JOURNAL OF CHEMICAL EDUCATION

Laboratory Experiment

pubs.acs.org/jchemeduc

The Two Faces of Sulfinates: Illustrating Umpolung Reactivity

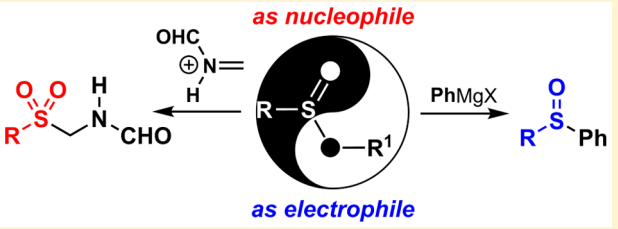
Adabelia Tapia-Pineda,[†] Carlos Perez-Arrieta,[†] Carolina Silva-Cuevas,[†] Ehecatl Paleo,[†,‡] and J. Armando Lujan-Montelongo*[,†]

[†]Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional (Cinvestav), Avenida Instituto Politécnico Nacional 2508, San Pedro Zacatenco, 07360 Ciudad de México, México

[‡]Facultad de Ciencias, Universidad Nacional Autónoma de México (UNAM), Ciudad Universitaria, 04510 Ciudad de México, México

Supporting Information

ABSTRACT: A simple, microscale experiment was developed with the aim of demonstrating the concept of umpolung in synthetic organic chemistry. Starting from a common alkyl sulfinate, students perform a polarity inversion by performing a Grignard-based sulfoxide synthesis and a Mannich-type formamide synthesis. The products are purified without chromatography and are easily characterized. Procedural optimization established an experiment time of less than 3 h. Spectroscopic characterization includes the interpretation of ^{1}H NMR, ^{13}C NMR, and FTIR spectra. This experiment, therefore, is suitable for a mid- to upper-level undergraduate organic lab curricula for illustrating advanced synthetic methods.



KEYWORDS: *Laboratory Instruction, Upper-Division Undergraduate, Organic Chemistry, Collaborative/Cooperative Learning, Amides, Grignard Reagents, Organosulfur Compounds, NMR spectroscopy, IR spectroscopy, Synthesis*

INTRODUCTION

The concept of polarity reversal in organic functional groups, known as *umpolung*, was introduced by G. Wittig in the early 1950s emanating from the reaction of aryl halides exchange with phenyllithium.[1] Although initially a surprise, more examples emerged and almost 15 years later, D. Seebach[2] popularized the umpolung principle with the chemistry of dithianes as a strategy to gain access to the acyl anion, an important synthon in the context of the ideas proposed by E. J. Corey.[3] Today, the term umpolung refers to synthetic strategies that achieve the inversion of the intrinsic reactivity of a functional group and features in the preparation of natural products and valuable targets.[4]

Unexpectedly, the corpus of chemistry education literature does not have a substantial number of organic chemistry laboratory experiments or demonstrations featuring umpolung chemistry. The majority of the umpolung-related chemistry is focused on carbon-based functional groups, with emphasis on the carbonyl functional group (Scheme 1). Examples include the Corey−Seebach dithiane chemistry,[5] Stetter-type reactions,[6] and benzoin-type condensations.[7] The benzoin condensation is the most frequently cited reaction that showcases umpolung chemistry, both in the lab and in the classroom, and is often cited in cases where a reversal of reactivity is featured in biological systems (e.g., reactions catalyzed by the pyruvate dehydrogenase complex).[8]

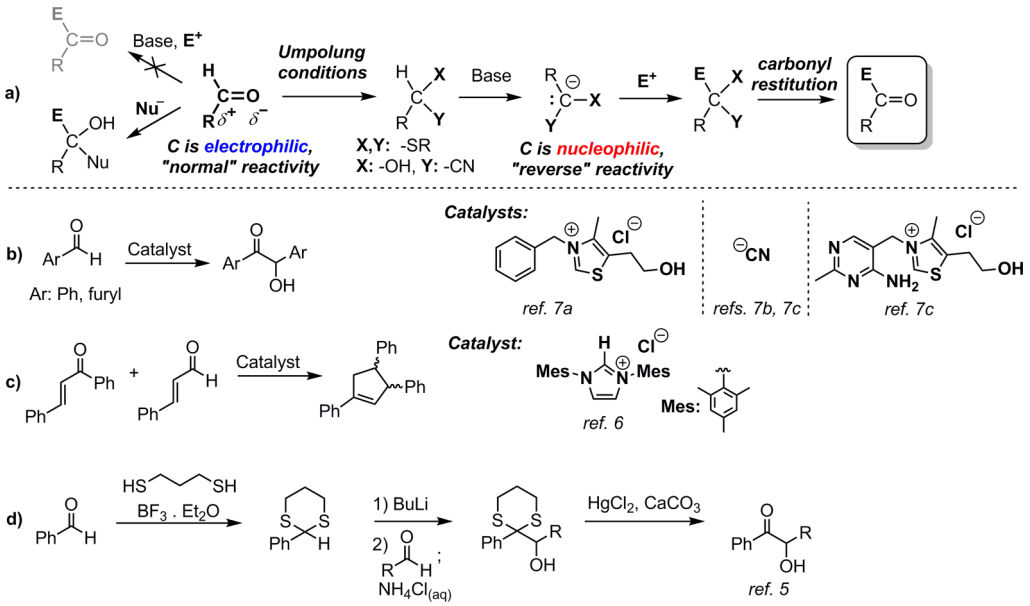
We recently discovered that alkyl arylsulfinates (**1**) could be utilized in Mannich-type reactions as formal nucleophiles, to give structurally diverse (arylsulfonylmethyl)formamides (**2**) (Scheme 2e).[9] Mechanistic studies suggest the in situ formation of free sulfinic acid (**4**), which is rapidly trapped by a Mannich reagent (**3**) derived from formaldehyde and formamide. Although the Mannich-type synthesis has been considered the prevalent method to access *N*-(tosylmethyl)formamide (**2a**), the precursor of the valuable isonitrile building block TosMIC (**7a**) (Scheme 2f),[10b,c] the procedure to access most of the *N*-(arylsulfonylmethyl)formamides (**2**) was confined to sulfinic acids and their salts as reactants.[10] Both species are limited in commercial availability, restricting structural diversity.[11] Interestingly, the use of alkyl arylsulfinates (**1**) in Mannich-type reactions depicted the first time where formal reversal of reactivity of the alkyl sulfinate functional group was introduced, since these sulfur species had been exploited solely as electrophiles (Scheme 2a-d).[12]

To address the interest around introducing mid- to upper-level organic synthesis concepts into the undergraduate lab, we developed a *microscale* experiment, starting with methyl 4-methylbenzensulfinate **1a** or methylbenzenesulfinate **1b** (Scheme 3). Students can prepare both a diarylsulfoxide (**5a** or **5b**) and an *N*-(arylsulfonylmethyl)formamide (**2a** or **2b**), so they can directly contrast both *electrophilic* and *nucleophilic* reactivity. Thus, students learn how to perform an umpolung *experimentally*, introducing the alkylsulfinate, sulfinyl, and sulfonyl functional groups, as novel, alternative probes to the classical, carbon-based functional groups.

Received: February 8, 2016
Revised: April 14, 2016

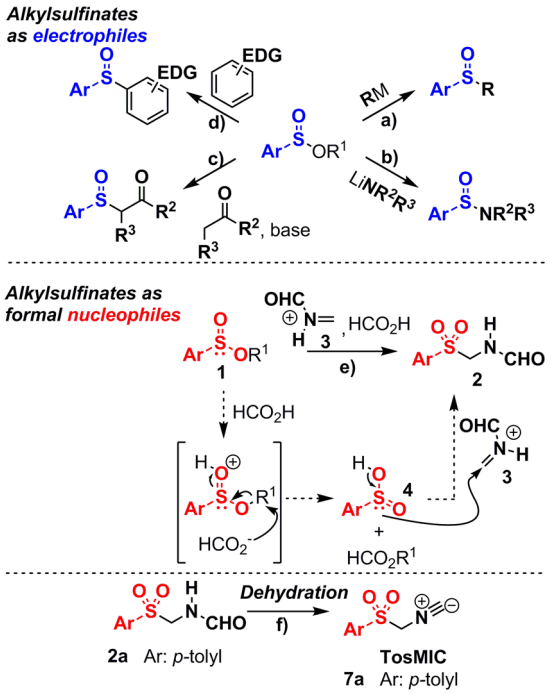
DOI: 10.1021/acs.jchemed.6b00102
J. Chem. Educ. XXXX, XXX, XXX−XXX

Scheme 1. Umpolung Examples Found in the Chemical Education Literature



[a]Classical umpolung approach on the carbonyl functional group. [b]Benzoin-type condensations (refs 7a−c). [c]A Stetter-type reaction (ref 6). [d]A Corey-Seebach reaction (ref 5).

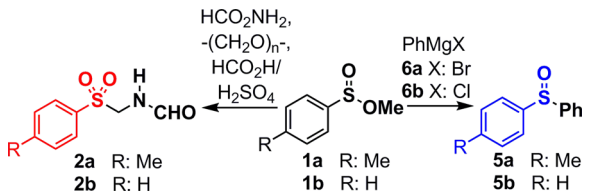
Scheme 2. Selected Methods of Alkyl Sulfinates as Electrophiles or Nucleophiles[a]



[a]Alkyl sulfinates as electrophiles reacting with [a]organometallic nucleophiles (refs 12a−e), [b]lithium amides (refs 12f−h), [c]enolates (refs 12i, j), [d]activated arenes (ref 12k). [e]Alkyl sulfinates as formal nucleophiles reacting with a Mannich reagent (ref 9). [f]TosMIC (**7a**) preparation by *N*-(*p*-tolylsulfonylmethyl)formamide (**2a**) dehydration.

In the development of this experiment, a primary consideration was experimental reproducibility with tolerance for detrimental issues, arising from equipment availability and experimental-human related factors. But most importantly, we

Scheme 3. Umpolung Chemistry on Methyl Arylsulfinates, Arylsulfonylmethylformamides, and Arylphenylsulfoxides preparation



aimed for an integrative experiment designed to harness diverse pedagogical goals such as (1) introduce students to the *umpolung* concept in synthetic organic chemistry through sulfinate chemistry, (2) improve spectroscopic characterization skills through NMR and IR experiments, (3) illustrate the correlation between structure, physical and chemical properties of sulfur based organic compounds, (4) illustrate organic reaction mechanisms through arrow-pushing sequences, (5) introduce delocalization and equilibria concepts through the analysis of ^{1}H NMR experiments of the some of the products.

LABORATORY PROCEDURES

Sulfinates as Electrophiles

Comprehensive experimental procedures and additional comments can be found in the Supporting Information. We suggest students work in pairs, so one can perform the sulfoxide synthesis and the other the formamide preparation. In the standardized procedure for the sulfoxide synthesis, a solution of methyl 4-methylbenzenesulfinate (**1a**) or methylbenzenesulfinate (**1b**) in toluene is prepared by the students. After cooling to 0 °C, phenylmagnesium bromide (**6a**) or chloride (**6b**) solution (1.6 equiv) is added to the mixture. After 10 min, an aqueous workup is performed, followed by liquid−liquid extraction and condensation in vacuo to yield a grayish solid. The material is then purified by recrystallization. 1-Methyl-4-(phenylsulfinyl)benzene (**5a**) or sulfinyldibenzene ("diphenyl-

DOI: 10.1021/acs.jchemed.6b00102
J. Chem. Educ. XXXX, XXX, XXX−XXX

sulfoxide") (**5b**) are obtained as white solids. The student yields of **5a** and **5b** ranged from 34 to 53%.

Sulfinates as Nucleophiles

The standardized procedure begins with the preparation of a mixture of methyl 4-methylbenzenesulfinate (**1a**) or methylbenzenesulfinate (**1b**), paraformaldehyde (4 equiv), formamide (7.5 equiv), and a 9:1 (v/v) mixture of formic and sulfuric acids. The flask is heated by immersion into a hot water bath at 80 °C while stirring for 30 min. Afterward, the reaction is cooled and diluted with water, extracted by liquid−liquid extraction, washed and dried, and concentrated in vacuo. The resulting yellowish syrup is induced to crystallize by the addition of ethyl ether. *N*-(Tosylmethyl)formamide (**2a**) or *N*-((phenylsulfonyl)methyl)formamide (**2b**) are obtained as white solids. The student yields of **2a** and **2b** ranged from 20 to 51%.

Characterization

Students are required to dry the synthesized products by suction or standing within a desiccator. Qualitative TLCs are encouraged through all stages of the experiment. Melting points are measured outside of class, but measurements should be brought for discussion and included within the report. If time allows, selected students can run the FTIR and ^{1}H NMR experiments the same day the experiment is performed or during off-class hours.

■ HAZARDS

Eye protection, gloves, and lab coat must be worn while performing these experiments. All the reagents must be dispensed in a fume hood or a well ventilated place in order to avoid the inhalation of vapors. Paraformaldehyde is considered a potential carcinogen. Pregnant women should not perform the experiment because formamide may harm the unborn child or cause developmental defects. Gloves used for dispensing formamide should be replaced after handling this reagent. Disposable insulin syringes are suitable for dispensing formamide and should be disposed properly after use. Both the formamide-exposed gloves and the syringes should be treated as solid hazardous waste. Phenylmagnesium halides are highly harmful on contact and the instructors are encouraged to dispense the reagent to students directly. Formic and sulfuric acids are irritants and corrosive. Diethyl ether, toluene, and methanol are flammable and toxic by inhalation or contact. Methyl arylsulfinates (**1a** and **1b**), diaryl sulfoxides (**5a** and **5b**), and (arylsulfonylmethyl)formamides (**2a** and **2b**) have not been fully tested for toxicity and therefore must be handled with care to avoid contact or inhalation.

■ RESULTS AND DISCUSSION

Methyl 4-methylbenzenesulfinate (**1a**) is an ideal probe for umpolung chemistry in both sulfone (**2**) and sulfoxide (**5**) syntheses. No difference was observed with the use of methylbenzenesulfinate (**1b**) as a replacement of **1a**. Both **1a** and **1b** are easily prepared from the corresponding thiols[9] (see Supporting Information) or can be purchased from chemical suppliers.[13] In practice, students gave preference for **1a** over **1b** and the given rationale[14] was that formamide **2a** and sulfoxide **5a** derivatives were easier to isolate than the phenyl analogs (**2b** and **5b**). Earlier explorations of reactions suitable to demonstrate the electrophilicity of alkylsulfinates involved aromatic substitutions with sulfinate **1a** on activated arenes.[12k] Unfortunately, attempts to optimize the reaction time[15] of the $AlCl_3$ catalyzed reaction of activated arenes (such as anisole and trimethoxybenzene) were unsuccessful. Similar results were obtained when sodium enolates or amines were used (see Supporting Information for details). To further explore the conversion of sulfinate **1a**, a more reactive nucleophile such as a Grignard reagent was used for a faster reaction. The reaction of phenylmagnesium bromide with sulfinate **1a** could be considered as a continuation of the preparation of a phenylmagnesium halide **6**, a common experiment performed in undergraduate organic chemistry laboratories.[16] Additionally, sulfoxide **5a** is an easily isolated product with desirable physical properties.[17] To our delight, exposure of sulfinate **1a** to Grignard reagent **6a** for 15 min yielded the desired sulfoxide **5a** with complete conversion. The preparation of **5a** benefits from the possibility of performing the reaction in a not strictly dry environment. Pretreatment of the solvent (toluene) with common drying agents (e.g., sodium sulfate) is sufficient for students to reach yields ranged from 40 to 65%.[18]

The Mannich-type formamide synthesis was selected to demonstrate the nucleophilicity of alkyl sulfinates. However, two concerns had to be addressed in order to overcome other potential issues with the literature reported procedure. First, according to the reported method,[9] a successful preparation of *N*-(tosylmethyl)formamide (**2a**) requires heating via a conventional oil bath or microwave irradiation for 2−3 h. This exceeds the time limitation of an hour, necessary to conduct the whole experiment within a 3 h time frame. Second, heated oil baths are a higher safety risk for students than salt or water baths. Also, microwave reactors are not common in the academic organic lab; consequently, the procedure had to be optimized. The mechanistic proposal suggests that sulfinic acid intermediate **4** is generated in situ by formic acidolysis of sulfinate **1** (Scheme 2). The addition of a strong mineral acid such as sulfuric acid (in small amounts) as a cocatalyst, therefore, could enhance the release of sulfinic derivative **4** and thereby increase the reaction rate if this step is rate-determining for the whole process. Varying amounts of sulfuric acid were screened, and we were delighted to find that replacing formic acid with a 9:1 (v/v) mixture of formic and sulfuric acid yielded a reaction time of 30 min while heating at 80 °C with a water bath (see Supporting Information for more details). In rare cases (less than ∼5% of students), incomplete conversions complicated the isolation of the formamides **2a** and **2b**. Quick filtration using Pasteur pipet silica gel chromatography is suitable for purification (see Supporting Information). Student reported yields ranged from 14% to 60%. Melting points comparable with those reported within the literature could be obtained after drying **2a** and **2b** within a desiccator for >48 h.

FTIR and ^{1}H NMR spectra can be acquired during the last hour of the experimental session or off-class hours. Prior to the discussion session, students were encouraged to identify new and absent signals of their own spectra compared with reference spectra (included within Supporting Information). For example, because the —OMe group from reactants **1a** and **1b** is lost through both sulfoxide and formamide syntheses, the related 3.4−3.5 ppm singlet in ^{1}H NMR spectra is significantly absent. As counterexamples, the emergence of the singlet formyl signal at 8.1 ppm and a doublet signal at 4.7 ppm belonging to the methylene bridge in the case of the formamides **2a** and **2b** were easily identified by students. In the case of sulfoxides **5a** and **5b**, a new subset aromatic signals at 7.3−7.7 ppm were effectively highlighted. The presence of a small signal at 4.5 ppm accompanying the main methylene signal at 4.7 ppm in formamides **2a** and **2b** is relevant if the

DOI: 10.1021/acs.jchemed.6b00102
J. Chem. Educ. XXXX, XXX, XXX−XXX

instructor intends to discuss three-atom delocalization and equilibria concepts.[19] Although students did not conduct ^{13}C NMR experiments, instructors discussed the reference spectra highlighting the carbonyl (160 ppm) and methylene bridge (59 ppm) for both **2a** and **2b**, and the new aromatic absorptions (120−145 ppm) for **5a** and **5b**. FTIR spectra was more helpful in the case of formamides (**2a** and **2b**) than sulfoxides (**5a** and **5b**), as amino (NH) and carbonyl (C═O) stretching absorptions (3247, 3368 cm^{-1} and 1665, 1692 cm^{-1}, respectively) are easily identified. In the case of the sulfonyl group, students had difficulties attributing the stretching absorptions at 1310 and 1138 cm^{-1} for **2b**, together with 1319 and 1141 cm^{-1} in the case of **2a**. However, they could easily identify the stretching vibration for the sulfinyl group of **5a** and **5b** at 1020−1040 cm^{-1}.

The students adapted quickly and conscientiously to experimental procedures and could harness relevant chemical concepts. We carried out both pre- and postlab questionnaires (included within the Student Guide, see Supporting Information), where topics such as organic reaction mechanisms of the performed reactions, knowledge into workup techniques for organic reactions, spectroscopic characterization, identification of the oxidation state of atoms within an organic molecule (e.g., sulfur), knowledge of synthetic methods, and discussion of delocalization and equilibria through ^{1}H NMR spectra analysis were included in order to measure student's assessment. Additionally, a laboratory report was required where students were to include an introductory background including most of the topics covered by the pedagogical goals, experimental methodology and its analysis, interpretation and analysis of the results, and conclusions. Feedback from oral surveys carried out by TAs illustrated virtually no frustration and a positive experience overall. With the chemistry featured in this experiment, the umpolung or reversal of polarity strategy was addressed in an organic synthesis case, featuring both Grignard and Mannich-type reactions on sulfinates. Chemical concepts such as polarity, oxidation state, reactivity and applicability of sulfur derivatives, delocalization, and equilibria were also discussed. Such chemistry concepts, bound together with a comprehensive revision of characterization techniques such as melting point, IR, and NMR spectra, resulted in an integrative experience.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.6b00102.

Detailed experimental procedures, full characterization data such as melting point, ^{1}H NMR, ^{13}C NMR and FTIR spectra. (PDF, DOCX)

Instructor Notes including general guidelines, a comprehensive list of materials, equipment and chemicals, troubleshooting advice, and examples of solved pre- and postlab questionnaires are available. (PDF, DOCX)

A Student handout including introduction and description of the experiment, safety recommendations, examples of pre- and postlab questionnaires, and step by step experimental procedures is also available. (PDF, DOCX)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jalujanm@cinvestav.mx.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Authors are grateful to the CONACYT (Mexico) for financial support via grant CB-2014-241455. E.P. also thanks CONACYT (Mexico) for a postdoctoral fellowship (217966). Miguel Ángel Jaime is acknowledged for assisting Ehecatl Paleo during the experimental sessions with the Chemistry (1104) and Organic Chemistry (1203) classes at the Faculty of Sciences of the National Autonomous University of Mexico (UNAM). We are grateful with the Chemistry Department staff at Cinvestav for acquiring some of the spectra. We also thank Fraser F. Fleming and Allen Chao for helpful suggestions on the manuscript.

■ REFERENCES

(1) (a) Wittig, G.; Davis, P.; Koenig, G. Phenanthrensynthesen über intraionische Isomerisationen. *Chem. Ber.* **1951**, *84* (7), 627−632. (b) Wittig, G. Nobel Lecture: From Diyls to Ylides to My Idyll. http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1979/wittig-lecture.html (accesed Jan 2016).

(2) Seebach, D. Methods of Reactivity Umpolung. *Angew. Chem., Int. Ed. Engl.* **1979**, *18* (4), 239−339.

(3) Corey, E. J. General Methods for the construction of complex molecules. *Pure Appl. Chem.* **1967**, *14* (1), 19−37.

(4) Smith, A. B., III; Adams, C. M. Evolution of Dithiane-Based Strategies for the Construction of Architecturally Complex Natural Products. *Acc. Chem. Res.* **2004**, *37* (6), 365−377.

(5) Ball, D. B. Diastereoselectivity in the Reduction of α-Hydroxyketones. An Experiment for the Chemistry Major Organic Laboratory. *J. Chem. Educ.* **2006**, *83* (1), 101−105.

(6) Snider, B. B. Heterocyclic Carbene-Catalyzed Reaction of Chalcone and Cinnamaldehyde To Give 1,3,4-Triphenylcyclopentene Using Organocatalysis To Form a Homoenolate Equivalent. *J. Chem. Educ.* **2015**, *92* (8), 1394−1397.

(7) (a) Hanson, R. W. The preparation of furoin-A biomimetic reaction. *J. Chem. Educ.* **1993**, *70* (3), 257. (b) Bhattacharya, A.; Purohit, V. C.; Beller, N. R. Benzoin Condensation: Monitoring a Chemical Reaction by High-Pressure Liquid Chromatography. *J. Chem. Educ.* **2004**, *81* (7), 1020−1022. and references within. (c) Williamson, K. L.; Masters, K. M. The Benzoin Condensation: Catalysis by the Cyanide Ion and Thiamine. *Macroscale and Microscale Organic Experiments*, 6th ed.; Cengage Learning: Belmont, CA, 2011; pp 655−660.

(8) Bodner, G. M. Metabolism Part II. The Tricarboxylic Acid (TCA), Citric Acid, or Krebs Cycle. *J. Chem. Educ.* **1986**, *63* (8), 673−677.

(9) Lujan-Montelongo, J. A.; Ojeda Estevez, A.; Fleming, F. F. Alkyl Sulfinates: Formal Nucleophiles for Synthesizing TosMIC Analogs. *Eur. J. Org. Chem.* **2015**, *2015* (7), 1602−1605.

(10) (a) Olijnsma, T.; Engberts, J. B. F. N.; Strating, J. Formamide as the Amine Component in the Mannich-type Condensation with Sulfinic Acids and Aldehydes. *Recl. Trav. Chim. Pays-Bas.* **1972**, *91* (2), 209−212. (b) Hoogenboom, B. E.; Oldenziel, O. H.; van Leusen, A. M. p-Tolylsulfonylmethyl Isocyanide. *Org. Synth.* **1977**, *57*, 102−106. (c) van Leusen, D.; van Leusen, A. M. Synthetic Uses of Tosylmethyl Isocyanide (TosMIC). *Org. React. (Hoboken, NJ, U. S.)* **2001**, *57* (3), 424−425 references included within.

(11) Even though recently more metallic sulfinates are commercially available, resulting from Baran's late stage C—H functionalization methods (see Gianatassio, R.; Kawamura, S.; Eprile, C. L.; Foo, K.; Ge, J.; Burns, A. C.; Collins, M. R.; Baran, P. S. Simple Sulfinate Synthesis

DOI: 10.1021/acs.jchemed.6b00102
J. Chem. Educ. XXXX, XXX, XXX−XXX

Enables CH Trifluoromethylcyclopropanation. *Angew. Chem. Int. Ed.* **2014**, *53*, 9851−9855 and references included within), most sulfinates are considered "expensive", as their cost is more than US$100 per gram.

(12) Methyl *p*-tolyl/phenyl sulfinates, and menthyl *p*-tolylsulfinate (Andersen's sulfinate) are the most popular sulfinates encountered in the chemical literature. Recent and selected literature classified according to reaction partners (i) **Grignard reagents:** (a) Bürgi, J. J.; Mariz, R.; Gatti, M.; Drinkel, E.; Luan, X.; Blumentritt, S.; Linden, A.; Dorta, R. Unprecedented Selectivity via Electronic Substrate Recognition in the1,4-Addition to Cyclic Olefins Using a Chiral Disulfoxide Rhodium Catalyst. *Angew. Chem., Int. Ed.* **2009**, *48* (15), 2768−2777. (b) Kosugi, H.; Konta, H.; Uda, H. Highly Diastereoselective Reduction of Chiral *β*-Ketosulfoxides under Chelation Control: Application to the Synthesis of (*R*)-(+)-n-Hexadecano-1,5-lactone. *J. Chem. Soc., Chem. Commun.* **1985**, No. 4, 211−213. (ii) **Li organometallics:** (c) Nath, D.; Fleming, F. F. Sulfinylnitriles: Sulfinyl-Metal Exchange-Alkylation Strategies. *Chem. - Eur. J.* **2013**, *19* (6), 2023−2029. (d) Buezo, N. D.; De la Rosa, J. C.; Priego, J.; Alonso, I.; Carretero, J. C. Sulfoxides as stereochemical controllers in intermolecular Heck reactions. *Chem. - Eur. J.* **2001**, *7* (18), 3890−3900. (e) Rayner, P. J.; Gelardi, G.; O'Brien, P.; Horan, R. A. J.; Blakemore, D. C. On the synthesis of *α*-amino sulfoxides. *Org. Biomol. Chem.* **2014**, *12* (21), 3499−3512. (iii) **Li amides:** (f) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. Improved Synthesis of Enantiopure Sulfinimines (Thiooxime S-Oxides) from *p*-Toluenesulfinamide and Aldehydes and Ketones. *J. Org. Chem.* **1999**, *64* (4), 1403−1406. (g) García Ruano, J. L.; Parra, A.; Marzo, L.; Yuste, F.; Mastranzo, V. One-pot synthesis of sulfonamides from methyl sulfinates using ultrasound. *Tetrahedron* **2011**, *67* (16), 2905−2910. (h) Maldonado, M. F.; Sehgelmeble, F.; Bjarnemark, F.; Svensson, M.; Åhman, J.; Arvidsson, P. I. Synthesis and Arylation of Unprotected Sulfonimidamides. *Tetrahedron* **2012**, *68* (36), 7456−7462. (iv) **Enolates:** (i) Wei, L.; Xiao, M.; Xie, Z. Total Syntheses of (−)-Spirooliganones A and B. *Org. Lett.* **2014**, *16* (10), 2784−2786. (j) Coates, R. M.; Pigott, H. D. Preparation of *α*-toluenesulfinyl ketones via enolate condensation with methyl p-toluenesulfinate. *Synthesis* **1975**, *1975* (5), 319−320. (v) **Activated arenes:** (k) Yuste, F.; Hernández Linares, A.; Mastranzo, V. M.; Ortíz, B.; Sánchez-Obregón, R.; Fraile, A.; García Ruano, J. L. Methyl Sulfinates as Electrophiles in Friedel-Crafts Reactions. Synthesis of Aryl Sulfoxides. *J. Org. Chem.* **2011**, *76* (11), 4635−4644.

(13) Methyl benzenesulfinate (670-98-4) price: US$ ∼130−320 per 25 g (Oakwood Chemical, Sigma-Aldrich), January 2016. We suggest experimenters to prepare methyl 4-methylbenzenesulfinate (672-78-6) (ref 9) since availability and prices varies constantly.

(14) During the experimental sessions, the students that used sulfinate **1a** as reactant commented that the isolation of derivatives **2a** and **5a** was easier (e.g., solids crystallized faster) than the corresponding of derivatives **2b** and **5b**. These claims were shared by most of the students even though the yields were comparable for all the reactions involving both reactants.

(15) In order to stablish the viability of an experiment in a single experimental session, we aimed for a reaction time of less than 1 h.

(16) (a) Eckert, T. S. An improved preparation of a Grignard reagent. *J. Chem. Educ.* **1987**, *64* (2), 179. (b) Williamson, K. L.; Masters, K. M. *Macroscale and Microscale Organic Experiments*, 6th ed.; Cengage Learning: Belmont CA, 2011; pp 495−497.

(17) Mp 66−69 °C. Tohma, H.; Maegawa, T.; Kita, Y. Facile and efficient oxidation of sulfides to sulfoxides in water using hypervalent iodine reagents. *ARKIVOC* **2003**, No. vi, 62−70.

(18) Through the experiment survey, a couple of students where provided with a Schlenk line and anhydrous tetrahydrofuran (freshly distilled from a benzophenone-ketyl still pot). In this case, students reported much higher yields (>90%).

(19) Clayden, J.; Greeves, N.; Warren, S. *Organic Chemistry*, 2nd ed; Oxford University Press: Oxford, U.K., 2012. pp 154−156, 241−243.

DOI: 10.1021/acs.jchemed.6b00102
J. Chem. Educ. XXXX, XXX, XXX−XXX