combined in a collection flask and concentrated by rotary evaporation under reduced pressure (31 ºC, 90 mmHg). The material is then transferred to an 8-dram vial and dried under high vacuum for 30 min (<1 mmHg) to afford 6-acetylbenzothiophene (**1**) as a yellow powder (4.15 g, 63% yield) (Notes 16, 17 and 18).

Figure 2. Isolated 6-acetylbenzothiophene (1) (photo provided by 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 acetyltrimethylsilane, 6-bromobenzothiophene, tetrakis(triphenyl-phosphine)palladium (0), 1,2-dichloroethane, hexanes, ethyl acetate, silica gel, and cesium fluoride.

2. The authors performed the reaction under an atmosphere of nitrogen.
3. 6-Bromobenzothiophene (97%) was purchased from Combi-Blocks and used after crushing the material into a fine powder with a mortar and pestle. Checkers purchased 6-bromobenzothiophene (98%) from Fluorochem and the material was used as received.
4. Cesium fluoride (99%) and $Pd(PPh_3)_4$ (99%) were purchased from Strem Chemicals and used as received. Checkers purchased cesium fluoride (99%) from Fluorochem and the reagent was used as received. A third run was conducted with $Pd(PPh_3)_4$ (98%), purchased from Fluorochem and used as received.
5. Acetyltrimethylsilane (97%) was purchased from Sigma Aldrich and used as received.
6. 1,2-Dichloroethane (99%) was purchased from Fischer Scientific and passed through an activated alumina column with argon before use. Checkers purchased 1,2-dichloroethane (99.5%) from Acros Organics and the solvent was used as received.
7. The air condenser is equipped with a rubber septum with a nitrogen inlet needle to maintain an inert atmosphere and positive pressure. The joint of the round-bottomed flask and reflux condenser is sealed with Teflon tape (Figure 3) before placing the reaction flask in an oil bath.

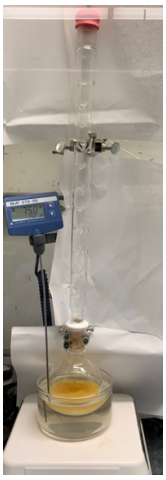


Figure 3. Full reaction setup with air condenser and nitrogen inlet needle (photo provided by submitters)

8. Reaction progress was monitored after 24 h using TLC analysis on silica gel with 9:1 hexanes:EtOAc as eluent. Visualization of the TLC plate was performed with UV irradiation (254 nm) and *p*-anisaldehyde. The starting material has $R_f = 0.73$ (no color, UV active), the desired ketone product has $R_f = 0.32$ (pink, UV active).

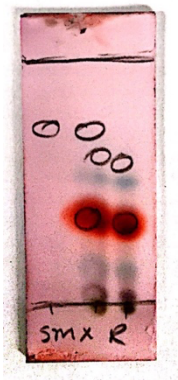


Figure 4. TLC of the crude reaction mixture (SM = starting material, X = co-spot of SM and R, R = reaction mixture) (photo provided by submitters)

9. Checkers used heptane, which was purchased from Donauchemie and used after distillation. The authors used hexanes (98.5%), which were purchased from Fisher Scientific and used as received.
10. SiliaFlash P60 (particle size 0.040–0.063 mm) was purchased from SiliCycle and used as received. The checkers used silica gel purchased from Macherey-Nagel (particle size 0.040–0.063 mm), which was used as received.
11. Filtration used a 150 mL medium porosity fritted Büchner funnel under vacuum.
12. Ethyl acetate (99.5%) was purchased from VWR and used as received. The checkers used ethyl acetate, which was purchased from Donauchemie and used after distillation.
13. The reaction flask was rinsed with ethyl acetate until all of the material was transferred onto the pad of silica on the fritted funnel. Filtrate is a light brown color as shown in Figure 5.

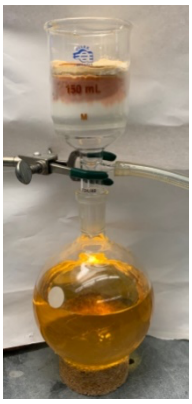


Figure 5. Filtration apparatus (photo provided by submitters)

14. The column is wet-packed using 250 g of silica and 600 mL of 14:1 heptane:EtOAc. The crude material is dissolved in benzene (20 mL) and loaded on the column with subsequent rinses of the round-bottomed flask using benzene (3 x 1 mL) to ensure quantitative transfer. The authors used hexanes instead of heptane.
15. Fractions containing the product were identified by TLC analysis (9:1 heptane:EtOAc as eluent). Fractions 65–77 contained the desired product and two impurities that can be visualized by UV irradiation and by *p*-anisaldehyde stain as a blue spot (R_f = 0.54, Figure 6) and a faint brown spot (R_f = 0.46, Figure 6). These fractions were not collected. Fractions 98–106 contained an impurity that can be visualized by UV irradiation and by *p*-anisaldehyde stain as a faint black spot (R_f =0.37, Figure 6). This impurity does not impact the purity of the desired compound as judged by qNMR, so these fractions were also collected. Test tubes containing the desired product were each rinsed with EtOAc (3 x 1 mL), and the rinses were transferred into the collection flask.

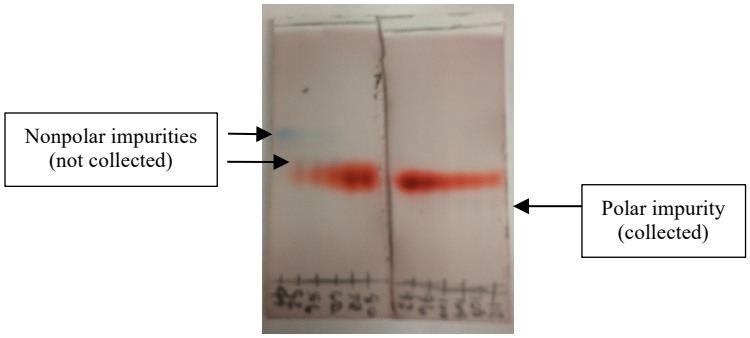


Figure 6. Representative TLC analysis showing impurities in column fractions (photo provided by submitters)

16. 6-Acetylbenzothiophene: mp 72.4–74.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.68 (s, 3H), 7.39 (d, J = 5.6 Hz, 1H), 7.67 (d, J = 5.3 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.96 (dd, J = 8.4, 2.3 Hz, 1H), 8.51 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.9, 123.7, 123.7, 123.9, 124.1, 131.0, 133.4, 139.8, 143.0, 197.8; IR (film): 3106, 1677, 1593, 1391, 1356, 1269, 1249, 1237, 827, 762 cm^{-1}; HRMS–ESI (m/z) [M + H]+ calcd for $C_{10}H_9OS^+$ 177.0369; found, 177.0369.
17. The purity of **1** was determined to be >95 wt% by qNMR using 1,3,5-trimethoxybenzene (Alfa-Aesar, 99%) as the external standard. Elemental analysis performed by the checkers provided the following data: Elemental analysis: Calcd for $C_{10}H_8OS$: C, 68.15; H, 4.58; N, 0.0; S, 18.19; O, 9.08. Found: C, 67.75; H, 4.44; N, <0.05; S, 17.96; O, 9.21.
18. A second run performed at full scale provided 4.51 g (68%) of **1** at >97% purity. Three reactions were performed at approximately half-scale and provided product **1** in yields that ranged between 65% and 73%.
19. Another run on half-scale was performed using $Pd(PPh_3)_4$ (98%) purchased from Fluorochem. For this reaction, TLC analysis showed remaining starting material after 24 h, for which reason an additional 2.5% of catalyst were added (total: 7.5%) and stirring was continued for 5 h. After this time, the reaction was treated as above to yield 2.51 g (76%) of **1**.

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

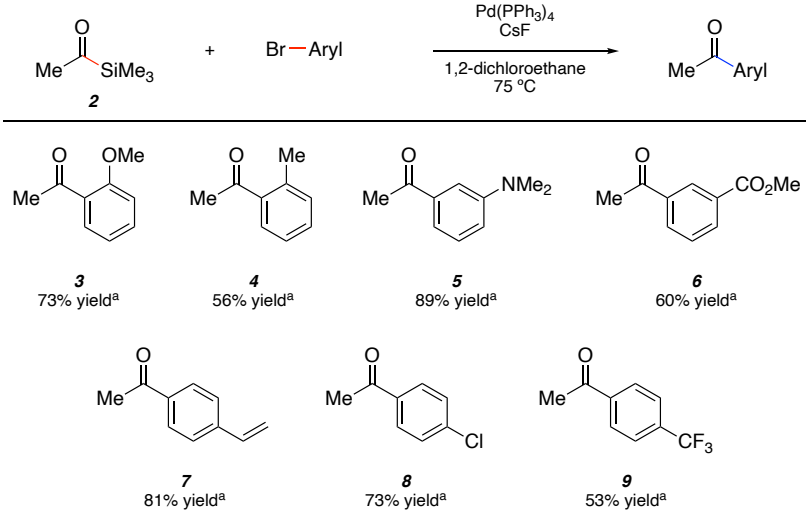
Aryl methyl ketones and heteroaryl methyl ketones are versatile building blocks in the syntheses of fragrances,[2] resins,[3] and drug candidates.[4] Traditionally, Friedel–Crafts acylation[5] or addition of organometallic reagents into carboxylic acid derivatives[6] have been employed to access alkyl–aryl ketones. Despite the synthetic utility of these methods, several drawbacks exist, such as the necessity to use stoichiometric reagents, poor

functional group tolerance, and competitive over-alkylation in the case of organometallic additions.[5a,6c–d,7]

To overcome these challenges, transition metal catalysis has made available new mechanistic paradigms that offer improved chemo- and regioselectivity in the formation of the desired aryl–acyl linkage.[8–12] Several cross-coupling approaches to form methyl aryl ketones have been reported, including carbonylative cross-couplings employing CO or CO_2 as the carbonyl source.[8,9] Although this strategy has proved effective, the necessity of manipulating toxic, gaseous reagents remains a limitation.[13] Alternative cross-coupling approaches include Heck reactions of enol ethers, followed by subsequent hydrolysis[10] and cross-couplings of α–alkyoxyvinyl metal reagents with ensuing hydrolysis.[11,12] Though these strategies eliminate the necessity to employ CO or CO_2, multiple steps are required to furnish the desired alkyl-aryl ketone. Therefore, a methodology that forms the desired aryl–acyl linkage in a single step, while avoiding the use of gaseous reagents, would be useful. The one-step procedure reported here circumvents these limitations by providing a mild, catalytic alternative that relies on commercially available reagents (i.e., acetyltrimethylsilane (**2**) and (hetero)aryl bromides) to construct aryl–acetyl linkages.[14]

This methodology is tolerant of a variety of substitution patterns on the aryl bromide coupling partner as summarized in Table 1. Substrates with electron-donating groups at the *ortho* position underwent the coupling smoothly, as demonstrated by products **3** and **4**. Amine and carboxylic ester functionalities were employed as shown by the formation of products **5** and **6**. Furthermore, vinyl, chloro, and trifluoromethyl moieties at the *para* position are well tolerated in this transformation. Notably, an aryl chloride was not disturbed in this methodology, as demonstrated by the formation of ketone **8**.

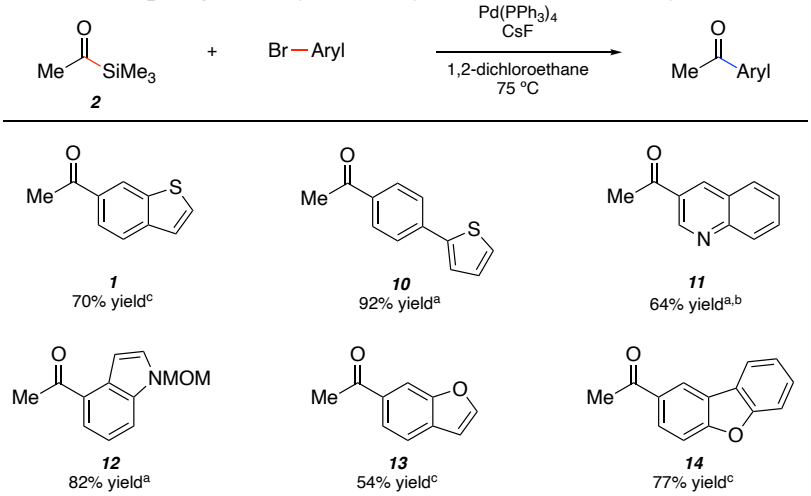
Table 1. Coupling of acetyltrimethylsilane and aryl-bromides



Conditions: $Pd(PPh_3)_4$ (5.0 mol%), CsF (4.0 equiv), substrate (1.0 equiv), **2** (2.0 equiv), 6 h.[15] [a]The yield of the product was determined by ^1H NMR analysis of crude reaction using 1,3,5-trimethoxybenzene as an internal standard (0.1 equiv).

Heteroaryl bromides are valuable test substrates because of the ubiquity of heterocycles in bioactive molecules and pharmaceutical targets. Gratifyingly, heteroaryl bromides proved to be viable cross-coupling partners as depicted in Table 2. Sulfur-containing substrates afforded desired compounds **1** and **10** in excellent yields. Quinoline and indole motifs furnished ketones **11** and **12** in good yields, respectively. This methodology is also tolerant of oxygen-containing heterocycles as indicated by the formation of ketones **13** and **14**.

Table 2. Coupling of acetyltrimethylsilane and heteroaryl-bromides



Conditions: $Pd(PPh_3)_4$ (5.0 mol%), CsF (4.0 equiv), substrate (1.0 equiv), **2** (2.0 equiv). [a]**10**, **11**, **12** were stirred for 6 h[15] and the yield of the product was determined by ^1H NMR analysis of crude reaction using 1,3,5-trimethoxybenzene as an internal standard (0.1 equiv). [b]For **12**, $Pd(PPh_3)_4$ (10.0 mol%) was used. [c]**1**, **13**, and **14** are isolated yields.

In summary, this methodology provides facile access to acetylated arenes from commercially available acetyltrimethylsilane (**2**) and (hetero)aryl bromides. Its operational simplicity and wide substrate scope render it an attractive alternative protocol to traditional methods for the construction of aryl–carbonyl linkages.

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15. Tables 1 and 2 were adapted from the original report by Ramgren and coworkers (reference 14). The reaction time in the original report was 6 h for reactions run on 0.05 mmol scale, however scaling up to 37.5 mmol required longer reaction times to ensure full consumption of starting material, thus a reaction time of 24 h is reported for this procedure.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

6-Bromobenzothiophene; (17347-31-9)
Acetyltrimethylsilane; (13411-48-8)
Cesium fluoride; (13400-13-0)
Tetrakis(triphenylphosphine)palladium (0); (14221-01-3)

Milauni Mehta was born in Mumbai, India and raised in Princeton, New Jersey. In 2018, she received her B.A. in Chemistry from The Ohio State University, where she carried out research under the direction of Professor T. V. RajanBabu. In 2018, she began graduate studies at the University of California, Los Angeles, where she is currently a third-year graduate student in Professor Neil K. Garg's laboratory. Her studies primarily focus on developing transition metal-catalyzed cross-coupling reactions.

Andrew Kelleghan was born in Santa Monica, California. In 2018, he received his B. S. in Chemical and Biomolecular Engineering from University of California, Berkeley where he carried out research under the advisement of Professor Phillip Messersmith. He then pursued graduate studies at the University of California, Los Angeles, where he is currently a third-year graduate student in Professor Neil K. Garg's laboratory. His studies primarily focus on developing synthetic methods utilizing strained cyclic allenes.

Neil Garg is a Professor of Chemistry and the Kenneth N. Trueblood Endowed Chair at the University of California, Los Angeles. His laboratory develops novel synthetic strategies and methodologies to enable the total synthesis of complex bioactive molecules.

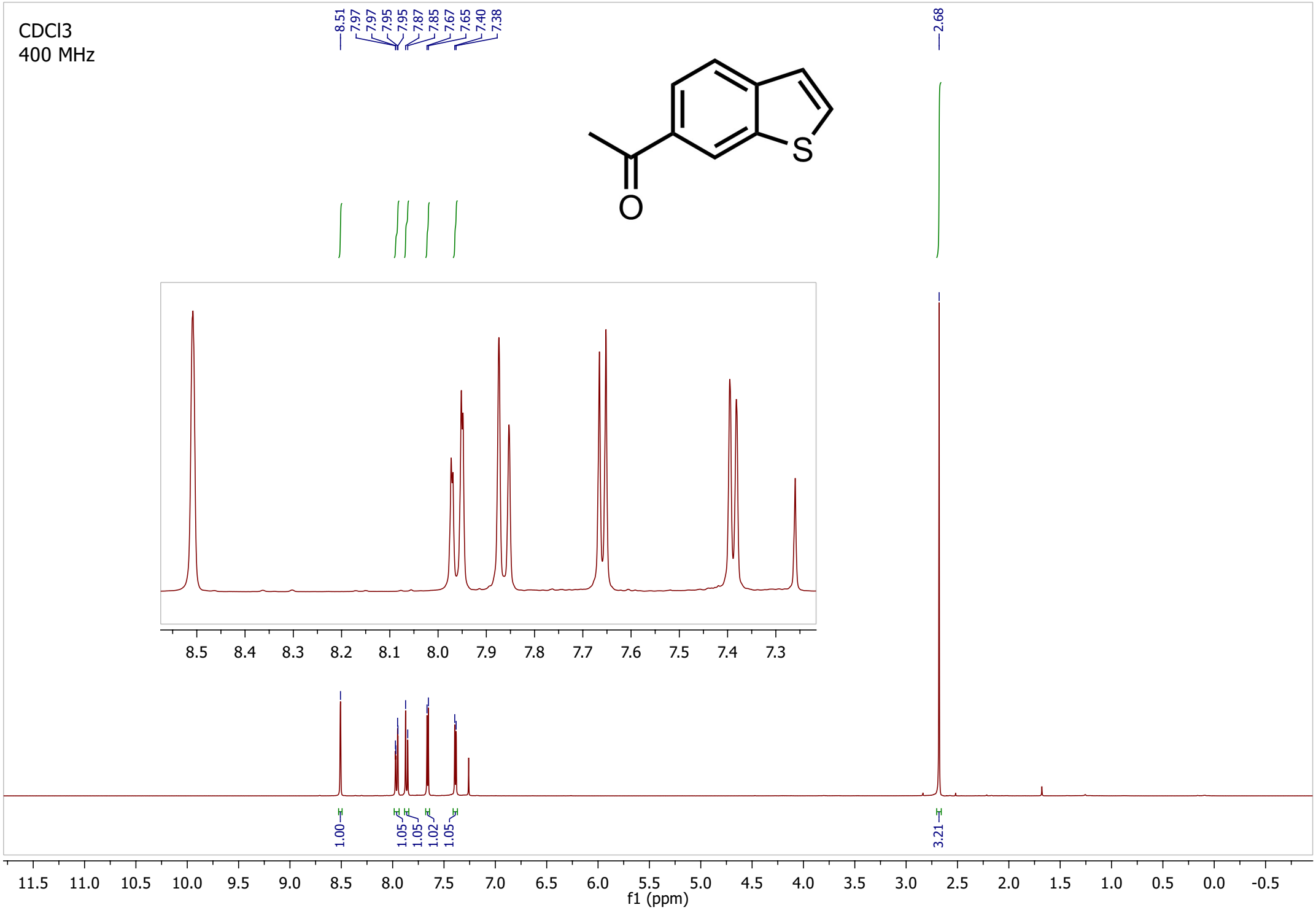
Martina Drescher is the lead technician of the Maulide group at the University of Vienna, where she has worked with several group leaders over the course of 38 years.

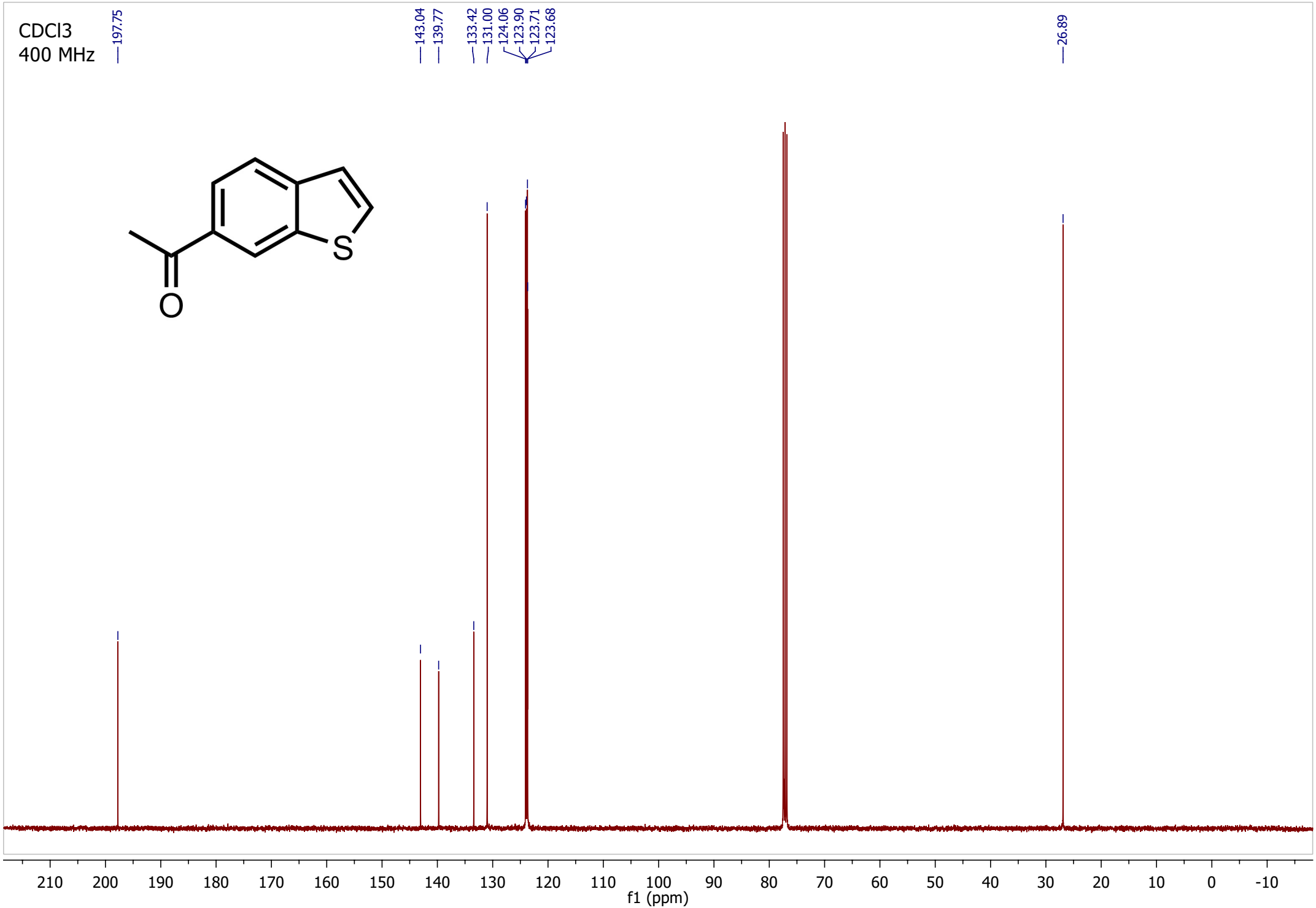
Daniel Kaiser received his Ph.D. at the University of Vienna in 2018, completing his studies under the supervision of Prof. Nuno Maulide. After a postdoctoral stay with Prof. Varinder K. Aggarwal at the University of Bristol, he returned to Vienna in 2020 to assume a position as senior scientist in the Maulide group. His current research focusses on the chemistry of destabilized carbocations and related high-energy intermediates.

Zach Ariki was born in Colorado, USA. He obtained his B.A. in Chemistry from Boston University in 2014 and completed his Ph.D. (2021) under the supervision of Professor Cathleen Crudden at Queen's University. His thesis focused on the development of transition metal catalyzed cross-coupling methodologies using alkyl sulfone electrophiles. Following the completion of his graduate studies, he joined GreenCentre Canada as a Development Scientist.

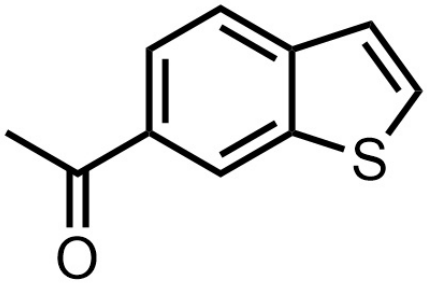
Yuuki Maekawa received his Ph.D. from Gifu University in 2017 under the supervision of Professor Toshiaki Murai. In 2017 he joined the Crudden group as a postdoctoral fellow, where he studied the use of sulfur-containing compounds in metal-catalyzed cross-coupling reactions. In 2019, he was awarded a JSPS Research Fellowship for Young Scientists. He is currently a Scientist at Paraza Pharma in Montreal, Canada.

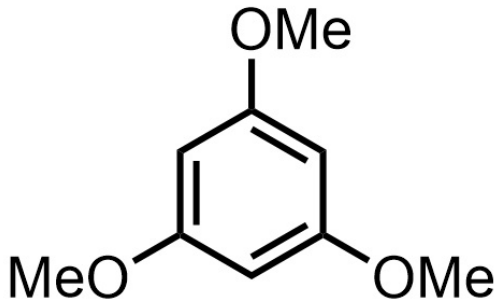
CDCl3
400 MHz




CDCl3
400 MHz
197.75
143.04
139.77
133.42
131.00
124.06
123.90
123.71
123.68
26.89
O
S
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)

CDCl3
400 MHz





8.51
7.97
7.95
7.87
7.85
7.66
7.65
7.39
7.38
6.09
3.76
2.68

0.90
0.94
0.96
0.94
0.96
3.00
9.52
2.85

16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)